HEALS Newsletter

Health and Environment-wide Associations based on Large population Surveys

Project No 603946 of the European Union's Seventh Framework Programme

Contents

Editorial Note

Welcome to the fifth issue of the HEALS Newsletter!

This issue includes a series of short notes on the progress of HEALS. First, a note by Spyros Karakitsios (AUTH, Greece) presenting the **Generic PBPK model for HBM data assimilation**, which has been already tested against several pollutants. Second, Miranda Loh (IOM, UK) and Anjoeka Pronk (TNO, The Netherlands) describes the **HEALS Pilots Sensor Technologies** developed within WP9 for assessing the external exposome. Third, a short note written by Martine Aggerbeck and other HEALS researchers from UPD (France), AUTH (Greece) and PCB (Spain) reports the **effects of mixtures of persistent organic pollutants on hepatic carbohydrate metabolism**. Fourth, a short note by Christian Schieberle (USTUTT, Germany) verses on the **Integrated External Exposure Assessment** that will be applied for the first time in the field of environmental epidemiology within the HEALS project. Fifth, Lauren Smith and Clive Sabel (UNIVBRIS, UK) report on the **socioeconomic (SES) effect on the external exposome**, presenting a conceptual model using an agent-based approach to simulate multiple time activity patterns. This methodology, employed in the conceptual model, is fully explained in Deliverable 10.2. The last short note, by Dimitris Chapizanis (AUTH, Greece), deepens in **agent-based modelling for assessing external exposure assessment** that has been developed in two city scale models (Thessaloniki and Edinburgh).

The Newsletter also described **two research issues** currently developed within HEALS: Cara Henson-Maesano, Shreosi Sanyal and Isabella Annesi-Maesano, from the Université Pierre et Marie Curie (France), report the method for **data standardization and harmonization** and Gemma Calamandrei, from the Instituto Superiore di Sanità (Italy) summarizes the recently published paper on **Understanding the link between environmental stressors and neurodevelopmental disorders**.

The *Who is Who* section outlines the professional profiles of several researchers who are actively involved in the project and participate in different work packages: Robert Barouki from the University Paris Descartes (France), Thomas Maggos from the National Centre for Scientific Research Demokritos (Greece), Sara Maio from the National Research Council (Italy), Christian Schieberle from the University of Stuttgart (Germany) and Eliandre de Oliveira from the Barcelona Science Park.

As usual, the issue ends with a list of the scientific publications, public presentations, workshops, conferences and other knowledge-dissemination activities generated by the HEALS researchers in this case since January 2016.

We take this opportunity to inform that HEALS is co-organizing the **8th International Network on Children's Health, Environment and Safety (INCHES) Conference**, which will be held in Barcelona (Catalonia, Spain) on 14–16th September 2016.

8th INTERNATIONAL CONFERENCE ON CHILDREN'S HEALTH AND THE ENVIRONMENT
14th – 16th of September 2016
Location: Parc de Recerca Biomèdica de Barcelona - PRBB
Doctor Aiguader, 88 (at CREAL), Barcelona

Highlights on HEALS progress

Generic PBPK model HBM data assimilation

by Spyros Karakitsios

Aristotle University of Thessaloniki (AUTH)
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In the frame of HEALS, a generic multi-route lifetime PBBK model (including gestation and breastfeeding) that also incorporates in utero exposure and interactions of mixtures has been developed. The model describes in as much detail as possible the ADME processes occurring in the human body at different life stages for direct application to a broad variety of chemicals after proper parameterization.

In its generic form the model includes the parent compound and up to three generations of potential metabolites. Quantitative structure-activity relationships (QSARs) coupled to artificial intelligence algorithms are used to estimate physicochemical and biochemical parameters to expand the domain of application of the model to a large chemical space.

A major advantage of PBBK modelling is that it allows to estimating the actual internal exposure or the Biologically Effective Dose (BED) that is associated to the observed health effects. In this way, differences in BED related to

a) age- and gender-dependent differences in physiology,

b) inter-individual susceptibility related either to age or to genetic polymorphisms of the enzymes involved in the metabolism of xenobiotics, and

c) route dependent bioavailability differences,

are captured. Hence, phenomenally similar external exposure levels are properly attributed to significant internal exposure differences.

The PBBK model is geared with reverse modeling algorithms in order to reconstruct exposure from human biomonitoring (HBM) data. This further allows us to estimate the time history of the internal exposome, focusing on critical age windows and to link external exposure (consumer and environmental) to target tissue dose. The latter is then used to design in vitro testing of the mechanistic hypotheses made on pathways of toxicity. This exposure reconstruction framework has been successfully tested against several scenarios. These include major endocrine disruptors such as bisphenol-A, bis(2-ethylhexyl) phthalate and DiNP. Additional exposures scenarios that have been successfully reconstructed include the multi-route (oral, inhalation, dermal) exposure to trichloromethanes, oral and inhalation exposure to 2,3,7,8 tetrachlorodibenzodioxines, oral exposure to triclosan, oral exposure to endosulfan and inhalation exposure to volatile organic compounds.

HEALS Pilots Sensor Technologies for the External Exposome

by Miranda Loh and Anjoeka Pronk

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HEALS WP9 has successfully completed two pilot studies to test the use of sensor technologies in characterising the external exposome. These include a small "pre-pilot" study to test location and physical activity sensors and a full pilot exposure study with a variety of personal and in-home sensor-based and smart technologies. With smartphones and wireless devices becoming ever more popular, there is growing interest in using these devices, along with the development of lower cost pollution sensors, for environmental health research. Because these technologies are developed for the wider public, they are generally less expensive than research grade instruments and open up the possibilities for long-term data collection in a more personalized way.

The HEALS pilot projects provide important information about the utility of such devices for use in exposome studies, and in research in general. HEALS selected a set of devices available to the general public, such as the Fitbit Flex for physical activity, the Netatmo for indoor climate, and the Moves smartphone app for location (Figure 1).

Figure 1: Data collection mechanisms for the HEALS sensors pilot.

