CALL FOR APPLICATIONS

NEUROSOME

14 Early Stage Researcher positions in the field of "Neurological Exposome" in the EU- funded Marie Skłodowska-Curie Innovative Training Network (ITN) *NEUROSOME*

COORDINATING ORGANISATION

Aristotle University of Thessaloniki on behalf of the NEUROSOME consortium

RESEARCH FIELD

Computational biology, Genetic epidemiology, Bioinformatics, Systems biology, Metabolomics, Human biomonitoring, Behavioural toxicology, in vitro/in vivo testing, health impact assessment, environmental, exposure, GWAS, EWAS, personal sensors.

RESEARCHER PROFILE

Early Stage Researcher (ESR)

APPLICATION DEADLINE

16/04/2018 23:00 – CET (Europe/Brussels)

LOCATION

Multiple locations, see link below for detials.

TYPE OF CONTRACT

Temporary

JOB STATUS

Full-time

INDICATIVE WORKING HOURS PER WEEK

40

OFFER STARTING DATE (INDICATIVE)

01/05/2018

EU RESEARCH FRAMEWORK PROGRAMME

H2020 / Marie Skłodowska-Curie Actions

MARIE CURIE GRANT AGREEMENT NUMBER

766251

We announce the start of the application period for **14 ESR** positions offered by the ten host organisations participating in the Innovative Training Network (ITN) "Exploring the Neurological Exposome (***NEUROSOME)***"***.*** The Marie Skłodowska-Curie Action "Exploring the Neurological Exposome (*NEUROSOME)* is an international research project, coordinated by Prof. Dimosthenis Sarigiannis from the Aristotle University of Thessaloniki (EL) and is financed under the funding line "excellent science" of the Horizon 2020 research and innovation programme of the European Commission.

We welcome applications from early stage researchers from all over the world for the fourteen research projects until April 16, 2018 via our application system.

NEUROSOME focus is on the investigation of causal associations among genetic predisposition, cumulative exposure to multiple environmental chemicals of children and neurodevelopmental disorders. The project brings together beyond- the-state-of-the-art advances in human biomonitoring and systems biology, exposure monitoring and toxicological testing technologies and advanced tools for computational analyses of the exposure-to-health effect continuum according to the exposome paradigm. The NEUROSOME methodology will be applied in population studies across different exposure settings to neurotoxicants (metals and selected organic compounds) in Europe. This will help us understand how environmental stressors lead to or exacerbate neurodevelopmental disorders. New standards for human biomonitoring data interpretation in conjunction with environmental and exposure information will be developed for ready use in chemical mixture risk assessment.

NEUROSOME seeks to train the next generation of exposome scientists able to tackle the global challenges associated with the impact on human health due to environmental exposure. Great emphasis is placed on training ESRs through collaborative exchanges and practical courses. The ultimate goal is to produce a new generation of exposome researchers, trained in academia, applied research and industry, with transdisciplinary skills (environmental end exposure modelling, human biomonitoring, in vivo and in vitro testing, -omics technologies, high dimensional bioinformatics and environmental epidemiology,) and understanding of fundamental science and its direct application to environmental health challenges.

Members of this **interdisciplinary and intersectoral scientific research network** acting as ESR **hosts** are:

- Aristotle University of Thessaloniki (EL), Coordination
- Istituto Superiore di Sanità (IT)
- Spanish Council for Scientific Research (ES)
- Jožef Stefan Institute (SI)
- University of Paris Descartes (FR)
- Universitat Rovira I Virgili (ES)
- ToxPlus SA (EL)
- Institute for Advanced Study (IT)
- Istituto di ricovero e cura a carattere scientifico Burlo Garofolo (IT)

The following institutions **take part in the network** and will **receive ESRs seconded from their host institution** for limited periods of time (between 6 and 10 months):

- Johns Hopkins University School of Public Health, Department of Environmental Health Engineering, Baltimore, MD, USA
- Emory University Rolling School of Public Health, Atlanta, GA, USA
- United States Environmental Protection Agency, Office of Research and Development /Human Exposure Modeling Branch, Research Triangle Park, NC, USA
- Harvard University, Department of Biomedical Informatics, Boston, MA, USA
- UPCOM SA, Brussels, Belgium

