

HEALS Newsletter

Health and Environment-wide Associations based on Large population Surveys

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Editorial Note

Welcome to the second issue of the HEALS Newsletter!

This issue reports progress in developing the HEALS project after the first year of implementation. It also includes two articles. One by Virgilia Toccaceli and Ludwine Casteleyn that addresses ethical concerns in research using confidential health information. The other by Nour Baiz and Isabella Annesi-Maesano describes the critical life stages for exposome assessment and health outcomes need to be studied in priority.

The Newsletter also describes three of the most important meetings organized within HEALS during 2014: the *HEALS Concept and Methodology Workshop* held in Thessaloniki, Greece, in March (article written by Dimosthenis Sarigiannis); the *Workshop on Internal Exposome Markers in HEALS* held in Ljubljana, Slovenia,

in May (article written by Milena Horvat); and the *First Annual Meeting of the HEALS Project* in Edinburgh, UK, conducted in September (article written by John Cherrie).

The *Who is Who* section shows the professional profiles of John Cherrie and Marta Schuhmacher, two Stream Leaders, and Joana Madureira and Juha Parkka, two leading young researchers involved in several WPs.

The issue also lists the scientific publications, presentations at meetings, workshops and conferences, and other dissemination activities (e.g. press releases) performed by HEALS researchers after March 2014. Interesting forthcoming events for HEALS participants and exposome researchers are also announced.

Our best wishes for a happy and productive 2015!



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HAPPY NEW YEAR

The complexity of HEALS from an ethical and legal perspective

by VIRILIA TOCCACELI and LUDWINE CASTELEYN

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HEALS aims at being a forefront project, whose underlying hypothesis of complex and dynamic interactions between DNA sequence, epigenetic DNA modifications, gene expression and environmental factors that all combine to influence disease phenotypes, implies investigations of sensitive data that raise ethical concerns and require adequate protection of privacy. HEALS will not only produce knowledge for advancements in public health, but will also generate procedures, data and information significant at individual level that need to be carefully dealt with from the start. The implications and consequences which might derive from the "actions" taken within HEALS have to be assessed and addressed as early as possible.

First of all, the right for information of the study subjects requires clear communication procedures at several stages of the study, from recruitment till dissemination of results. Informed consent procedures need to guarantee accurate and relevant information to participants. Moreover, the biomarker results will need to be clarified with respect to their significance (or lack of significance) at individual level and the eventual implications for health. Another central issue relates to the potential psychological and/or social vulnerability of subgroups of participants that may necessitate adapted procedures.

Finally, data sharing issues are of major concern in a project like HEALS and, above all, a harmonized treatment of sensitive data is required despite differences in legal context across Europe. Furthermore, taking into account advancements in the field of IT and data networking, it will be essential to define also the extent to which privacy and confidentiality can be really guaranteed.

A focus on the ethics of communication for the Exposome

Biomonitoring programmes conducted in many countries are increasingly using new methods and technology that allow the detection of ever lower levels of concentration of substances, chemicals and pollutants for which both animal and cell studies show troubling biological effects. However, harmful concentration levels, sources of exposure, potential health effects are often not yet fully understood and exposure reduction strategies not available. This "lack" of knowledge brings a series of ethical concerns regarding, most of all, the reporting of results to individuals. What is more, when human biomarkers are used within a research framework, these concerns become even more serious being the experimental aspect of the monitoring enhanced.

Fundamental questions arise: "when" is it right to report? "How" is it efficient and effective to report? There is a strong need to relate to a widely agreed framework addressing policies for communication both to the participants as a group (or subgroups) and to each individual.

There are cornerstone documents like the Belmont Report, the Helsinki Declaration, and more specifically at the EU level, the Oviedo Convention and the Privacy Directives '95 and 2002 which provide guidelines and ethical principles to be applied. Respect for persons (and their human dignity and autonomy), beneficence and no maleficence, social justice, the right "not to know" and the right "to be forgotten", etc. are some of the main principles to consider. Nevertheless, what researchers continuously discover is that principles cannot be unproblematically applied, they cannot be prescriptive but only critically weighed with several rights and duties at stake. For example, while the respect for individual autonomy could favor a clear-cut reporting of individual results, the no maleficence principle obliges to consider that reporting might in some cases result in harmful experiences such as undue anxiety, stigmatization, or legal constraints. Moreover, the costs of customizing results reports might be high in terms of efforts and finances considered by some a waste of "limited resources" that could be used for other goals.

Other relevant questions relate to: *What should be the extent of the information given? What kind of results/findings should be disclosed? When should such information be communicated? How should the right to know be applied regarding children?* Large-scale, high-throughput 'omics studies like those in HEALS complicate this particular context by raising these questions at a larger scale.

Different reference models for disclosure of results can be outlined and some of them are already widely recognized by experts. They relate to the responsibility of the research group and to the adoption of decisions on the basis of the clinical significance of the results (i.e. results are communicated to individuals whenever they indicate, for experts, an adverse health outcome or they trigger an intervention. If the health effect is not known it is considered not cautious to communicate), or they involve a dynamic model with the participation of different stakeholders in all decision making processes. All these models contain positive aspects as well as specific weak points.

The study methods, the potential social impact of the results, the biological material collected, the significance of the "omics", the huge amount of phenotypic data and the sharing of these make of HEALS an original ethical challenge, addressing a series of ethical, social and legal issues that can be tackled only if the work begins "near to the bench", with an early commitment of the research group. What, nowadays, seems to be urgent for the development of both science and research, for a new culture of respect for human dignity, and for motivating individuals to participate in research is an "Ethics of responsibility" which leaves out paternalistic attitudes by researchers and, at the same time, takes into account the needs at both individual and collective levels. A research project like HEALS should adopt an approach that eases the dialogue between researchers and participants. ☺

Critical life events and stages: when to measure the exposome?

by NOUR BAÏZ and ISABELLA ANNESI-MAESANO

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The exposome can be defined as the measure of all the exposures of an individual in her/his lifetime, from conception throughout the lifespan (Wild, 2005).