The "pre-pilot" focused on the use of the Fitbit and Moves app for ascertaining a subject's microenvironment (*e.g.* indoors at home, walking or cycling). Four participants from each of WP9's seven partners carried the devices and a GPS and paper log for validation. Results show that both Moves and Fitbit data can be used as substitutes for more expensive research-grade instruments for measuring location and physical activity. Predicting if a person

is indoor or outdoors, however, remains a challenge. Additional analyses are ongoing to improve the predictive power of Moves for assessing people's microenvironmental location.

The larger sensor pilot was completed in Greece (Athens and Thessaloniki), the Netherlands (Utrecht), and the United Kingdom (Edinburgh) between 2015 and 2016. In each city, 25-50 families with children under the age of 3 years were recruited. The harmonized core protocol included measurements of air quality (*i.e.* particulate matter), dust, diet, activities, and socioeconomic status via questionnaire over a week (Figure 1). An online portal and database was developed to centralize sensor data collection across all cities.

A preliminary look at the results for indoor environmental quality show clear differences between each country in terms of climate variables and particulate matter, due to differences in climate and behaviours across countries. Nested validation studies with conventional equipment demonstrated that the Dylos low cost particulate matter monitor performed well. Additional measurements to validate other parameters and to supplement the sensor data were taken variously by each study center. Participants also provided valuable feedback about the study design and use of the various technologies which will help the development of future environmental exposure and epidemiology studies.

Effect of the mixture of dioxin and an organochlorine pesticide on hepatic carbohydrate metabolism in the HepaRG cell line

by Martine Aggerbeck, Emilie Distel, Etienne Blanc, Alix Leblanc, Eléonore Attignon, Robert Barouki, Dimosthenis Sarigiannis, Spyros Karakitsios, Nafsika Papaioannou, Eliandre de Oliveira and Ramon Diaz

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Co-exposure to persistent organic compounds such as dioxins and OC pesticides is an important part of the human exposome in Europe. The HEALS paradigm couples molecular epidemiology with systems toxicology via Physiologically-Based BioKinetic (PBBK) modeling to explore the adverse health outcome pathways induced by chronic exposure to POPs.

This is one of the first examples of this integrated multi-omics approach to link complex exposure to chemicals and health effects. In a previous transcriptomics study in the human liver-derived cell line HepaRG (Ambolet-Camoit *et al.*, 2015), UPD demonstrated that treatment for 30h with a combination of two persistent organic pollutants (POPs), 25nM TCDD (Seveso dioxin) and 10µM alpha-endosulfan (an organochlorine pesticide), drastically reduced the mRNA expression of genes involved in glucose metabolism, and, in particular, the bidirectional glucose transporter GLUT2 (SLC2A2) and the ultimate enzyme of gluconeogenesis, G6PC (glucose 6 phosphatase, catalytic subunit).

AUTH used available human exposure data and a PBBK model to estimate the doses of the two pollutants under various conditions including basal environmental exposure and accidental exposures and compared them with the concentrations used in the in vitro studies. These studies showed that the highest in vitro concentrations used are within the upper range of accidental exposure doses. We also tested lower concentrations of the POPs and found similar results.

The effect of the combination of TCDD and alpha-endosulfan was further studied at the mRNA and protein level and we analyzed in more detail the signaling pathways (AhR/ARNT complex and estrogen receptor respectively for TCDD and alpha-endosulfan) involved in the regulation of various glucose metabolism genes, using siRNA transfection. We showed that the production of glucose by the cells was greatly decreased (80%) after exposure to the pollutant mixture under gluconeogenic culture conditions, whereas under glycolytic culture conditions glucose oxidation was also decreased by the mixture (40%). UPD has begun proteomic studies of HepaRG cells treated with TCDD/alpha-endosulfan in collaboration with CERETOX, using LC/MS technology. In the first experiment, several targets deregulated in the transcriptome experiments were also deregulated at the protein level as well as several ribosomal proteins. We are currently repeating these experiments. Metabolomics studies have started recently in collaboration with AUTH for the same treatments (UPLC-MS/MS technology).

In parallel, NMR experiments also started this year within the NMR platform at UPD. A modification of metabolites in the cell medium was found using supervised analysis for TCDD as compared to the control, a finding suggesting, at the very least a perturbation of energy metabolism. These preliminary experiments will be continued for each pollutant alone and their combination. We believe that the integrated multi-omics studies coupled with internal dosimetry via the PBBK model will give a better idea of the effects of chronic exposure to POP mixtures on energy metabolism in the liver. Our analysis will serve as mechanistic underpinning of observations derived from epidemiological studies relating lifelong exposure to POPs to the metabolic syndrome.

Integrated External Exposure Assessment

by Christian Schieberle

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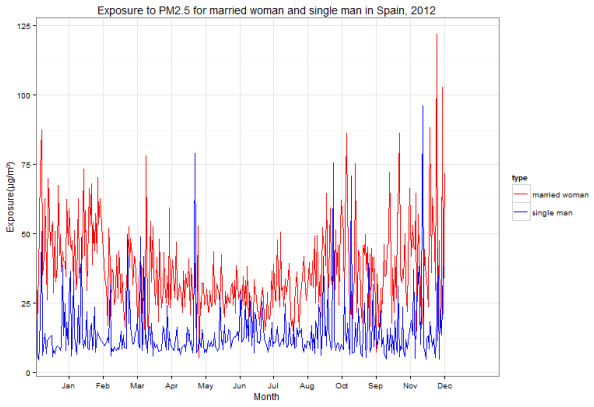
The untargeted approach in HEALS is supported by evaluation of exposure to a wide variety of stressors via different exposure routes and pathways. Properly estimation of external exposure rquires the integration of the tremendous amount of data provided by several sources, that however are not always fit for the purpose addressed. In HEALS, an innovative and integrative approach with the goal to retrospectively and prospectively assess the external exposures – and eventually the exposome – is followed.