14 ESRs positions will be filled with a focus on the topics of neurodevelopmental disorders. All individual projects will have a duration of 36 months. Early stage researchers (ESRs) will be hired under a full-time, temporary contract at one of the host institutions. Their research would preferably lead to the awarding of a PhD in scientific domains relevant to environment and health science. The partners engaged in the project will work closely together, with each of the partners supervising at least one research project. ESRs will be trained through a structured and comprehensive programme and will not only learn the theory but will gain first-hand lab experience. All ESRs will spend time not only at the hosting institution but also in one of the other partner universities/research centers/regulatory agencies/companies involved in NEUROSOME throughout Europe and the USA.

Please find details about the application process and modalities at http://www.neurosome.eu

We are looking forward to your application.

Best regards

Prof. Dr. Dimosthenis Sarigiannis

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Eligibility criteria

- You have a relevant university degree (master's degree or equivalent) in biomedical/bioinformatics sciences or biological sciences, life sciences or environmental/engineering science or related fields.
- You have excellent proficiency of the English language.
- Only applications that are complete, in English and in the right order, have been named as needed (SURNAME.pdf; avoid special characters) and that have been submitted by the deadline (**April 16, 2018**) will be considered eligible.
- The positions are open to all nationalities. However, your application has to comply with the European **Commission's Mobility Rules**, meaning that at the time of recruitment you must not have resided or carried out your main activity (work, studies, etc.) in the country of the host organisation for more than 12 months in

the 3 years immediately before the reference date (indicative start of the employment contract, 1 May or June 2018). Compulsory national service and/or short stays such as holidays are not taken into account (European Commission's Guide for Applicants, p. 16).

- You are **an Early-Stage Researcher (ESR)**, i.e. in case you have already gained prior work experience in academia, you shall be in the first four years (full-time equivalent research experience) of your research career at the time of recruitment by the host organisation and have not been awarded a doctoral degree. Full-time equivalent research experience is measured from the date when you obtained the degree entitling you to embark on a doctorate, even if a doctorate was never started or envisaged. Part-time research experience will be counted pro-rata (European Commission's Guide for Applicants, p. 16).
- You cannot apply for more than three of the ESR positions, the research projects of which are listed in detail below.

Selection process

The selection committee will check applications against the following criteria:

- Scientific background and potential as indicated by candidate experience.
- Fit to a research project.
- Evidence of ability to undertake research.
- Evidence of working within groups or teams.
- Impact and benefit of the proposed training to the candidate's research career.

Gender equality and minority rights will be promoted in the selection process.

Three candidates will be short-listed for each research project and invited to an interview (interviews by video link will be held if candidates are not able to travel).

Interviews will consist of two parts: 1) a short presentation by the candidate followed by questions and answers, and 2) competence-based interview.

NEUROSOME is looking for a broad international representation of early stage researchers. The network clearly acknowledges its responsibility for the recruitment of the researchers, their working and living conditions, as stated in the document "The European Charter for Researchers - Code of Conduct for the Recruitment of Researchers".

Projects description

Selected projects: Subproject Title (you can apply for a maximum of three projects):

- **ESR 1 - Functional integration of different omics results using bioinformatics tools towards development of AOPs for neurodevelopmental disorders (Host: Institute for Advanced Study , Pavia (IT)).**

  Main objectives: To develop an integrative biology approach for developing AOPs for neurodevelopmental disorders building systems biology hypotheses based on multiple -omics data.