The individual exposome has to be intended as dynamic and continually changing. Indeed, all exposures and their determinants and modifiers can vary over the course of a day, not to mention over the weeks, months, and years that make up a lifetime, as our bodies, diets, risk factors and lifestyles change. Because sources and levels of exposure change over time, and because capturing all these changes verges on the impossible in the impracticality of "high-resolution real-time" monitoring of all the exposures for the entire lifetime, the exposome has to be constructed by assessing the exposures at the critical life periods of life through representative snapshots that act as demonstrative measures of these critical periods. In particular, for the comprehension of the mechanisms underlying the development of the diseases, the assessments of the internal chemical environment in biological specimens at critical life stages is mandatory. The major challenge consists then in identifying critical life stages that are informative at most as well as the snapshots reflecting the exposures and the downstream consequences at the individual level.

So, the main question that needs to be answered is "in which period of life is it important to monitor the exposome?". This question implies one further consideration: "When are data collections of exposure and health outcomes respectively, and when in the case of biomarkers of exposure, effect and disease and omics..., is human biomonitoring (HBM) most informative?". Literature shows that the answer depends on the type of health event and related endotypes, phenotypes and sub-phenotypes, the target organ, the type of agent (diet, pollutant, toxicants...), its action, and the individual's characteristics. Theoretical knowledge on individual development was retrieved for the entire lifespan from the literature and findings from population-based data were investigated.

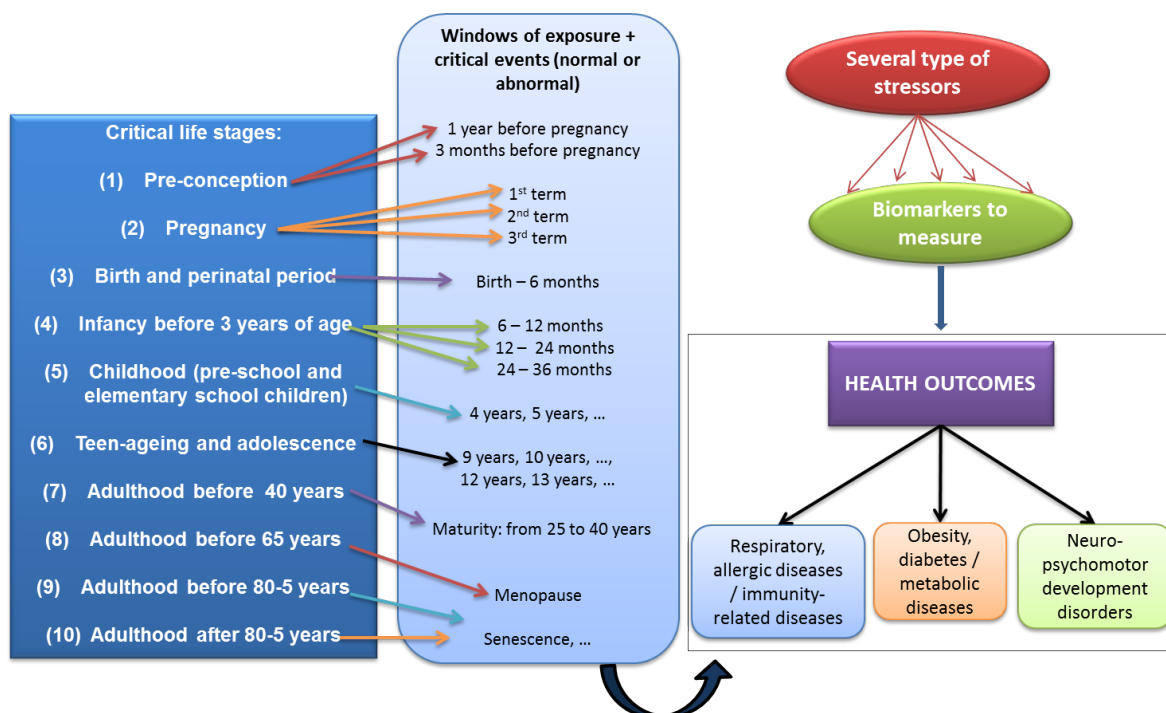
As a result, in spite of the heterogeneity of existing findings that precludes comparisons and the lack of convincing evidence from population data, the following facts emerged:

- i Onset of age-dependent diseases such as asthma and allergic diseases, diabetes, Parkinson disease and of subclinical phenotypes as allergic sensitization, overweight and neurodevelopmental troubles is strongly dependent on multifactorial interactions with other features such as: Presence of specific susceptibility genes/alleles; Vulnerability increasing the exposure; Methylation status; Environmental insults; and among adults, pre-existing health status and comorbidities.
- ii Preconception is a crucial period for making change to the lifestyle and diet that can both help increase the chances of getting pregnant and birthing a healthy baby.

- iii Early-life influences, beginning with the intrauterine environment and continuing through the first few years of life, shape the trajectory of the various organs throughout the life course and are responsible for health outcomes. Prenatal and early-life environmental insults ranging from malnutrition to toxic exposures can tilt the odds toward development of adverse health effects decades later. These effects likely occur, at least in part, through alterations in an individual's genetic potential to thrive in the environment in which he or she will live. These early challenges set the bar for what's "normal", and the foetus and infant adapt for a less-than-optimal environment in ways that may contribute to adult-onset disease. Vulnerability to chemical toxicity after birth may be highest during the first 6 months and continue for years before maturation.
- iv Both puberty and menopause and the pre-existing periods constitute essential steps in asthma, weight and behaviour changes and downstream health conditions, through significant changes in endocrine system and hormonal status.
- v Old age relates to a multidimensional process of physical, psychological and social change and seems to be an especially vulnerable period. From existing data (The GERIE study, ERJ 2015, *in press*) two old ages deserve to be considered, before and after 80 years.

As a main result, based on existing knowledge and findings, ten critical life stages were identified as of interest for the exposome of the major health outcomes considered in HEALS, namely asthma and allergies, overweight and diabetes and neurodevelopmental troubles (see figure).