For the first time in environmental epidemiology, we make optimal use of a lot of heterogeneous datasets (stored in the EBDMS

as part of the HEALS Geodatabase platform) and information fusion. Data from mobile low-cost sensors for continuous monitoring and the data collected from fixed location monitors are fused.



The dynamics of agent-based models that simulate individuals and their interactions with others and their environments (informed by sensor technologies) are incorporated. The above is integrated within a probabilistic framework to estimate external exposure. The available data and information are transformed into external exposure estimates. The exposure modelling is made specific to vulnerable groups and improved by using probabilistic approaches in conjunction with and support of the dynamic approach of ABM.

We estimate the retrospective and prospective trajectories of an individual's life-course within the probabilistic framework. The aim is to cover all critical life events from pre-conception, pregnancy, birth, infancy, childhood, teen-ageing and adolescence, followed by several stages of adulthood. The framework is rooted in findings of statistical discrepancy analysis of individual life courses from EU-wide surveys. Probabilities are assigned on future trajectories and emphasis is put on periods when the individual is most susceptible or vulnerable to adverse effects caused by exposure to stressors ("windows of exposure"). The approach is applied and tested in Stream 5 on regional studies to support the analysis of existing cohort studies. It will also provide an estimation for the EXHES pilot study.

SES effect on external exposome

by Lauren Smith and Clive Sabel

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In environmental health research there is increasing interest on how to disentangle the effects of socioeconomic parameters of environmental exposure on populations. It is often observed that lower socioeconomic (SES) groups of society have a disproportionate share of the burden of social and environmental stressors, partly due to issues of environmental injustice or inappropriate consumer choices and also lifestyle. Evidence exists of links between the health disorders relevant for HEALS and sociodemographic characteristics such as children under 7 years of age, females, and lower SES groups being more susceptible to asthma. As links have been established, we moved on to explore how time exposure modifiers such as activity patterns vary between people with different socio-demographic characteristics.

Limited European literature exists on sociodemographic exposure modifiers, particularly socioeconomic status patterns, and thus these are poorly understood. Our conceptual model (*Deliverable 10.2*) provides a methodology to estimate exposure at the individual level and uses this data to inform a population wide exposure assessment. An important aspect of this model is accounting for demographic attributes in addition to several SES measures, as demographic characteristics influence socioeconomic status. One SES measure alone is not sufficient to account for cultural and demographic difference within and between countries. Through the use of agent-based modelling (ABM) we are able to simulate multiple time activity patterns and thus exposure estimates for whole populations.

Figure 1 shows a small scale example of how ABM is being used in Edinburgh to model and account for SES difference and thus difference in the external exposome.

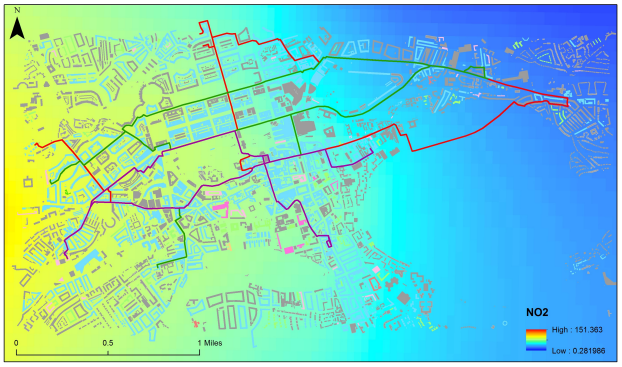

Figure 1: An example of modelling air pollution exposure for 3 different groups in Edinburgh.

Agent-based modelling for external exposure assessment

by Dimitris Chapizanis

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Thessaloniki, Greece

In order to fill the data gaps regarding real individual space-time movement data for whole populations, HEALS simulates movement, interaction and consumer behaviour using Agent Based Modelling (ABM), informed by multiple sensor technologies (HEALS campaigns) and environmental monitoring systems.

Two city scale models are being developed (Thessaloniki and Edinburgh) that can feed into a population-based exposure assessment, basing their estimations onto emerging properties of the behaviour of the agents that compose the modelled system (city). The agents are computerised autonomous decision makers, programmed to react and act in an artificial environment. Social structures and behaviours emerge from the agent interactions, operating under rules that place only bounded demands on each agent's information and computational capacity. Specifically, road and building shapefiles on building block resolution, together with population data are transformed into building, road and human agents respectively. Questionnaires and measured data derived from the HEALS sensors campaigns are analysed and extrapolated to a city scale representative population before being transformed into human agents' behavioural rules. Particular emphasis is given in the case of in-model incorporation of socioeconomic status (SES) data, derived by

local and EU scale survey outputs. Different human agents based on different age, gender or income follow different rules and express different behaviours, as the move in space and time. At the end of a model run, activity patterns can be determined for every individual, as an outcome of the prevalence of specific preferences and decision-making throughout the simulated time of experiment. Then, combining information on position with spatially resolved pollution levels we can assign pollutant concentrations to a person's individual space-time trajectories, leading us to the estimation of their personal exposure profile.

This approach can produce data that can be used to fill in the gaps that exist in traditional datasets. Moreover, it's a first step towards a method that can explicitly and quantitatively capture how SES affects exposure patterns.

Standardization and harmonization of data in view of unraveling the HEALS paradigm

by Cara Henson-Maesano, Shreosi Sanyal and Isabella Annesi-Maesano

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Standardized and harmonized data are needed to allow comparisons among data coming from different studies and to get overall results.

The purpose of data standardization is to make disparate sets of data consistent and clear, allowing for an overall analysis, for example a meta-analysis, of multiple studies on the basis of comparable data. Consistency is ensuring that the output is reliable so that related data can be identified using a common terminology and format. Clarity is to ensure that the data can be easily understood by those who are not involved with the data maintenance process.