  Expected Results: The project aims at training an ESR on integrative biology tools such as Agilent GeneSpring, Thompson-Reuters MetaCore™ and Reactome/Functional Interaction network plug-in for Cytoscape, so as to create systems toxicology hypotheses from human data, with emphasis on inter-organ system changes. Bioinformatics algorithms will be used to identify common nodes across several pathways perturbed from co-exposure to the compounds of interest to NEUROSOME (organics and metals). This is expected to allow the identification of the most critical regulatory pathway nodes that regulate the onset of pathways beyond cellular homeostasis - thus identify potential candidates for adverse outcome pathways. The critical question is whether there is a limited number of Pathways of Toxicity (PoT). It is likely that the number of critical cellular infrastructures is limited; thus the points of vulnerability, to which the PoT would converge, should also be limited, however, this is one of the major scientific questions to be answered within this project. ESR2 will work in close collaboration with ESR12 and ESR13.

- **ESR 2 - Development of an integrated exposure model coupled to PBBK model for mixtures of neurotoxicants (Host: Institute for Advanced Study , Pavia (IT))**

  Main objectives: To develop the proper modelling framework for estimating population external and internal exposure to xenobiotics, aiming to link external exposure metrics used in association studies to internal dosimetry metrics used in different toxicological testing strategies and identified omics signatures.

  Expected Results: The work will include the development of lifetime (including gestation and breastfeeding) generic physiology-based biokinetic (PBBK) models for humans and animal models (e.g. rodents), able to describe internal exposure on susceptible developmental stages. The model will take into account interaction of multiple chemicals (mixtures interaction) at the level of metabolism, including enzyme inhibition (e.g. competitive, non-competitive and uncompetitive inhibition) and mechanism-based inhibition. To cover a large chemical space and so to assure a more “generic” character of the model, biological properties (e.g. partition coefficients and metabolic parameters such as the maximal velocity (Vmax) and Michaelis affinity constant (Km) or the intrinsic clearance (Vmax/Km)) will be derived from advanced QSAR/QSPR accessory models, using both quantum descriptors and artificial intelligence techniques such as artificial neural networks. Validation of the PBBK model will be done using the data from the ESR3, ESR6 and ESR11 projects. Receiving input from ESR9 project (external dose estimation), is

going to produce the internal doses relevant for in vitro testing (ESR4, and ESR8 projects).

- **ESR 3 - Human biomonitoring of toxic metals associated to neurodevelopmental disorders (Host: Istituto Superiore di Sanità, Rome (IT)).**

  Main objectives: To identify the levels of internal exposure to toxic metals through human biomonitoring.

  Expected Results: Studies have shown associations between exposure to environmental concentrations of individual toxic metals such as lead, mercury, arsenic, cadmium, and manganese and developmental outcomes in children, including reduced IQ and decreased performance on developmental tests. The simultaneous exposure of an individual to mixtures of chemicals, which may interact in an additive, synergistic, or even antagonistic way, remains to be explained and defined, especially in a mechanistic perspective. ESR3 project, aims at the collation of exposure to toxic metals related HBM data since the very early developmental stages, providing an overview of the actual population exposure to different potentially neurotoxic metals. These data will be also used for the validation of the PBBK model developed in ESR2 project.

- **ESR 4 - Targeted in vitro and in vivo testing of neurodevelopmental disorders focusing on exposure to heavy metals (Host: Istituto Superiore di Sanità, Rome (IT)).**

  Objectives: To assess in vivo and in vitro models the neurodevelopmental toxicity of co-exposure to metals to identify omics biomarkers associated with the behavioural phenotype in peripheral and brain tissues.

  Expected Results: Targeted in vivo studies in laboratory rodents will be performed to derive a set of peripheral accessible markers of susceptibility, vulnerability and effects, able to predict the effects in the brain and the neuropsychological outcome. To this aim, wild-type mouse strains or carrying common and potentially functional polymorphisms (SNPs identified by other partners in this network) will be used to verify the impact of varying doses of contaminants (heavy metals, alone or in combination), administered at different critical stage of development (pregnancy, infancy, adolescence). A battery of behavioural tests including evaluation of sensorimotor, social, emotional and learning/memory functions (mirroring those applied to evaluate infants' and children's development) will be performed at different life stages to identify both short- and long-term effects and evaluate the risk of aging-related impairments. In parallel, omics biomarkers (oxidative stress markers, , protein and metabolite levels and epigenetic markers) will be measured in peripheral organ/tissues and in the brain to evidence parallel changes and possible differences anchored to the behavioural phenotype, eventually to validate the peripheral biomarkers as indexes of abnormal brain and behaviour development. In vitro (using the novel iPSC-derived 3D BMPS) and in silico models based on the findings in the animal models will be tested out in collaboration with ESR2, ESR8 and ESR13.