1. Pre-conception
2. Pregnancy
3. Birth and the period from the perinatal (28 days after birth) period up to 6 months
4. Infancy between 6 months and 3 years of age
5. Childhood (school children)
6. Teen-ageing and adolescence
7. Adulthood before 40 years
8. Adulthood before 65 years (in the 50s)
9. Adulthood before 80-5 years (according to the gender, 85 years in women)
10. Adulthood after 80-5 years



HEALS targets both existing datasets of individuals and twins having participated in epidemiological, toxicological and HBM surveys which allow covering the entire life time as well as forthcoming dataset in the frame of the European Exposure and Health Examination Survey (EXHES), where children (both singleton and twins) are recruited since *in utero* life, with their siblings, parents and other relatives, thus constituting a transgenerational study including almost the entire lifespan. Therefore, critical life stages and the specific feature identified as of interest for HEALS are:

- **Preconception** that has to be target in terms of lifestyle, diet and other exposures.
- The **three trimesters of pregnancy** have to be monitored for organs' development as a function of environmental exposures according to the event of interest.
- **Before and after 3 years** of age constitute also important periods for individual normal and pathological growth and development.
- **Puberty** with hormones changes is crucial for asthma, weight and behaviour variations.
- **Middle age** (after the age of 30) lifestyle parameters (nutrition, exercise, smoking...), environmental exposures (air pollution, water content, other toxicants...), health status (lung function, hypertension, metabolic disorders, cognitive problems...) and use of drugs are determinant for the onset and the progress of several diseases. Lifestyle changes are related to professional advancement for most individuals, altering significantly their daily time-activity patterns leaning towards relatively higher caloric intake, more sedentary life spent indoors and thus exposure to xenobiotics. Gene-environment interactions worsen asthma and allergies, overall in women due to changes in hormonal factors. Stress and obesity can also be at the origin of asthma in adulthood.

• There is sufficient evidence that **menopause** in women (between the age of **45** years and **55** years) is a period of significant changes in the hormonal status, impacting a cascade of health outcomes: asthma, increasing susceptibility metabolic disorders, as well as to neuro-inflammation. At the age of **50** years, significant changes in gene expression related to brain related function seem to be determinant for the onset of neurodegenerative disorders.

- **After 65** years both males and females are more susceptible to environmental insults, due to reduced detoxification capacity, as well as reduced capacity of maintaining homeostasis.
- At **80** and **85** years, normal ageing is accompanied by pathological ageing.

In HEALS, data on the relationships between exposome and the targeted health outcomes will be drawn from questionnaires, HBM, omics (genomics, epigenomics, metabolomics, proteomics...) and clinical tests in singletons, twins and parents. The investigation of the interrelationships among the three considered health outcomes and their exposome as well as the underlying mechanisms will pave the way to better understand the development of these chronic diseases.

Some definitions

Critical life stages. Critical life stages are defined as the periods of time in an individual's lifespan in which critical life events occur characterized by changes of the organism status, because some quality, property or phenomenon suffers a definitive modification. Examples of critical life events include, for instance, foetus development according to the stage of growth, immune system maturation, organs development, puberty, menopause... These changes can be normal or abnormal as result of either reshaping of the ordinary pattern (for instance: anticipation of puberty) or modification of the event (for instance: event amplification, increase in severity...) (see figure), the latter because of external or internal influences. Vice

versa, changes in exposures may be present as a consequence of developmental changes or altered patterns of behaviour.

Windows of exposures. Windows of exposures are the periods of time in an organism's lifespan in which the organism is the most susceptible or vulnerable (see the definitions below) to the adverse effects caused by exposure to stressors including toxicants at the origin of abnormal and pathophysiological changes. It is important to underline here that a same critical life event can be observed at different life stages.

Susceptibility. Refers to the degree to which individuals or groups may respond to a given exposure to a hazard. Susceptibility can be subdivided into innate and acquired susceptibility. Innate susceptibility is to a large extent due to genetic predisposition or to incomplete development of normal (adult) physiological functions. For example, a young child may be susceptible to a given pollutant because detoxification processes are not yet fully developed. Such susceptibility is transient and disappears with age and growth. Acquired susceptibility may be due to disease or age.

Vulnerability. Refers to the variations in exposure between individuals or groups —and thus to the potential for health effects. This is likely to be due to variations in the hazards themselves as well as to the fact that exposure is also a function of where people live, how (and where) they spend their time, and their more general lifestyle. In the case of pesticides, living close to areas where crops are sprayed or eating foodstuffs that have been heavily treated during production, storage or processing likewise acts to increase exposure, and thus vulnerability.

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HEALS Concept and Methodology Workshop

Thessaloniki, Greece (17–20 March 2014)

by DIMOSTHENIS SARIGIANNIS and ALBERTO GOTTI

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The *HEALS Concepts and Methodology Workshop* took place at the Aristotle University of Thessaloniki from Monday 17th to Wednesday 19th March 2014. The workshop was a successful opportunity to create a common understanding of the exposome concepts and to share and discuss the HEALS approach to unravel the exposome.

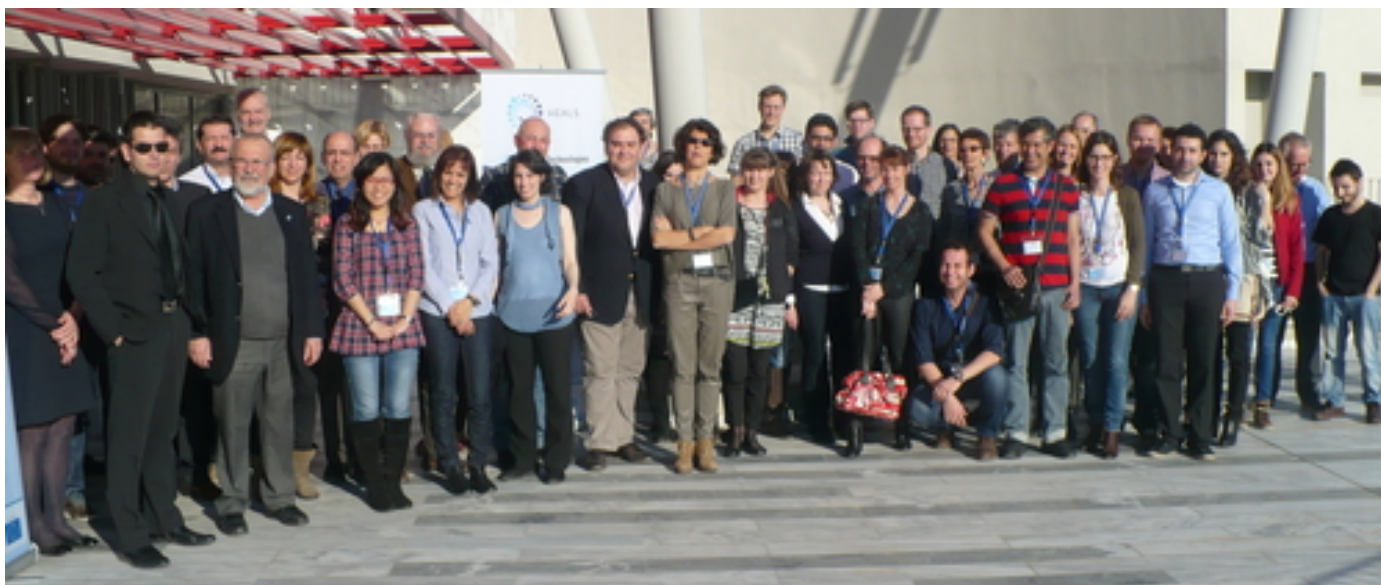
The workshop was led by Prof. Denis Sarigiannis. Around 70 delegates from the 29 HEALS Partners took part and delivered a number of presentations on the different facets of the exposome concept. The event consisted of one day Technical meeting (17 March) on the project workpackages, which was followed by an one and a half day scientific workshop (HEALS concepts and methodology – 18 and the morning of 19 March). In addition to presentations from the project team, from the afternoon of March 19 until lunch time of March 20, Agilent Technologies co-hosted a dedicated event on the Agilent exposomics workflows with external high-level expert discussion on the use of advanced analytical and -omics technologies for exposome research both in the EU and the USA and demonstration of Agilent technology and data analysis tools. Both the HEALS workshop and the Agilent seminar were held at the Research Dissemination Center of Aristotle University of Thessaloniki (KE.D.E.A).