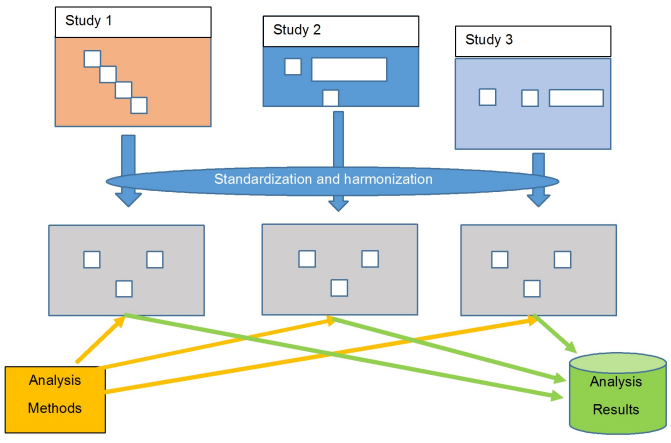
Data standardization is the critical process of bringing data from different studies into a common format (see figure) that allows for collaborative research, large-scale analysis, and sharing of sophisticated tools and methodologies. This approach is important because data can vary greatly from one study to the other as they are collected for different purposes. In addition, data may be stored in different formats using different database systems and information models. Lastly, despite the growing use of standard terminologies in healthcare, the same concept (*e.g.*, blood cholesterol) may be represented in a variety of ways from one setting to the next.

Data harmonization is the adjustment of differences and inconsistencies between different measurements, methods, procedures, schedules, specifications or systems to make them uniform or mutually compatible. Harmonization also aims to avoid duplication of effort or place an undue burden on informants. The main difference between the harmonization and standardization processes lies in the degrees of strictness of the standards. Standardization entails moving towards the eradication of any variation among variables and data, whereas harmonization involves a reduction in variations.

The HEALS project is deeply involved in the adoption of a stardardized and harmonized common data model in order to provide a unique dataset to build the exposome of various health outcomes.

In HEALS, we have converted a wide variety of datasets from pre-existing population-based studies of singletons and twins into a unique database. Data from each study were combined into a common format as well and variables were converted to a common representation (terminologies, vocabularies, coding schemes). This enables systematic analyses using a library of standard analytic routines that have been written based on the common format.

In HEALS, in order to harmonize the data sets from different cohort studies, a standardized format of the variables were created in an excel file. Altogether, 396 variables were included in the final file. The individual worksheets consists of "Identification and individual characteristics", "Health data by questionnaire and medications used", "Factors and exposures", "Exposure assessments", "Neurodevelopment and neuropsychological outcome", "Additional Data" and "Comments regarding the preparation of the data". For each of the variables, a description, a common variable name, the format of the variables (character/numeric categorical/numeric binary) with the maximum number of digits or letters; along with its domain, core and role are included in the file. This file was sent to the different partners who are responsible for the individual studies and twins registries, such that they can retrieve the information on the required variables from their studies using the standardized format. The partners were contacted via email, with the request for providing their data in the specific standardized format. In addition to the data harmonization file, a "Data Request and Transfer Agreement Form" was also prepared and attached to the email. For the purpose of data protection and confidentiality, the individual partners were requested to send their data sets encrypted by email to the members responsible for the mentioned work.



Singleton studies data come from countries as Croatia, France, Italy, Norway, Poland, Portugal, Slovenia, Spain and the United

Kingdom. Presently, the data obtained from the different singleton studies sources includes information from almost 25000 singleton individuals.

The same approach is being applied in the case of twins. General data from various twins registries across Europe, as well as datasets obtained within the context of specific studies, are being collected and harmonized for the purpose of aiding the health-exposome analyses conducted within HEALS and to provide insight into the role genetics and epigenetics plays in various health outcomes. The twins data is coming from registries of Denmark, Finland, Italy, Netherlands, Norway, Sweden, and the UK. Many of these registries have been collecting data over the course of decades, which makes combining and harmonizing a challenge. Although the detail for each set of twins varies, most include basic health data such as asthma status and some include highly detailed data from biospecimens such as selenium, zinc, arsenic, cadmium, mercury and lead levels within the blood. When completed, we expect to have data on at least 30,000 twins across Europe.

The combined dataset would be used for statistical analysis including EWAS (Environment-Wide Association Studies) relating to the investigation of the exposome impinging on the development and aggravation of chronic diseases. The focus of these analyses in HEALS is asthma and allergies, metabolic and neurodegenerative disorders caused by exposure to several internal and external environmental stressors. The data obtained from the birth-cohorts especially emphasizes on the risk factors associated with early life environmental exposures in case of mother (or both parents) and their offspring.

Altogether, the two datasets, one for singletons and one for twins, combined with internal and external environments data, will be invaluable in terms of exploring the effects of the exposome on health on a population level.

Understanding the link between environmental stressors and neurodevelopmental disorders

Key uncertainties, research needs and the exposomic perspective

by Gemma Calamandrei

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The brain has a protracted period of susceptibility to environmental inputs, which extends wellbeyond organogenesis up to the second decade of life [1]. Vulnerability to adverse environmental factors represents the drawback of this remarkable brain plasticity. The dynamic interplay between genes and environment, which forms the basis of typical neurobehavioral maturation is being also called upon to explain the etiology of complex neurodevelopmental disorders (NDDs) that are characterized by abnormal brain morphology and/or functional activity, even those with a strong genetic component. Diverse environmental stressors—chemical pollutants, drugs, nutritional factors, maternal infection, stress, deprivation—may interfere with typical brain developmental trajectories, eventually increasing the risk of either subclinical neuropsychological alterations or manifest clinical conditions such as learning disabilities, autism spectrum disorders (ASD) and attention deficit/hyperactivity disorder (ADHD).