- **ESR 5 - Development of analytical framework of environmental samples from different media towards exposome assessment (Host: Spanish Council for Scientific Research, Barcelona (ES)).**

Objectives: This Project is devoted to provide the needed relevant environmental contamination data for the compounds of interest for the exposure models to deploy the individual exposome.

Expected Results: The candidate will learn to review and collate relevant environmental contamination data for the compounds of interest. He also will be trained in several analytical chemistry techniques and instrumentation (GC-MS/MS, ICP-MS, HPLC-MS). The most advanced technologies for the targeted and untargeted analysis of trace pollutants will be available in this research group such as gas chromatography coupled to Q-exactive orbitrap mass spectrometry, and the equivalent method with liquid chromatography. In addition to these instruments, the partner has about 30 gas chromatography and liquid chromatographs coupled to electron impact MS, chemical ionization MS, time of flight MS, MS/MS and magnetic sector MS. The research work for development and training will also encompass methods for planning and implementing sampling, sample handling and analysis for environmental health association studies and for deploying the individual and population exposome. As a result, the knowledge gaps of environmental contamination for the different media will be identified and filled in by additional measurements in "fusion" to modelled data produced in WP4.2, providing as such a comprehensive picture of the contamination levels and the different synthesis of the neurotoxicants "cocktails" of the populations of the different regions. ESR5 will be in close collaboration to ESR9 project.

- **ESR 6 - Analysis of human biosamples for biomarkers quantification (Host: Jožef Stefan Institute, Ljubljana (SI)).**

  Objectives: To collect the biosamples from the selected population and to identify the exposure levels to mixture of organic compounds

  Expected Results: This project aims at the collection of the biosamples from the cross Mediterranean (Greece, Italy, France, Spain, Slovenia and Croatia) populations to be investigated. The ESR will gain experience on how to design an exposome based population study, how to identify representative population, what type of matrices to select, how to store and preserve the samples and what protocols to follow regarding further analysis. Identification of exposure levels to mixtures of organic compounds will be carried out through chemical analysis of commonly used matrices (e.g. urine, blood, hair) providing estimates for exposure levels of selected organic contaminants (flame retardants, phenols, phthalates, etc.). The ESR will get familiar with a broad range of analytical chemistry techniques (GC-MS/MS, ICP-MS, HPLC-MS) and protocols for human biosamples sampling, storage, preparation and analysis, as well as with the development of analytical techniques for emerging compounds. ESR6 project will be in close collaboration with ESR2, since the exposure biomonitoring data will also be used for the validation of the PBBK model.

- **ESR 7 - Integration of Health Impact Assessment (HIA), sustainability appraisal and environmental impact evaluations with development planning emphasizing the role of Human Biomonitoring in ex-ante HIA (Host: Jožef Stefan Institute, Ljubljana (SI)).**

Objectives: To demonstrate usefulness of the integration of HIA with environmental and other assessments at strategic level of development planning (sustainability). To clarify and understand role and importance of HBM in the context of exposure assessment and the two types of HIA: ex-post and ex-ante.

Expected Results: HIA+SA+SEA+EIA+CBA+CEA and their integration are not crucial for the sake of their good practice and from the scientific point of view but rather to make them as effective and beneficial as possible in the context of improving public health status, and optimization of the development proposals. That is the reason why assessments need to be integrated with planning. This philosophy will guide research and work of ESR8; expectations are that ESR will develop advanced competence in the field of HIA working on both theoretical (conceptual) and practical issues. By combining work in WP4 and WP5 – collaboration among ESRs1, 2, 3, and 13 – the key results of the work of ESR7 are expected to be:

- advanced understanding of the needs for, and role of, analytical results of the quality/contamination of environmental media (air, water, soil) in ex-post and ex-ante HIA.
- capability of developing conceptual exposure models linked to concrete development planning proposals, e.g. long-term electric energy planning, transport in urban conglomerations (ex-ante HIA).
- optimization of development proposals based on comparative evaluation of alternatives using CBA and CEA, and considering potential exposure assessment.