Prof. S. Kouidou-Andreou Vice-Rector of the Aristotle University of Thessaloniki opened the meeting and Profs Denis Sarigiannis and Isabella Annesi-Maesano highlighted that the aims of the workshop were to discuss, understand and expand the conceptual framework of HEALS and to bring all disciplines together in a coherent and harmonized framework.

During the first day of the workshop every work-package leader reported on work progress, current status, next steps and timeplan. The scientific workshop started on the second day and it was organized in three sessions: external exposome, internal exposome and data management and modeling for EWAS.

In the first session Prof. J. Bartzis presented the concept of the external exposome in the context of HEALS and proposed first suggestions on how to proceed. Although the exposome represents the totality of exposure over an individual's lifetime the HEALS approach will need to take into account 'critical' exposure periods and the varying spatial and temporal accuracy and availability of the input data sources.





In this light for each pollutant and each population subgroup, a combination of methods ('pathways to exposure') has to be chosen in order to transform the available information/data into external exposures. This approach will be applied and tested in Stream 5 on regional studies supporting the analysis of existing cohort studies and it will provide an EU-wide estimation for the EXHES pilot study.

Prof. J. Cherrie presented how personal sensors can support external exposome studies at the individual level. He provided examples of personal sensors that can be used for babies and for adults to track position and physical activities. Due to the large amount of information which can be collected as well as the ethical hurdles involved in collecting real individual space-time movement data for whole populations he pointed out how post-processing and integration with models are critical in retrieving the required information at the individual level. On this subject Prof. C. Sable presented the role of agent-based modelling (ABM) in constructing the exposome. These models can simulate individuals (agents) and their interactions with other agents and their environments informed by sensor technologies. In this light the use of ABM will enable us to better understand the behavior of individuals and populations in social and evolutionary settings, and to 'fill-in' the gaps in the exposome currently not available from real-world monitoring and sensor data. In order to derive estimates of external exposures of individuals and of vulnerable population subgroups all the data collected and modelled have to be merged through data fusion techniques. To this aim Prof. R. Friedrich proposed a conceptual framework to be applied for estimating the individual external exposures to multiple stressors via different exposure routes. Big data analysis techniques combining different data and methods including those developed in the previous WPs. This framework will be applied and will support the HEALS population studies. The morning session ended with a general discussion about the methodological approach to follow to unravel the external exposome. It was pointed out that untargeted-agnostic individual exposome derivation approaches have to be the main thrust of the project with regard to both the external and internal exposome.

The afternoon session was focused on the internal exposome. Prof. M. Horvat gave a presentation on the role of human biomonitoring in the context of HEALS and its links with -omics technologies. She pointed out the key role of human biomonitoring in the

HEALS methodology stressing the importance of a harmonized approach built on the outcomes of the DEMOCOPHES study. Within HEALS biological samples are available in bio-banks from previous population studies (WP14, WP15 and WP16) and they will be further analyzed. A further important issue is the identification of the laboratories for different analysis. On this point it was suggested to centralize the analyses in few laboratories so as to improve comparability and reduced inter-laboratory error. Dr. R. Stierum gave an overview of the several -omics technologies and infrastructure components available in HEALS and of the interdisciplinary omics data integration possibilities to bridge human clinical information and mechanistic toxicological information towards the exposome concept. A discussion followed on the minimum omics/biomarker requirements and feasibility in order for them to be applied on the already existing cohort samples and the samples collected through the pilot exposure and health examination (EXHES) survey foreseen in HEALS.

Prof. Sarigiannis illustrated the role of Internal dose modeling using physiology-based biokinetic (PBBK) models in the HEALS methodology to bridge the external and internal exposome. In HEALS PBBK models play a central role as they are a powerful tool to assess the time history of internal exposure, focusing on susceptible developmental stages. Furthermore, PBBK models link external exposure to target tissue dosimetry relevant to in vitro testing responses and support integrative bioinformatics and systems toxicology modelling to allow for reverse dosimetry assessment. In this way PBBK models will serve for linking exposure biomarkers to external exposures and biomonitoring data to internal concentration of xenobiotics and their metabolites in target tissues and the associated health effects.

The next session took started with a presentation on the HEALS GeoDatabase provided by Dr. Nousiainen. This will be a publicly available platform, which will systematically support the collection of and access to all datasets collected/developed for HEALS. Through the platform the users can manage and explore spatial data, process and visualize them.

The subsequent discussion focused on the functionalities the platform has to incorporate, the available IT solutions as well as the compatibility with existing platform such as the IPCheM platform of the European Commission.

