Issue No. 2,
November 2019

NEUROSOME

Neurosome Newsletter

Exploring the Neurological Exposomes

NEUROSOME is a Europe integrated training network funded in the frame of Marie Sklodwska-Curie action. This project brings together beyond-the-state-of-art advances in human biomonitoring and systems biology, exposure monitoring and toxicological testing technology and advanced tools for computational analyses of the exposure-to-health effect continuum according to the exposome paradigm. It will improve the scientific knowledge on cause and effect relationship between chemicals and neurodevelopmental disorders taking into account exposure and health effect modification due to intrinsic and extrinsic factors.

In this Issue:

Welcome to the second issue of Neurosome Newsletter!

Human biomonitoring of toxic metals associated to neurodevelopmental disorders (ESR3)

Byron Fuentes, Dr. Anna Pino, ISS

I am involved in mastering the skills needed to perform analysis of metals by the ICP-MS technique. Besides this, we are able to perform isotopic analysis, using the THERMO Neptune™ Series High Resolution Multicollector ICP-MS.

It is possible to follow the isotopic signature during analysis in the human biomonitoring (HBM). By means the isotopic ratios is possible to track the source of the exposure for the population and to match the different selected isotopes, found in the biomarker, with reported values in the literature or directly with samples of potential environmental sources of contamination as water, soil, paint, fuels and etcetera. As well the ensemble work developed with ESR3´s team, performing the analysis of lead (Pb) in blood and brain samples from mice exposed to Pb by the intake of water. The goal is to highlight the correlation between the intake/uptake/behaviour in vivo. The first results showed a positive correlation (intake/concentration) in both biomarkers.

Targeted in vivo testing of neurodevelopment focusing on exposure to heavy metals (ESR4)

Oyku Dinckol, G. Calamandrei, ISS

Currently, we are working on mimicking the real-life scenario of single heavy metal exposure during pregnancy and lactation in an in vivo mice model. As a start contaminant, we picked lead (Pb), a well-studied heavy metal. Pb is widely exposed pollutant to humankind during daily life and causes serious health conditions by building a body burden as well as affecting the developmental stage by altering molecular and/or endocranial mechanisms. We set an animal model to assess neurodevelopmental effects of prenatal and neonatal Pb exposure. Female mice were exposed to different concentrations of Pb via oral administration for 2 months including prebreeding period and time windows of gestation and lactation. Firstly, to assess the effects of Pb on maternal behaviour, dams were observed daily for the first 7 days after parturition. Secondly, to assess neurodevelopmental effects, offspring were examined with different behavioural tests during different development stages of life. Behavioural tests were conducted to test the progress of offspring on social, locomotor and cognitive skills and anxiety levels in neonatal, adolescent and young adult age.

Preliminary data were presented in the 17th biannual meeting of the International Neurotoxicology Association (INA 17) via poster presentation.

Development of an analytical framework of environmental samples from different media towards exposome assessment (ESR5)

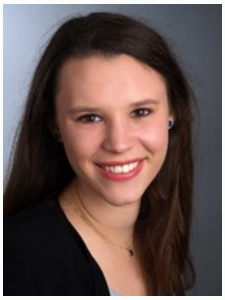
Marco Capodiferro, J.Grimalt, CSIC

My research is focusing on the analysis and evaluation of neuropollutants present in distinct samples from different media. Primarily, a study was performed on the levels of different chemicals on Greek soils after a huge fire. The levels of different persistent organic pollutants (POPs) were analyzed, in particular polycyclic aromatic hydrocarbons and organochlorine compounds (OCs), including dioxins and polychlorobiphenyls. Metals, sugars and fire molecular markers were also determined. Recently, a study on mercury levels in fish samples from the western Mediterranean has just been completed. Eight sampling campaigns were carried out in different sites scattered in the western part of the Mediterranean Sea and more than a thousand samples were collected, classified and analyzed.

Currently, we are analyzing human blood serum samples from a cohort of children between 7 and 8 years old. In our analysis, we are looking at a series of POPs, paying particular attention to benzyl paraben, and triclosan). After deconjugation of urine, solid phase extraction was applied using Oasis HLB (60 mg/1 ml) 96-well plates.
After derivatization, Two Strata Si (100 mg/1mL) 96-well plates are used for sample clean up and samples are eluted with dichloromethane. In a last step, samples are concentrated to 100 µL under nitrogen flow and transferred to inlets for analysis with GC-MS/MS. We are using an Agilent 7890 B gas chromatograph coupled to triple quadrupole mass analyser Agilent 7000 together with a DB5-MS UI column (30 m, 0.25 mm, 0.25 µm) and helium as carrier gas. The first article on urinary phthalate concentrations in Slovenia and associations with questionnaire data will be submitted shortly.