ESR7 will work in close collaboration with ESR13

- **ESR 8 - Targeted in vitro analysis associated to neurodevelopmental disorders, focusing on organic environmental compounds (Host: University of Paris Descartes, Paris (FR)).**

Objectives: To identify response of the relevant nervous system cells to combined effect to environmentally relevant mixtures.

Expected Results: Suggested mechanisms of neurotoxic action for some of these chemicals include oxidative stress, epigenetic effects, disruption of cell signalling and endocrine disruption. Yet to date, no single mechanism can account for the neurological toxicity of this group of chemicals, which differ widely in structure, chemical properties and reactivity. It is reported here, however, that there is indeed a unifying explanation for the induction of neurological diseases by this diverse group of chemicals. The studies referred to above show that accumulation of all of these chemicals in body serum was associated with increased incidence of neurological impairment, neurodevelopmental diseases. Several of these chemicals are lipophilic and all were shown to accumulate in body serum (and probably in the lipophilic parts of the brain) following exposure. We will use several cell lines and primary cells to characterize the toxic effects of contaminant combinations: on the neuronal cells derived from iPS cells, glial cells and endothelial cells representative of the blood brain barrier (BBB). Moreover we shall use the novel iPSC-derived human 3D brain microphysiological system (BMPS) developed at JHU that comprises mature neuron and glial cells and presents spontaneous electrical activity and axon myelination. We will assess the effects of contaminant

combinations on the major toxic pathways in those cells (AhR, NRF2, ER, PR, LXR, oxidative stress, etc.). We will also test the hypothesis that lipophilic chemicals could facilitate the absorption of hydrophilic compounds across the body's lipophilic membranes, particularly in BBB cells. It is proposed here that the lipophilia of these exogenous chemicals disorganizes lipophilic membranes including the blood brain barrier, leading to neurological disorders, thus enabling the entry for toxic hydrophilic species that would otherwise not be absorbed. Thus, in vitro testing of co-exposure to multiple lipophilic organic compounds in relevance to the compounds investigated in NEUROSOME is expected to contribute to the elucidation of the mechanisms resulting in neurological impairments and to the characterization of cross-talks between signalling pathways that are not characterized using single xenobiotics. Dosing for confirmatory in vitro analysis will be directed from the internal dose in target tissues calculated in the research project of ESR2.

- **ESR 9 - Development of multimedia environmental contamination and human exposure model (Host: Universitat Rovira I Virgili, Tarragona (ES)).**

  Objectives: To develop a comprehensive multi-media environmental contamination model for estimating contamination levels of contact media (air, water, soil, food wed, settled dust), indoor exposure and food items and validate it under different scenarios taking into account uncertainty.

  Expected Results: The project aims at the development of an exposure modelling framework that encompasses the – multimedia model for assessing environmental contamination levels for different media were people are exposed to. Existing modelling schemes (ChemCAN, CalTOX, BETR Global model, CHEMGL, MUM-Fate and Simplebox) will be reviewed and evaluated. It is known that the complexity of these models ranges from relatively coarse multiple linear box models (MCMs) which assume homogenous landscape properties in each medium and assume that all environmental compartments are mixed, over spatial multimedia models (SMs) that are collections of single medium models in which the output of one model serves as input for the others, and spatial multimedia compartmental models (SMCMs) which consider one or more environmental compartments as non-uniform regions. Exposure estimation should include multi-chemical and multi routes estimation and validation of long term exposure dose using reverse dosimetry model. The critical uncertainties and/or oversimplifications will be characterized and properly addressed, in the newly developed computational model. The later will be based on the existing model INTEGRA. Validation of the model will be carried out based on the data collated and originally derived from Task 4.1, so high level of synergies with ESR5 are expected. This model will be incorporated to a wider human exposure model that will fuse advances in personal sensors technology and agent based modelling.