The platform will be linked to the Environmental Data Man-

agement System (EDMS) of HEALS, which was presented by Dr. Karagiannis. He illustrated the main functionalities of the EDMS pointing out that it will accommodate geo-referenced environmental data retrieved data from existing Databases. The EDMS will be a module of the HEALS Geodatabase platform. The session continued with the presentation given by Prof. Papaloukas on bioinformatics strategies for biomarker prediction. He provided an overview of the current techniques for descriptive data mining, predictive data mining and model integration, which represent the methodological tools for integrating multiple biomarkers into a mechanistic description aiming at understanding the biological functions of toxicity pathway interactions in relation to external/internal exposure and confirming the causative effect between exposure and disease endpoints. The

session ended with an overview of the bio-statistical methods for Environment-Wide Association Studies given by Dr. Banerjee who illustrated the different statistical methods applied in environmental health sciences pointing out the advantage and limitations of each of them.

There was a general agreement that the workshop was a successful step toward the development of a common agreed methodology to unravel the exposome. The final discussion reflected this collective understanding as witnessed by the very active participation of all delegates. A number of issues were discussed and clarified reinforcing the energy needed to face the great challenges we will need to address in the next years.®

Workshop on Internal Exposome Markers in HEALS

Ljubljana, Slovenia (26–28 May 2014)

by MILENA HORVAT

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The workshop *Internal Exposome Markers in HEALS* was organised by Stream 2 (WP4 and WP5 leaders, JSI and TNO respectively) and took place in Ljubljana, Slovenia from May 26 to 28, 2014.

The meeting consisted of a two days workshop (Internal Exposome Markers in HEALS – 26 and 27 May) and one day



Technical meeting (28 May) for WPs 4 and 5. The meeting was organized in the Conference Center MONS and was attended by 39 participants.

The morning session of the first day provided the general understanding of what is needed in terms of biomarker and -omics research to support the construction of the exposome (D. Sarigiannis and I. Annesi-Maesano). The selection of exposure, susceptibility and effect biomarkers have been addressed for metals, metalloids and other elements (I. Falnoga), organic contaminants and their metabolites (J. Grimalt and L. Leondiadis) and other stressors related to health impacts: obesity, neurodevelopment and asthma (G. Calamandrei, G. Viegi and I. Annesi-Maesano).

The session on "omics" and biomarkers dealt with technology, concepts, possibilities, challenges and final suggestion & decision for inclusion in HEALS. This session covered presentations on Metabolomics at FERA and AUTH (M. Dickinson); Adductomics, exposure and susceptibility to endogenous and exogenous alkylating agents (A. Povey); SNP profiling: SNP genotyping, different platforms for different questions (W. van Workum); DNA methylation and epigenetics (S. Koudou); miRNA profiling technologies (G.

Viegi); Transcriptomics providing the mechanistic basis for causality in EWAS (D. Sarigiannis); and DNA repair functional assays within the HEALS project (E. Dogliotti). This session provided good background for further discussion on pre-selected biomarkers and -omics methodologies, taking into account the state of the art knowledge and recent practices.

The session on "phenotyping/endotyping in the HEALS paradigm" was chaired by I. Annesi-Maesano and included topics related to phenotyping/endotyping in asthma and allergies (I. Annesi-Maesano), diabetes and overweight (E. Ramos), neurodevelopmental troubles (G. Calamandrei) and the methodology for phenotyping/endotyping (S. Banerjee). The session provided background for further discussion on phenotyping/endotyping in relation with -omics and biomonitoring in view of EWAS, taking into account the state of the art knowledge and recent practices.

The following session was concentrated on existing cohorts of significance for the HEALS project (G. Calamandrei, G. Viegi and I. Annesi-Maesano). The following cohorts have been presented: REPRO_PL cohort from Poland (K. Polanska), PHIME Mediterranean (J. Snoj Tratnik), Slovenian DEMOCOPHES cohort (D. Mazej), Spanish INMA cohort (J. Grimalt), and the Italian twin study (L. Nistico).





This session provided scientific rationale of the existing HEALS cohorts, including practicalities of implemented protocols in existing exposome like studies performed so far, including truly available samples/study designs for HEALS from WPs 14, 15 and 16.

Round table discussion addressed urgent questions related to the use of existing data and samples and several questions were addressed related to comparability of data between cohorts, availability of samples, usefulness of existing exposure, effects, and susceptibility biomarkers. Moreover, gaps were identified and plans for future research were made between the partners. Most importantly, the suitability of -omics analysis/technologies on existing and new

samples were discussed in detail.

The workshop represented an important step forward in the implementation of the EWAS and EXHES protocols in HEALS. Active participation of HEALS participants resolved numerous issues related to the use of existing HBM samples available in cohorts as part of EWAS. Harmonization of approaches for the analysis of exposure and -omics markers has also reached and concrete planning of actions were set up.

Apart from reach discussion, participants were taken to the tour visit of old Ljubljana with a dinner entertainment at Ljubljana Castle.®

First Annual meeting of the HEALS Project

Edinburgh, UK (15-17 September 2014)

by JOHN CHERRIE

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The first HEALS annual meeting, hosted by the IOM, took place in Edinburgh between the 15th and the 17th September 2014. The meeting was organized as a three days workshop on recent advances in understanding links between environmental pressures and health outcomes. In addition to presentations for the project team and the HEALS advisors, the agenda included a public lecture given by Dr. David Balshaw, from the National Institute for Environmental Health Sciences (NIEHS).



Over fifty delegates from 28 partners attended the meeting, which was held at the COSLA Conference Centre in the Haymarket area of the city. In addition, a number of people participated via the telephone/web connection. The whole meeting took place against the backdrop of the referendum on Scottish independence, which ultimately (the day after the workshop ended) resulted in a vote in favour of Scotland remaining part of the United Kingdom. The campaign and discussions provided a memorable aspect to the meeting.

The first day kicked off with introductory lectures by Prof. Isabella Annesi-Maesano and Prof. Denis Sarigiannis. Specifically for this workshop we aimed to discuss:

- How to build the exposome into studies of asthma/allergies, overweight/diabetes and neurodevelopmental troubles.
- How best to utilize both existing and prospectively collected data
- To respond to specific questions in order to investigate *ad hoc* environment stressors and health phenotypes/endotypes.
- To build the EXHES study in the most efficient way.