Analysis of human biosamples for biomarker Quantification (ESR6)

Agneta Runkel, M.Horvat, JSI



My part is on targeted and non-targeted analysis of non-persistent contaminants in human samples to assess exposure of the general population. They analyzed samples from a Slovenian Human Biomonitoring project for target analytes (bisphenol A, bisphenol F, bisphenol S, ethyl paraben, methyl paraben, iso-propyl paraben, propyl paraben, iso-butyl paraben,

Integration of HIA, sustainability appraisal and environmental impact evaluations with development planning emphasizing the role of HBM in ex-ante hia (ESR7)

Tine Bizjak, B.Kontic, JSI

My research in the area of science to policy interaction requires good understanding of how policy decisions are made and what kind of information is best at informing them. I have been involved in preparing and evaluating the example of use of Cd HBM data for the purpose of HIA or HRA. Additional ongoing research will include a detailed evaluation of possible HBM uses for risk assessment. So far, my research, aiming to improve the understanding of the policymaking needs, included the evaluation of the status of current environmental, climate and health nexus policies in Slovenia and other European countries. Furthermore, my work also focused preparing a Survey, which will aim to identify if there are differences in understanding of science to policy interaction between the two main groups of stakeholders of interest - the scientists and the policymakers. The survey and its results will also be used to share and extend my research among everyone involved in NEUROSOME.

Short Commentary: Auditing in addition to compliance monitoring: a way to improve public health (International Journal of Public Health).

Generic Physiologically Based Pharmacokinetic (PBPK) model with Brain-Sub Compartments (ESR9)

Deepika Deepika, Marta Schuhmacher, URV

Currently, we are working on development of Generic Physiologically Based Pharmacokinetic (PBPK) model for mixture risk assessment

to assess neurotoxicity. This model includes brain subcompartments for assessing the neuronal risk based on mixture risk interaction. Model considers detailed physiology of brain, enzyme transport kinetics of mixture and blood brain barrier. Firstly, PBPK model mostly consists of three brain regions hippocampus, cortex and rest of brain tissue.

Only unbound fraction in plasma and brain tissue can pass through the brain barrier. Secondly, it consist of mechanistic blood brain barrier model. The model includes specific transport proteins and cellular enzymes. Active transport is also expressed by fraction unbound and Michaelis-Menten terms. Lastly, it takes into account cumulative exposure of mixture of chemicals. Toxicokinetic interactions may influence absorption, distribution, metabolism and excretion inside human body i.e., metabolizing enzymes, plasma protein binding and absorption rate. The PBPK model will be validated by Polyfluoroalkyl and perfluoroalkyl substances (PFASs) i.e. PFOS, PFOA & PFNA for assessing human risk. Ubiquitous presence of these substances in environment and raised concern towards neurotoxicity catch the attention towards mixture effect.

Genome-wide profiling and identification of single nucleotide polymorphisms (SNPs) relevant to susceptibility to neurodevelopmental disorders (ESR14)

Irene Fragkiadoulaki, V. Pecile, BURLO

The main objective of the research is based on the study of the interplay between genetic variability and co-exposure to chemicals

for extended period of time and how this contributes to the development or exacerbation of central nervous system disorders during child development. Identification of single nucleotide polymorphisms (SNPs) may help predict an individual's susceptibility to environmental pollutants, and the risk of onset of neurodevelopmental disorders. To this end, we are currently working on the analysis of existing bio-samples (cord blood/cord tissue) of the PHIME Mediterranean cohort, recruited in Italy, Slovenia, Greece, and Croatia, performing DNA extraction and genome-wide profiling. The bioinformatics analysis of the raw data corresponds to SNPs identification in specific genes related to either the toxicology or metabolism (Phase I & II) of xenobiotic. The last step to obtain an overall picture of the relationship between the genetic background of an individual and the adverse effects of environmental toxic factors, will be a wide-association analysis using information on maternal and infant levels of exposure to metals (Hg, Mn, Cu, Zn, As, Se, Cd, Pb), neuropsychological scores (through Bayley III test) of children at 18 months of age and socio-economic information of the individuals.