There is vast literature on the developmental neurotoxicity of environmental chemicals. In spite of the impressive number of epidemiological data that support the inverse association between chemical exposure and child neurodevelopment [2,3,4], there are still important knowledge gaps in this field that hamper the proper evaluation of neurobehavioral effects by risk assessors. In this framework, Dose-effect estimation requires linking environmental exposure to the biologically effective dose of xenobiotics at the main target tissues, and then relating internal dose at target tissue with the physiological perturbation/health outcome observed [5]. This implies both identification of reliable biomarkers of exposure (i.e., peripheral indicators predictive of concentrations at target tissues) and knowledge of the mechanisms of neurotoxicity for the chemical compounds in study. Another critical gap relates to the mechanisms by which different classes of chemicals act on behavioral development. Mechanistic studies carried out in animals and in in vitro models point to multiple pathways and targets of toxicity for several established neurotoxicants. The same chemical compound may affect different developmental processes or different cell types, depending on the time window of exposure. To complicate the picture further, the same chemical may have multiple mechanisms of action: agents endowed with endocrine disrupting activity may affect neurobehavioral development by directly interacting with steroid receptors in brain cells and/or in periphery, and at the same time influence the density of synaptic connections in specific brain areas with mechanisms possibly independent from their hormone-like action [6]. Thus, more experimental research is needed to elucidate the causal links between chemical exposure and disease, addressing different levels of biological organization through the combined use of in silico, in vitro and in vivo models. This will support building adverse outcome pathways for neurodevelopmental effects.

Even if the precision of dose estimates can be improved, a second main issue is how to capture the individual dimension of the exposure history. Different factors may indeed contribute to variability in the measured outcome, including the temporal dimension of the exposure, the co-exposure to other contaminants or stressors, and the existence of genetic vulnerability. In addition, chemical exposure may be associated with other risk factors that should be precisely measured to prevent underestimation or overestimation of toxicant effects [7]. These factors are usually taken into account as confounders or effect modifiers in the result interpretation: among them, the most frequently considered are child sex and age, and

SES indicators, whose association with neurocognitive outcomes (the higher the SES, the better the outcome) has been widely demonstrated (for a review on the effect of SES on the neurocognitive performance see [8]). Together with their role as confounders or effect modifiers with respect to toxicant exposure evaluation, these factors can have a direct beneficial or harmful effect on neurodevelopment that should be studied per se [9].

A third critical question, which is of particular significance for risk assessment, is that of the robustness of the outcome measurements. As a matter of fact, most of prospective epidemiologic studies on neurotoxicity do not report clinically defined conditions (i.e. autism or learning disability) but rather atypical behavioral traits that range from increased/decreased anxiety and aggressiveness, to poorer motor or intellectual development in a significant proportion of exposed infants/children [10]. Whether these subclinical behavioral alterations may signal increased risk to develop a frank neuropsychiatric disorder at some point in the individual's life course remains to be determined. As Bellinger [11] pointed out, the characteristics of the effect outcome in brain/mental diseases has generally led to under-estimation of health risk as far as a disease-oriented approach rather than a population-oriented approach is preferred. Even a small shift in the mean IQ score in a population will result in a substantial increase in the percentage of individuals with extremely low scores, with a significant impact on economic and health costs [12].

All this considered the complex etiology of neurodevelopmental and neurodegenerative diseases requires innovative study paradigms and multifaceted and multidisciplinary approaches, taking into account biological plausibility as supported by experimental data, exposure and health effect modification due to intrinsic (such as genetic susceptibility) and extrinsic (such as socio-economic status) factors. In this line, the exposomic approach adopted by the HEALS project is aimed at characterizing and quantifying the exogenous and endogenous exposures and modifiable risk factors that predispose to and predict NDDs. A critical issue in such context is the identification and validation of peripheral biomarkers of effects that can inform on typical and atypical brain development, and help to establish biologically plausible links between chemical exposure and health effects.

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This contribution is a synopsis of the review paper entitled *Multifactorial origin of neurodevelopmental disorders: approaches to understanding complex etiologies*, by **A. De Felice**, **L. Ricceri**, **A. Venerosi**, **F. Chiarotti** and **G. Calamandrei**, published in 2015 at *Toxics* 3: 89–129.

WHO is WHO

Eliandre de Oliveira is the head of the Proteomics Platform at the Parc Científic de Barcelona (PCB). She has a degree in chemistry and holds a Ph.D. in Science with more than 15 years experience in peptide chemistry and proteomics. Her main research is focused on the application of the proteomics approaches to compare protein expression levels in searches for biomarkers. Eliandre's current work involves non target proteomics analysis of different kind of samples using quantitative proteomics approaches based on mass spectrometry (label-free, iTRAQ and others). In addition to HEALS she is currently coordinating the proteomics work package of the EU project ShockOmics, in which she studies the proteomics profile of the blood plasma of patients with septic and cardiogenic shock in order to search for biomarkers of sepsis and also to better understand the mechanism of shock. She has published various articles in the field and attended numerous conferences in this area. She is also involved in the Spanish Human Proteome Project (sHPP) and ProteoRed-ISCIII network. Within HEALS, Eliandre is working on the proteomics profiling of in vitro samples. This involves the setting up of the conditions to simulate chronical exposure of in vitro models to different kind of pollutants such as pesticides and heavy metals in order to find out the pathways that can be affected by the exposure. She is involved in WPs 5 and 7.

Thomas Maggos, M.Sc, PhD, is a research Scientist in the Environmental Research Laboratory (EREL) of the National Centre for Scientific Research "Demokritos". Following his basic studies in Chemistry at the University of Crete, he joined the University of Athens where he received M.Sc in Environmental Chemistry & Technology. He received his PhD in the Mechanical Engineering department of the University of West Macedonia. In 1998 he joined the Institute of Nuclear & Radiological Sciences & Technology Energy & Safety at the National Center for Scientific Research 'DEMOKRITOS' in Athens. He has been working on innovative technological systems for the performance of air quality characterization in urban, indoor and occupational environment and on photocatalytic processes and applications for air pollutants abatement. He is in charge of the accreditation of EREL by the Hellenic Accreditation System S.A (ESYD) under the terms of ELOT EN ISO 17025:2005 standard for specific gas pollutant measurements. He is member of CEN/TC264/WG15 and CEN/TC382/WG2 working groups while he participated in various European (*e.g.* ICARUS, HEALS, EnTEC, PERL, AIRUSE, ACEPT AIR) and National R& D projects. He has also participated as national expert in authoring the Committee of the Regions (CoR) opinion on the COM(2012)39 of the European Commission titled "A Reinforced Era Partnership for Excellent and Groth". In 2015 he joined ERNCIP (European Reference Network for Critical Infrastructure Protection) as national expert. He has 54 publications in international peer-reviewed journals and more than 100 in international conferences.