Dr. Nour Baiz from UPMC presented the outcome of one of the key literature reviews being undertaken within HEALS, which was to consider "Critical life events in defining when and how frequently biological samples should be collected to define the exposome". She described the work and outlined ten critical life stages that are recommended for characterizing the exposome: from pre-conception to old age.

The meeting then went on to discuss studies of exposure to particulate matter and biological agents in relation to asthma, and gene-environment interactions for asthma and allergies. Dr. Gemma Calamandrei spoke on studies of neurodevelopmental and neurodegenerative disorders in relation to exposure to metals and pesticides, which highlighted some of the challenges involved in undertaking exposome assessments within existing cohorts. This session was followed by a more general discussion about common causal mechanisms for the diseases of interest in the HEALS project.

During the 1st day we also reflected upon the conclusions of the HEALS workshop on internal exposome markers, which had been held in Ljubljana. The output from this meeting provided a very helpful introduction to the biomarker discussions on the second day.

During the evening, HEALS delegates along with local scientists and policy makers listened to David Balshaw's public lecture, organised by the IOMs Centre for Human Exposure Science (CHES). David gave a very interesting and informative talk about "The Exposome Concept and its Implementation". He concluded with key questions, including what are the bounds of the exposome, how should we try to implement exposome projects and what should be the key "deliverables" from such projects. The questions prompted a lively discussion with the audience, which continued into the evening reception.

Day 2 began with a series of presentations and discussions about the internal exposome, including "Guidelines for Exposure Biomarkers in HEALS", including descriptions of the 51 Fact Sheets on specific stressors and associated biomarkers being prepared by WP 4. We then discussed the practicalities around using "omics" technologies in the HEALS study.

The meeting continued with joint presentations from Andy Povey and Michael Dickinson on sample optimization for metabolomics/adductomics in agnostic analyses. As part of the work it was agreed that the two labs doing this work should undertake inter-laboratory comparisons. Then Dr. van Workum spoke on genomic profiling – the HEALS SNP array. A number of suggestions were made to help improve this aspect of the work and the team agreed to consider these.

The morning concluded with a discussion on biomarker data integration and systems biology, led by Prof. Sarigannis.

After lunch we switched to talk about the external exposome with presentations by John Bartzis, Miranda Loh and Michael Jerrett. It was clear that although the sensor technologies available to measure the environment have developed rapidly they are probably still fairly immature and unsuitable for wide-scale deployment in the EXHES study as personal monitors. What emerged from the discussions were proposals to combine together low-cost sensors to track subject location and activity, with fixed location monitors sensor data and modeling approaches to synthesize estimates of exposure. Prof. Friedrich spoke about the planned work on exposure data assimilation to integrate the various data being generated, and Sami Nousiainen described the plans for the HEALS Geodatabase platform, which will incorporate public data and data generated in the EXHES.

We also discussed the availability of European data on air pollution (both outdoor and indoor) and data on water contamination. These data will provide an important resource for exposure estimation in both the existing cohorts studied in WPs 14, 15 and 16, and in the EXHES. The potential effect of socio-economic status on the external exposome was described by Dr. Smith.

The delegates continued their discussions over dinner at the Hilton Hotel, close to the meeting venue.

The final day, which included the project General Assembly, a discussion of ethical issues and practical arrangements for the EXHES, plus dissemination and training activities within HEALS. The HEALS data exchange policy was discussed and it was agreed that delegates would comment on the text.

Dr. Balshaw, who is a member of the HEALS Project Advisory Board, summarized the Board's opinions of the progress of the study. He recognized the good work that has been undertaken to date, but encouraged the HEALS team to identify the best practical way forward for the use of sensor technologies and the sample/data acquisition procedures for the EXHES.

He also recognized that the team should focus efforts on linking data across temporal and spatial domains. He highlighted issues around agreeing semantics, ontology and metadata terminology as being important for HEALS, to help ensure clear and efficient communication across this very large project. Dr. Balshaw finished by encouraging the HEALS team to organise a workshop on modeling and data integration within the exposome paradigm.

The final discussion offered an opportunity for delegates to ask further questions and to discuss the future plans for the project. There was general agreement that the meeting had been a successful milestone in the HEALS journey and the delegates left reinvigorated to address the upcoming challenges.©



WHO is WHO



Professor **John Cherrie** is currently Research Director at the Institute of Occupational Medicine (IOM) in Edinburgh, and Honorary Professor at the University of Aberdeen, UK. He originally trained as a physicist and then completed his PhD at the University of Aberdeen, working on retrospective occupational exposure assessment for epidemiological studies. He has a wide range of research interests including exposure assessment for environmental and occupational epidemiology, chemical risk assessment, dermal exposure assessment, inadvertent ingestion of chemicals and several other topics. He has been involved in a number of health impact assessment studies, including an evaluation of the socioeconomic, health and environmental impacts of changes to the EU Carcinogens Directive on behalf of the European Commission. He is leading Stream 1 and WP9 in HEALS, with a particular focus on developing methods to characterize the external exposome. The IOM is a not for profit research and consulting organization based in Scotland with three offices in England and one in Singapore. It employs over 140 staff, mostly scientists and technicians. Typically IOM is involved with 30 to 40 research projects at any one time, covering risks from chemicals, environment and health, nanotechnology, human sciences and other topics. John is a member of the Editorial Board of the *Annals of Occupational Hygiene and Particle and Fibre Toxicology*. He is also an Assistant Editor on the journal *BMC Public Health*. He is a Past President of the British Occupational Hygiene Society (BOHS), and in 2013 he won the Bedford Medal for outstanding contributions to occupational hygiene. At the start of 2015, John will take up a new part-time post as Professor of Human Exposure Science and Health at Heriot Watt University in Edinburgh. In this post he aims to develop new research involving the exposome and sensor technologies. He will continue to work on the HEALS project as part of the IOM team.