- **ESR 10 - Development of Quantitative Structure Activity Relationships for use in biokinetic models (Host: Aristotle University of Thessaloniki, Thessaloniki (EL)).**

  Objectives: To development Quantitative Structure Activity Relationships for use in biokinetic models, with a special focus on compounds relevant to neurodevelopmental disorders.

Expected Results: A current limitation to further introducing PBBK models in the risk assessment arena is the lack of generic character of these models. A critical limiting factor of describing ADME processes for a large chemical space is the proper parameterization for "data poor" compounds. In order to expand the applicability of PBBK models to cover as much as possible the chemical space, model parameterization for data poor chemicals is done using advanced quantitative structure-activity relationships (QSARs). In silico approaches, including QSARs, are widely used for the estimation of physicochemical and biochemical properties, biological effects as well as understanding the physicochemical features governing a biological response. QSARs are described as regression or classification models, which form a relationship between the biological effects and chemistry of each chemical and comprise the activity data to be modelled, the data with which to model and a method to formulate the model. The approaches for predicting metabolic rates are basically related to CYP-mediated metabolism and focus on the identification of substrate specificity. Additional parameters to be modelled in order to be able to reliably apply a lifetime PBBK model include renal clearance, tissue:blood partition coefficient, placental transfer and blood-brain barrier; the latter is very important for the case of neurodevelopmental diseases. Preliminary investigation has shown that Abraham's solvation equation combined with Artificial Neural Networks (ANN) is one of the most efficient methods for effectively predicting the parameters essential for a PBBK model. Predicted parameters for selected data poor chemicals will also be validated experimentally. ESR10 project is in very close link to ESR2 project, aiming at the development of a generic lifetime PBBK model for cumulative internal exposure.

- **ESR 11 - Advancing exposure assessment through environmental monitoring, human biomonitoring and use of personal sensors (Host: Aristotle University of Thessaloniki, Thessaloniki (EL)).**

  Objectives: To develop exposure models based on the assimilation of environmental, HBM and personal sensors data.

  Expected Results: The candidate will learn how to combine information from relevant environmental contamination data, HBM data and personal sensors data aiming at developing robust human exposure models. ESR11 project will rely on the analysis of multiple types of environmental samples (air, soil, water, settled dust, food items) as well as human specimens (urine, hair), thus training in several analytical chemistry techniques and instrumentation (GC-MS/MS, ICP-MS, HPLC-MS) will be required. Information from environmental contamination data will be combined with personal sensors data aiming at calculation of personal exposure. The latter will be validated against HBM data. Associations among these types of data will be investigated, aiming to identify the way environmental data and HBM data should be sampled, in order better reflect human exposure. It is expected that different recommendations will be derived, based on the physicochemical properties of the different compounds, depending on their persistency in the environment and human body as well. ESR11 will be in close collaboration with ESR2, ESR3, ESR6 and ESR9.

- **ESR 12 - Transcriptomics, metabolomics and toxicity pathway analysis of combined exposure to neurotoxicants (Host: Aristotle University of Thessaloniki, Thessaloniki (EL)).**

  Objectives: To identify the molecular signatures (transcriptomics, metabolomics) of co-exposure to neurotoxicants, aiming at pathway analysis

  Expected Results: The biosamples collected from the population studies will be further analysed, in order to understand the response of co-exposure to multiple stressors at the different levels of biological organisation. Transcriptomics will be evaluated in order to identify responses aiming at neural differentiation–related gene expression to mixtures of most commonly found combinations of neurotoxicants, which are expected to vary among the different regions (Greece, Italy, Spain, Slovenia and Croatia) included in the study. Differences in the metabolic signatures from urine and blood samples among the subjects of the populations to be investigated will be explored, aiming to further differentiate the profiles of healthy and non-healthy individuals. These two types of data will set the basis of toxicity pathway analysis for the health outcomes of interest. This will be analysed using advanced bioinformatics tools such as GeneSpring by Agilent and the outcomes of this project will be in close collaboration to ESR1 and ESR13 projects.