Sara Maio was born in Viareggio (Italy) in December 19, 1979. She is graduated in Environmental Science at Pisa Athenaeum (2004) and she received the Master of Epidemiology at Catholic University of Sacro Cuore, Rome (2006). Since 2006, she is a Researcher at the Pulmonary Environmental Epidemiology Unit of the Clinical Physiology Institute of the National Research Council (IFC-CNR), Pisa, Italy. In December 2008, she was the winner of a multicenter Italian Research Project (within the 2007 Young Researches Call), funded by the Ministry of Health. The project, named COMODHES (Global assessment of COPD burden: mortality and morbidity in different health systems), had the aim to assess, at national level, the real impact of COPD on general population samples. She organized and coordinated the whole project. Her daily work includes the assessment of indoor/outdoor air pollution effects on respiratory health (allergies, asthma and chronic obstructive pulmonary diseases) of general population samples (children, adults and elderly). In particular, she is involved in studies about the effect of outdoor air pollution due to vehicular traffic and of indoor school air pollution. Her main activities regard the implementation of standardized questionnaire to develop epidemiological survey on general population samples, statistical analyses of the collected epidemiological data and presentation of results within national and international congresses. She has (co-) authored more than 50 scientific publications on peer-review national/international journals and books. In the HEALS project, Sara Maio is involved in several Work Packages (WPs 8, 9, 10, 13, 14, 17), together with her colleagues of the IFC-CNR. In particular, she collaborates in the coordination of the WP14.

Robert Barouki is a biochemist and molecular biologist whose main research focus during the last twenty years has focused on the impact of environmental contaminants on human health and the mechanisms of action involved in those effects. In particular, he has studied the biological consequences associated to the activation of the dioxin receptor AhR and delineated the different mechanisms of toxicity. He has studied the different effects triggered by different ligands of the AhR using in particular "-omics" technologies, suggesting that part of the toxicity may be related to the disruption of endogenous functions. He has also studied the effects of combination of contaminants. In addition, as head of the clinical metabolic biochemistry department, he has initiated and organized a shared mass spectrometry facility at the Necker hospital. His focus is on developing multiplex targeted proteomic and metabolomic assays, notably in the field of metabolic diseases and in toxicodynamics. In a more general perspective, he has been involved in the networking of French and European research in the field of environment and health and he has a keen interest in communicating scientific conccepts and data to large audience.

Christian Schieberle is a researcher at the Institute of Energy Economics and the Rational Use of Energy at the University of Stuttgart, Germany. After obtaining his diploma from the faculty of Computer Science, Electrical Engineering and Information Technology he joined the department of Technology Assessment and Environment. His PhD studies focus on an optimal transport policy selection approach specifically taking into account uncertainty in travellers' response to policies and uncertainty in the resulting impact on the environment and on human health. His major research areas cover technology assessment, identification of emission mitigation strategies, and quantification and uncertainty of externalities. Within HEALS, Christian coordinates work towards a probabilistic framework for retrospectively estimating the external exposures of differently vulnerable population groups to multiple stressors via different exposure routes and pathways. The framework of exposures for the whole lifetime are estimated using a probabilistic model of life-course trajectories which allows specific assessment of the external exposure of population subgroups during critical life windows. In addition to HEALS he is currently participating in the EU-funded project REEEM. This project aims to gain a comprehensive understanding of the system-wide implications of energy strategies to support the transitions to a competitive low-carbon society. He also participates in the EU-funded project ICARUS which will develop integrated tools and strategies for urban impact assessment with the aim to improve the air quality and to reduce the EU carbon footprint.

Publications

The scientific contributions of the HEALS Project are hosted on ZENODO, an open digital repository that enables researchers, scientists, EU projects and institutions to share and showcase multidisciplinary research results (data and publications).

The collection of HEALS scientific papers on ZENODO can be found in the following website:

https://zenodo.org/collection/user-heals

Papers published since January 2016 include:

- Rovira J, Roig N, Nadal M *et al.* (2016) Human health risks of formaldehyde indoor levels: An issue of concern. Journal of Environmental Science and Health - Part A Toxic/Hazardous Substances and Environmental Engineering 51(4): 357–363.
- Karri V, Schuhmacher M, Kumar V (2016) Heavy metals (Pb, Cd, MeHg, As) as risk factors for cognitive dysfunction: A general review of metal mixture mechanism in Brain. Environmental Toxicology and Pharmacology.
- Prevendar Crnić A, Zgorelec Ž, Šuran J *et al.* (2016) Mercury in Eisenia fetida and soil in the vicinity of a natural gas treatment plant in northern Croatia. Journal of Environmental Science and Health, Part A: Toxic/Hazardous Substances and Environmental Engineering 51(2): 114–120.
- Schröder W, Nickel S, Schönrock S *et al.* (2016) Spatially valid data of atmospheric deposition of heavy metals and nitrogen derived by moss surveys for pollution risk assessments of ecosystems. Environmental science and pollution research international 23(11): 10457–10476.
- Polanska K, Krol A, Sobala W *et al.* (2016) Selenium status during pregnancy and child psychomotor development—Polish Mother and child cohort study. Ped. Research 79: 863–869.
- Medda E, Minoprio A, Nisticò L *et al.* (2016) The response to oxidative stress and metallomics analysis in a twin study: The role of the environment. Free Radic Biol Med. 97: 236–43.
- Bose-O'Reilly S, Schierl R, Nowak D *et al.* (2016) A preliminary study on health effects in villagers exposed to mercury in a small-scale artisanal gold mining area in Indonesia. Environ Res 149: 274–281.
- Doering S, Bose-O'Reilly S and Berger U (2016) Essential Indicators Identifying Chronic Inorganic Mercury Intoxication: Pooled Analysis across Multiple Cross-Sectional Studies. PLoS One 11(8): e0160323.
- Schoierer J and Böse-O'Reilly S (2016) [Adaptation to climate change and pediatrics] Anpassung an den Klimawandel in der Pädiatrie. Umweltmedizin Hygiene Arbeitsmedizin 21(3): 137.
- Schoierer J, Lob-Corzilius T, Wermuth I *et al.* (2016) [Does the Prevention Act Improve Prevention in Pediatric Outpatient Settings!?] Mehr Prävention durch das Präventionsgesetz in der kinder- und jugendärztlichen Praxis!?" Gesundheitswesen.
- Steckling N, Bose-O'Reilly S, Gotti A *et al.* (2016) [Use of biomarkers of exposure in large population studies to assess the association between environment and health] Verwendung von Biomarkern der Exposition in großen Populationsstudien zur Assoziation zwischen Umwelt und Gesundheit." Umweltmedizin Hygiene Arbeitsmedizin 21(3): 118.
- Sarigiannis DA and Salifoglou A (2016) Research directives toward deciphering adverse outcome pathways induced by environmental metallotoxins. Current Opinion in Chemical Engineering 13: 161–169.
- Ha E, Basu N, Bose-O'Reilly S *et al.* (2016) Current progress on understanding the impact of mercury on human health. Environ Res. (*In press*).
- Birks L, Casas M, Garcia AM *et al.* (2016) Occupational Exposure to Endocrine-Disrupting Chemicals and Birth Weight and Length of Gestation: A European Meta-Analysis. Environmental Health Perspectives (*In press*).
- Tratnik JS, Falnoga I, Trdin A *et al.* (2016) Prenatal mercury exposure, neurodevelopment and apolipoprotein E genetic polymorphism. Environmental Research (*In press*).
- Sharma RP, Schuhmacher M, Kumar V (2016) Review on crosstalk and common mechanisms of endocrine disruptors: scaffolding to improve PBPK/PD model of EDCs mixture. Environment International (*In press*).