Marta Schuhmacher is Professor of Environmental Engineering at the University Rovira i Virgili (URV) (Catalonia, Spain). She is the head of the Laboratory of Environmental Engineering research group (AGA) (<http://www.etseq.urv.es/aga>) and the Technical Director of TecnATox (www.tecnatox.cat) both in URV. In HEALS context, Marta Schuhmacher is leader of the stream on dissemination, training and knowledge transfer, and drafting guidelines stream (Stream 6). Her principal research interests are, among others, environment monitoring and risk assessment, human biomonitoring, environmental modelling and simulation, PBPK modelling, environmental indicators, data mining, multicriteria analysis, and environmental decision making. As a result of the work in these areas, Dr. Schuhmacher has published more than 180 papers in top scientific journals (h index of 30). She has contributed with more than 220 studies to international scientific meetings, 21 of which were invited keynote lectures. She has been the member of three congress organizing committees and plenary lecturer in 6 international conferences. She has supervised 40 master theses and 19 Doctoral theses (plus 3 ongoing). She is member of the Editorial board of *Environmental Toxicology and Chemistry* (ET&C) and *Integrated Environmental Assessment and Management* (IEAM). She is member of the network on "Contaminated sites and Health" coordinated by WHO Regional Office for Europe, the Society of Environmental Toxicology and Chemistry (SETAC) and The Society for Risk Analysis (SRA). She has participated in other European Funded projects: The Use of Life Cycle Assessment Tools for the development of integrated Waste Management Strategies for Cities and Regions with Rapid Growing Economies (LCA-IWM), Integrated Multiscale Process Units with Locally Structured Elements (IMPULSE), A Neuro-Fuzzy Model for the Ecological Risk Assessment in Wetlands and Risk-based management of chemical and products in a circular economy at a global scale (RISKCYCLE).



Juha Parkka received the Master of Science (Tech) and Doctor of Science (Tech) degrees in information technology (digital signal processing) from Tampere University of Technology, Tampere, Finland, in 1997 and 2011, respectively. Since 1997, he is working as a Senior Scientist at VTT Technical Research Centre of Finland, in Tampere. His daily work includes ICT for Health research and development as well as project management. His research interests include biomedical signal processing, data analysis, classification, software development and quality assurance. In 2010, he received the VTT Certificate of Recognition for active and high-level scientific publishing. He has (co-) authored more than 50 scientific publications. In HEALS, his main interest is to find new ways to study how different exposures (the exposome) affect health. His work focuses on data analysis and management as well as on data collection using wearable and other sensors (WPs 9, 12 and 13).



Joana Madureira holds a PhD on Occupational Safety and Health from the Faculty of Engineering of the University of Porto (FEUP). She integrated the Institute of Mechanical Engineering – FEUP since 2007 attached to the R&D Unit UEAEAC (Unit of Advanced Studies on the Urban Environment). Since that date she has been participating in research projects related to air pollution in different indoor micro-environments and co-related basic risk management strategies. She is author and co-author of some publications in international journals, conference proceedings, posters and scientific reports in environment and environmental health. In the HEALS project, Joana Madureira is involved in several Work Packages (WPs 1, 2, 3, 8, 12, 13, 17, 18 and 19), together with professor Eduardo de Oliveira Fernandes.

Press Releases

- OIKON (Croatia). Promotion of the HEALS project at various web sites and occasions/meetings/panels (in Croatian). Further information in:

- <http://www.simet.unizg.hr/dokumenti/Vijesti/novi-eu-projekt-fp7-heals?searchterm=heals>
- <http://www.hrpsor.hr/hrpsor/>



- NIOM (Poland). Presentation of HEALS at the 60 Anniversary of NIOM. The audience was composed of health professionals, stakeholders and scientists.



Publications

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) that are not part of the existing institutional or subject-based repositories of the research communities.

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

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

Papers published from March 2014:

- Fort M, Grimalt JO, Casas M *et al.* (2014) Food sources of arsenic in pregnant Mediterranean women with high urine concentrations of this metalloid. *Environmental Science and Pollution Research* 21: 11689-11698.
- Linšak DT, Linšak Ž, Špirić Z *et al.* (2014) Influence of cadmium on metallothionein expression and products of lipid peroxidation in the organs of hares (*Lepus europaeus* Pallas). *Journal of Applied Toxicology* 34(3): 289-295.
- Vizcaino E, Grimalt JO, Glomstad B *et al.* (2014) Gestational weight gain and exposure of newborns to persistent organic pollutants. *Environmental Health Perspectives* 122(8): 873-879.
- Grgurić S, Križan J, Gašparac G *et al.* (2014) Relationship between MODIS AOD (Aerosol Optical Depth) and PM10 over Croatia. *Central European Journal of Geosciences* 6(1): 2-16.
- Špirić Z, Vučković I, Stafilov T *et al.* (2014) Biomonitoring of air pollution with mercury in Croatia by using moss species and CV-AAS. *Environmental Monitoring and Assessment* 186(7): 4357-4366.
- Fort M, Grimalt JO, Casas M *et al.* (2014) Interdependence between urinary cobalt concentrations and hemoglobin levels in pregnant women. *Environmental Research* 136: 148-154.
- Grimalt JO, Torrent M and Sunyer J (2014) The influence of organochlorine compound exposure on the physiological development of children. *Medicina Balear* 29(3): 25-36.

Presentations at International Meetings and Workshops

Dissemination and networking activities since March 2014 included the participation of several HEALS members at international workshops, conferences and scientific events hereinafter summarised:

- **Joan O. Grimalt (CSIC).** *Inverse age-dependent accumulation of decabromodiphenyl ether and other PBDEs in serum from a general adult population* (platform presentation) and *The HEALS approach to health and environment-wide associations* (poster). SETAC Europe 24th Annual Meeting. Basel, Switzerland. 11-15 May 2014.
- **Mercè Gari (CSIC).** *Impacts of atmospheric chlor-alkali factory emissions in surrounding populations* (lecture). CREAL Seminars. Barcelona, Catalonia, Spain. 20 May 2014.
- **Kinga Polanska (NIOM).** *Environmental and occupational exposures and population health* (lecture) and *The HEALS approach to health and environment-wide associations* (poster). 60 Anniversary of NIOM. Poland. 3-6 June 2014.
- **Dimosthenis Sarigiannis (AUTH).** *The HEALS approach to health and environment-wide associations* (oral presentation). Workshop "Modeling from external exposure dose down to internal doses – bridging the gap" organized by ICCA-LRI & JRC 2014. Lugano, Switzerland. 17-18 June 2014.
- **Dimosthenis Sarigiannis (AUTH).** *Health and Environment-wide Associations via Large population Surveys to unravel the Exposome* (lecture). NIEHS Exposure Science and the Exposome Webinar. 14 July 2014.
- **Joan O. Grimalt (CSIC).** *Determinants of the accumulation of polybromodiphenyl ethers in general adult population from Catalonia and other European Countries* (oral presentation). 26th Annual Conference of the International Society for Environmental Epidemiology (ISEE). Seattle, Washington, USA. 24-28 August 2014.
- **Jutta Lindert and Dimosthenis Sarigiannis (AUTH).** *Air Pollution Impacts on Pregnancy Occurrence and Outcome* (oral presentation). 26th Annual Conference of the International Society for Environmental Epidemiology (ISEE). Seattle, Washington, USA. 24-28 August 2014.
- **Dimosthenis Sarigiannis (AUTH).** *Exposome Ethics: An Important Dimension in Individual, Lifelong Exposure Characterization* (oral presentation). Symposium on International Collaboration on the Exposome at the ISEE Annual Conference. Seattle, Washington, USA. 24-28 August 2014.
- **Joan O. Grimalt (CSIC).** *Impacts and potential effects of DDT reintroduction against malaria in African populations* (Opening Plenary Lecture) and *Health and environment-wide associations based on large population surveys* (oral presentation). 34th International Symposium on Halogenated Persistent Organic Pollutants (Dioxin 2014). Madrid, Spain. 31 August – 5 September 2014.
- **Marta Fort (CSIC).** *Association between metal body burden in pregnant women and atmospheric traffic pollution and Assessment of exposure to trace metals in a cohort of pregnant women from an urban center by urine analysis in the first and third trimesters of pregnancy* (oral presentations). 17th International Conference on Heavy Metals in Environment (ICHMET 2014). Guiyang, China. 22-25 September 2014.
- **Janja S. Tratnik (JSI).** *Toxic and potentially toxic microelements in EXPOSOME* (oral presentation). 17th International Conference on Heavy Metals in Environment (ICHMET 2014). Guiyang, China. 22-25 September 2014.
- **Janja S. Tratnik (JSI) and Alessandro Alimonti (ISS).** *Toxic metal exposure and effects – the EXPOSOME approach* (session chairs). 17th International Conference on Heavy Metals in Environment (ICHMET 2014). Guiyang, China. 22-25 September 2014.
- **Dimosthenis Sarigiannis (AUTH).** *Radiological exposome: lifelong ionising and non-ionizing radiation exposure and human health* (lecture). ENMF International Workshop "Expanding Nuclear Medicine Frontiers". Thessaloniki, Greece. 27 September 2014.
- **Marta Fort (CSIC).** *Interdependence between urinary cobalt concentrations and hemoglobin levels in pregnant women* (poster). 1st Young Researchers Conference on Environmental Epidemiology (ISEE). Barcelona, Catalonia, Spain. 20-21 October 2014.
- **Mercè Gari (CSIC)** *Impacts of atmospheric chlor-alkali factory emissions in surrounding populations* (oral presentation) and *Inverse age-dependent accumulation of decabromodiphenyl ether and other PBDEs in serum from a general adult population* (poster). 1st Young Researchers Conference on Environmental Epidemiology (ISEE). Barcelona, Catalonia, Spain. 20-21 October 2014.

Forthcoming Events

- **ICEPPHI 2015: XIII International Conference on Environmental Pollution, Public Health and Impacts**
26–27 January 2015, Istanbul (Turkey)
<https://www.waset.org/conference/2015/01/istanbul/ICEPPHI>
- **Children's Environmental Health Network (CEHN) 2015 Research Conference. Children: Food and Environment**
4–6 February 2015, Austin, Texas (USA)
http://www.cehn.org/2015_research_conference
- **ICAPC 2015: XIII International Conference on Air Pollution and Control**
23–24 February 2015, Paris (France)
<http://www.waset.org/conference/2015/02/paris/ICAPC>
- **SETAC Europe 25th Annual Meeting. Environmental Protection in a Multi-Stressed World: Challenges for Science, Industry and Regulators.**
3–7 May 2015, Barcelona (Catalonia, Spain)
<http://barcelona.setac.eu/>
- **ICCBES 2015: International Congress on Chemical, Biological and Environmental Sciences**
7–9 May 2015, Kyoto (Japan)
<http://www.iccbes.org>
- **Healthy Buildings Europe 2015. Stepping beyond traditional boundaries, (re)creating healthy buildings.**
18–20 May 2015, Eindhoven (The Netherlands)
<http://www.hb2015-europe.org>
- **ICACI 2015: XIII International Conference on Allergy and Clinical Immunology**
25–26 May 2015, London (UK)
<https://www.waset.org/conference/2015/05/london/ICACI>
- **EAACI 2015 Annual Congress: European Academy of Allergy and Clinical Immunology.**
6–10 June 2015, Barcelona (Catalonia, Spain)
<http://www.eaaci2015.com>
- **DIOXIN 2015**
23–28 August 2015, Sao Paulo (Brazil)
<http://www.dioxin20xx.org>
- **ISEE 2015. 27th Conference on the International Society for Environmental Epidemiology. Addressing Environmental Health Inequalities.**
30 August – 3 September 2015, Sao Paulo (Brazil)
<http://www.isee2015.org>
- **Eurotox 2015. 51st Congress of the European Societies of Toxicology. Bridging Sciences for Safety.**
13–16 September 2015, Porto (Portugal)
<http://www.eurotox2015.com>
- **European Academy of Paediatrics. Congress and Master-Course 2015.**
17–20 September 2015, Oslo (Norway)
<http://www.eapcongress.com>
- **25th Annual ISES Conference. International Society of Exposure Science. Exposures in an Evolving Environment.**
18–22 October 2015, Las Vegas, Nevada (USA)
http://www.isesweb.org/Meetings/mtgs_cur.htm
- **ICCE 2015. 15 EuCheMS International Conference on Chemistry and the Environment.**
20–25 September 2015, Leipzig (Germany)
<http://www.icce2015.org/>
- **ERS International Congress 2015. European Respiratory Society**
26–30 September 2015, Amsterdam (Netherlands)
<http://www.erscongress.org/>

Editorial Board

Prof. Joan O. Grimalt Dr. Mercè Garí



Editorial Information

If you wish to contribute to the *Newsletter* or share information for publication, please contact Mercè Garí:

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