- **ESR 13 - Development of "big data" analytics approaches and their use to relate -omics, exposure and health outcome data (Host: ToxPlus SA, Heraklion (EL)).**

  Objectives: To develop advanced methods for big data analytics, such as methods for multi-output classification/regression. To collate and organize existing omics, exposure and health outcome data (related to neurodevelopmental disorders). To apply the developed methods to the data and find genome-exposome-wide health associations.

  Expected Results: Unravelling the causal links between environmental exposure and disease is the ultimate goal of exposome-related studies. The development and use of the methodology for carrying out genome-exposome-wide health association studies (GEHAS) will be carried out within the ESR13 project. Multiple indicators (e.g., clinical scores) of health/disease status will be considered (both separately and jointly).

  The ESR13 will develop methods for predictive modeling and feature ranking (marker discovery) in the context of multiple outputs (health outcomes). These will be based on existing approaches to multi-target regression and classification. It will also collate and coherently store multiple types of data (environmental, exposure, biomonitoring, multi-omics, toxicological testing), e.g., via NoSQL (Not only SQL). For assessing environmental exposure contribution to neurodevelopmental disorders, internal doses will be coupled to health impacts on the local population through the methods developed by this ESR. The internal doses will be derived from the measured biomarker, quantified in different biological matrices, estimated by the application of the lifetime generic PBBK model. This will correspond to the biological effective dose in the target tissue, which is consistent with the measured biomarker level. To estimate the health impacts, multi-output regression will be used, accounting for the different covariates (age, sex, socio-

economic status etc.). This ESR project will link internal doses (calculated in ESR2 project) with health effects or intermediate biological events (as identified in ESR1 project) that can be associated to health perturbations through pathway analysis (ESR1 and ESR12 projects) considering the interdependence of the covariates (using as metric an analogy of the "linkage disequilibrium" metric used in genome-wide association studies).

- **ESR 14 - Genome-wide profiling and identification of single nucleotide polymorphisms (SNPs) relevant to susceptibility to neurodevelopmental disorders (Host: Istituto di ricovero e cura a carattere scientifico Burlo Garofolo, Trieste (IT)).**

  Objectives: To identify the different polymorphisms that affect the response to exposure to chemical agents towards metabolic and neurodevelopmental disorder.

  Expected Results: Common gene variants may induce susceptibility to environmental factors by increasing or decreasing physiological responses to adverse effects from environmental toxins, through the mother's internal or external environment. Much research has been devoted to find SNPs that may help predict an individual's susceptibility to environmental pollutants, and risk of developing particular diseases. With regard to neurodevelopmental disorders, it has been found that same alleles from two single-nucleotide polymorphisms (rs3785143 and rs11568324) genetically predispose for attention-deficit hyperactivity disorder (ADHD). Beyond the SNPs that increase population susceptibility to neurodevelopmental disorders, there are SNPs affecting the metabolism of xenobiotics, increasing in this way the biologically effective dose and the overall effects of environmental exposure. For examples SNPs in genes involved in the detoxification of environmental pollutants have been found in some individuals with Autism Spectrum Disorders (ASD). Members of families CYP1, CYP2, and CYP3 —especially CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 in liver—metabolize about 95% of xenobiotics. In order to better understand the way exposure to xenobiotics results in disease, we need to investigate the involvement of genetic susceptibility parameters in real low-exposure scenarios. This project will focus on genome-wide analysis of cord blood samples obtained from newborns originally enrolled in the PHIME cohort (about 1200 subjects). This will allow us to establish robust associations between health outcomes and gene polymorphisms implicated in neurodevelopment and /or response to xenobiotics. The outcomes of ESR14 project will provide significant input in the development of the generic biokinetic model (ESR2 project), as well as ESR1, ESR12 and ESR13 projects.