Presentations at International Meetings

Dissemination and networking activities since January 2016 included the participation of several HEALS members at international workshops, conferences and scientific events hereinafter summarised:

- **J.O. Grimalt (CSIC)** *Effects of marine pollution on human health* (Lecture). Cosmocaixa. Barcelona, Catalonia, Spain. 27th January 2016.
- **J.O. Grimalt (CSIC)** *Effects of climate change on human health* (Lecture). Central headquarters of CSIC in Catalonia. Barcelona, Catalonia, Spain. 1st February 2016.
- **J.O. Grimalt (CSIC)** *Effects of climate change on human health* (Lecture). Palace of Arts and Science. Valencia, Spain. 9th February 2016.
- **D.A. Sarigiannis (AUTH)** *Mixtures Assessment: the exposome paradigm* (Lecture). EEA Workshop on Activities on

Mixtures under the European Human Biomonitoring. Copenhagen, Denmark. 11th February 2016.

- **J.O. Grimalt (CSIC)** *Effects of climate change on human health* (Lecture). Juan March Foundation. Madrid, Spain. 29th February 2016.
- **D.A. Sarigiannis (AUTH)** *Personal exposure assessment using portable sensors and Agent Based Modelling* (Lecture). Air Quality 2016. Milan, Italy. 14–18 March 2016.
- **D.A. Sarigiannis (AUTH)** *Reactive oxygen species found in urban PM2.5 and PM10: chemical analysis and sources apportionment* (Lecture). Air Quality 2016. Milan, Italy. 14–18 March 2016.
- **D.A. Sarigiannis *et al.* (AUTH)** *Cosmic radiation exposome* (Lecture). ENMF 2016: Exploring Novel Medical Frontiers. Thessaloniki, Greece. 9–10th April 2016.
- **D.A. Sarigiannis (AUTH)** *Multi-omics for exposome analysis* (Lecture). 4th Workshop on Holistic Analytical Methods for Systems Biology Studies. Thessaloniki, Greece. 17–19th April 2016.
- **K. Polanska *et al.* (NIOM)** *Impact of phthalate exposure on pregnancy outcomes, children's health and neurodevelopment* (Invited Lecture). Reproductive Health Summit. London, United Kingdom. 19–21 April 2016.
- **J.O. Grimalt (CSIC)** *Effects of atmospheric pollution on human health* (Lecture). Veterans of the Spanish Army and Guardia Civil Police. Asador del Mar. Barcelona, Catalonia, Spain. 27th April 2016.
- **J. Cherrie (IOM)** *The Exposome: Understanding Causes of Diseases* (Lecture). Heriot Watt University. 27th April 2016.
- **J.O. Grimalt (CSIC)** *Effects of climate change on human health* (Lecture). El Casino. Manresa, Catalonia, Spain. 29th April 2016.
- **L. Barandovski Lambe *et al.* (OIKON)** *Study of Nitrogen pollution in Macedonia by moss biomonitoring technique and Kjeldahl method* 29th Task Force Meeting of the ICP Vegetation: Programme and abstracts / Harmens, Harry ; Frontasyeva, Marina (ur.). Bangor, UK : ICP Vegetation Programme Coordination Centre, 2016. 38-38
- **Z. Špirić *et al.* (OIKON)** Study of lead pollution in Croatia by using moss biomonitoring and ICP-AES // 29th Task Force Meeting of the ICP Vegetation: Programme and abstracts / Harmens, Harry ; Frontasyeva, Marina (ur.). Bangor, UK : ICP Vegetation Programme Coordination Centre, 2016. 74-74
- **A. Stajnko *et al.* (JSI)** "Evaluation of urine and blood Cd levels, and their associations to renal function biomarkers, at low level of exposure" (Lecture). 2nd International Conference on Human Biomonitoring. Berlin, Germany. 17–19th April 2016.
- **D.A. Sarigiannis (AUTH)** *The exposome in Europe* (Invited Lecture). Emory Exposome Summer Course. Emmory University. Atlanta, USA. 13–17th June 2016.
- **J.O. Grimalt (CSIC)** *Human exposure to polycyclic aromatic hydrocarbons and other pollutants in schools. Are indoor atmospheres really indoor?* (Lecture). Research Center for Toxic Compounds in the Environment. Masaryk University. Brno, Czech Republic. 16th June 2016.
- **A. Stamatelopoulou *et al.* (DEMOKRITTOS, AUTH, IOM)** "Assessing the utility of low-cost sensors in exposure studies". 8th Annual AAMG Conference on monitoring and analysis using sensor technologies. Londo, United Kingdom. 21st June 2016.
- **D. Sarigiannis *et al.* (AUTH)** *Health and monetary impact of biomass burning for space heating* (Lecture). SIDISA 2016. X International Symposium on Sanitary and Environmental Engineering. Rome, Italy. 20–22nd June 2016.
- **D. Sarigiannis *et al.* (AUTH)** *Combined exposure to indoor air pollutants in Europe* (Lecture). SIDISA 2016. X International Symposium on Sanitary and Environmental Engineering. Rome, Italy. 20–22nd June 2016.