Work of the remaining ESRs will be included in the next issue of newsletter

DISSEMINATION ACTIVITIES

NEUROSOME TRAINING SCHOOL

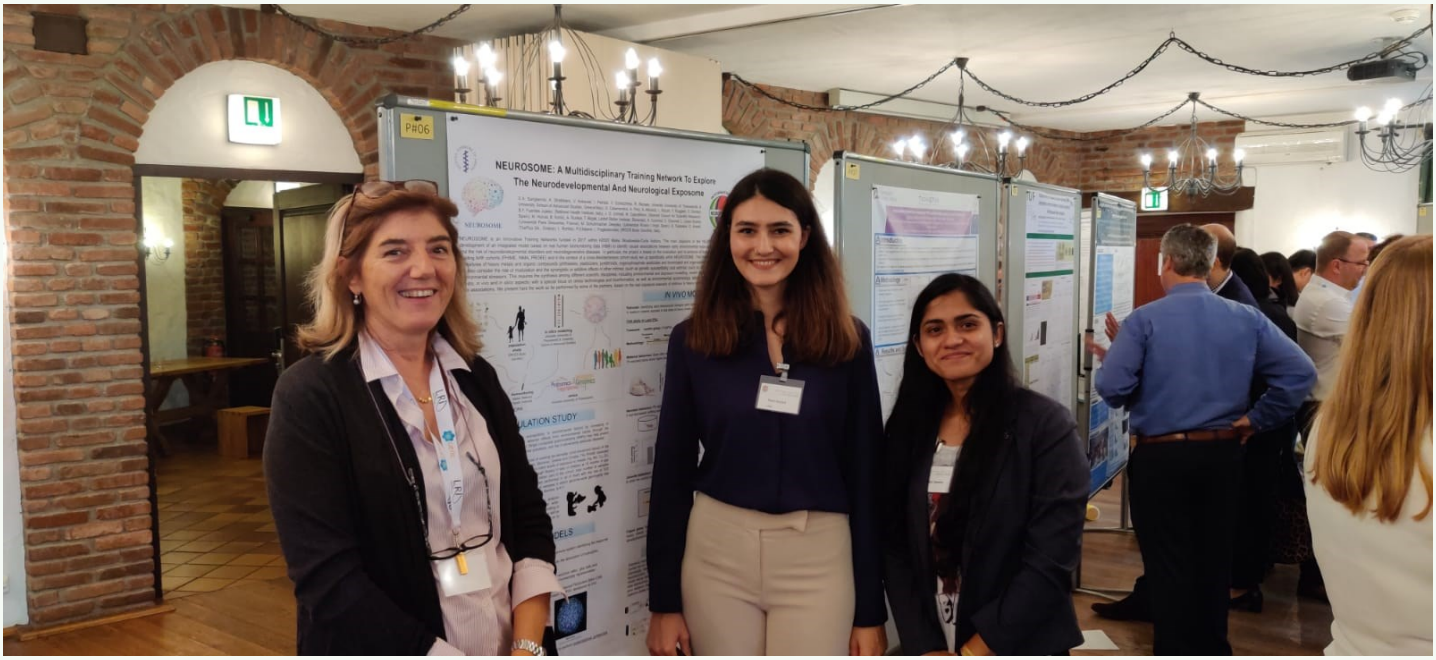
The first NEUROSOME training school has been co-organised by Prof. Dimosthenis Sarigiannis and Prof. Aris Tsatsakis in the frame of the BIONANOTOX conference that was held in Heraklion, Crete, Greece (https://bionanotox.org/). The training school consisted of a one-week course from 5th May to 12th May 2019.

It included a vast majority of topics like exposome science in the advent of OMICS– the connectivity approach, sampling and analysis of environmental and biological matrices, advanced exposure science, environmental and integrated exposure modelling and computational methods in toxicology.

INA17 Meeting on Neurotoxicology

17th Biannual meeting of International Neurotoxicology Association was held in Dusseldorf, Germany for the discussion on Translational Neurotoxicology (https://ina-17.ifado.de/).

Meeting was from 29th Sept to3rd Oct 2019. The main agenda of meeting was the ways for translation of knowledge into neurotoxicity, advancements in neurotoxicity testing and human risk assessment. We presented a poster to give a brief overview about the activities in NEUROSOME projects.



FORTHCOMING EVENT

The Interim meeting for the Neurosome project will be held on December 19 in Athens at the premises of the National Centre for Scientific Research 'Demokritos'.

The project has receiver funding from European Union Horizon 2020 Research and Innovation programme under the Marie Skłodowska-Curie grant agreement No. 766251