Other dissemination activities

- **OIKON** Press Release in a Croatian Newspaper. *Retrieved from:* http://www.novilist.hr

novilist.hr

Živa šteti mozgu beba, riječki liječnici ispituju može li se to spriječiti

KAKO ZAŠTITITI TRUDNICE

12. listopad 2015 14:32

Najnovije: Ljerka Bratanija Martinović

Projekt Heals ispituje utjecaj gena i prehrane u štetnom djelovanju Žive na bebin mozak. Nakon što je potvrđen štetan utjecaj, u nastavku istraživanja riječki će tim utvrditi koliko utjecaja na to ima genetika, te koliku zaštitu trudnicama može pružiti pravilna prehrana

ZAGREB Poznato je da živa i drugi teški metali imaju štetan utjecaj na razvoj fetusa i na neurološki razvoj djeteta. Koliku ulogu u tome igra genetsko nasljeđe, te može li se štetan utjecaj žive umanjiti povećanom konzumacijom omega 3 i omega 6 masnih kiselina, tema je istraživanja koje u okviru projekta EU FP7 – HEALS provodi liječnički tim KBC-a Rijeka. Riječ je o nastavku projekta EU FP6 – PHIME, u okviru kojeg su se ispitivale posljedice konzumacije žive kod trudnica na središnji živčani sustav fetusa, odnosno novorođenih beba. Projekt HEALS najveći je znanstvenoistraživački projekt u Europi koji proučava utjecaj okoliša te životnih, radnih i prehrambenih navika na ljudsko zdravlje. U projektu ukupne vrijednosti 18 milijuna eura sudjeluje trideset uglednih institucija iz Europe i SAD-a, a cilj im je definirati ekološki inducirane bolesti i shvatiti mehanizme kojima ekološki stresori i hrana uzrokuju bolest.

- **CSIC** Visit to Flix area for description of the results of HEALS to TV3 (Public Catalan TV network). Program "Què Qui Com" – "What Who How".
- **URV–TNO** On 12th February 2016, Dr. Rob H. Stierum (TNO, The Netherlands) visited the Chemical Enginering Department at Universitat Rovira i Virgili (URV, Tarragona, Spain). Multidisciplinary seminar entitled *Application of systems toxicology towards improved model development for human hazard and risk assessment*.
- **CSIC**. Meeting with environmental researchers from the Autonomous University of Barcelona on May 12th, 2016 in Barcelona (Catalonia, Spain) for discussion on the available health exposure and environmental results of the Flix area.
- **CSIC**. Master Thesis presentation. On June 29th 2016, presentation of the master thesis entitled **Analysis of organochlorine compounds in food items from Minorca and Mallorca Islands**, by Anna Arce. University Pompeu Fabra (Barcelona). Supervisor: Prof. Joan O. Grimalt (IDAEA–CSIC)

- **OIKON** Within the university study for Sanitary Engineering at the Medical faculty University of Rijeka, on 22nd March 2016 in the framework of the elective course *Environmental and health safety and security*, and on the occasion of *International World Water Day 2016*, a lecture on very demanding and complex challenges, opportunities and goals in relation to the water resources as well as importance of the Environmental & Health Education was held by Prof. Zdravko Spiric.

  Guest speaker on the event was Dr. Zeljko Linsak with his presentation with research results from several projects dedicated to the environmental and health safety, with emphasis on education and research (with a special example of the EU FP 7 HEALS project). The discussion that followed thereafter, especially on sustainable development goals and role of youngsters was additionally supported and enhanced by the students through their interesting lectures and presentations.

Forthcoming Events

HEALS meetings

- **3rd HEALS Annual Meeting**
  6-7 October 2016, Leiden (The Netherlands)
  http://www.heals-eu.eu/index.php/heals-annual-2016/

Other releated meetings

- **8th International Congress on Environmental Modelling and Software (iEMSs 2016): *Supporting a sustainable future***
  10–14 July 2016, Toulouse (France)
  http://www.iemss.org/sites/iemss2016/
- **36th International Symposium on Halogenated Persistent Organic Pollutants (DIOXIN 2016)**
  28 August – 2 September 2016, Firenze (Italy)
  http://dioxin2016firenze.org/
- **28th Annual Conference of the International Society of Environmental Epidemiology (ISEE 2016)**
  1–4 September 2016, Rome (Italy)
  http://eurotox2016.com
- **52nd European Congress of the European Societies of Toxicology (EUROTOX 2016)**
  4–7 September 2016, Seville (Spain)
  http://eurotox2016.com
- **8th International Network on Children Health, Environment and Safety Conference (INCHES 2016)**
  14–16 September 2016, Barcelona (Catalonia, Spain)
  http://inchesnetwork.net/upcoming-conferences/
- **International Society of Exposure Science (ISES 2016)**
  9–13 October 2016, Utrech (The Netherlands)
  https://ises2016.org/
- **27th Annual Meeting of the Society of Environmental Toxicology and Chemistry (SETAC Europe)**
  7–11 May 2017, Brussels (Belgium)
  http://brussels.setac.org/

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