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HEALS

Health and Environment-wide Associations
based on Large population Surveys

FP7-ENV-2013- 603946

<http://www.heals-eu.eu/>

Deliverable 2.1 – Preliminary networking plan and workshop on recent advances in the environmental pressure and health outcomes associations

WP 2

Version number 1 (06/02/2015)

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Foreword

The workshop “**Recent advances in understanding links between environmental pressures and health outcomes**” (organised by WP 2) took place in Edinburgh, UK from 15 – 17 September, 2014. The meeting comprised three days of plenary presentations and discussions.

The meeting was organized in the COSLA Conference Centre by the local organizer IOM and the HEALS Management Board.




The workshop provided an opportunity to discuss the scientific progress with the project and to future directions of work. There were important presentations on the EXHES study methodology, ethical issues for the project and various deliverables produced from the project so far.

The IOM also organised a public lecture on “The Exposome Concept and its Implementation”, which was delivered by Dr David Balshaw from NIEHS.

On the final day of the meeting the project General Assembly was held.

This report comprises five chapters:

- Agenda
- Minutes from the sessions
- List of participants
- Feedback from the participants
- Summary of conclusions from the meeting

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1 Agenda

HEALS Workshop - Recent advances in understanding links between environmental pressures and health outcomes

Edinburgh, UK
September 15-17, 2014

Monday September 15, 2014

11:00 – 11:15 Welcome address and Opening of the meeting (John Cherrie)

11:15 – 11:45 Introduction – Aim of the meeting (D. Sarigiannis and I. Annesi-Maesano)

11:45 – 12:30 The conceptual framework of HEALS and Work Progress (D. Sarigiannis and I. Annesi-Maesano)

12:30 – 13:30 Lunch

Chairs: Isabella Annesi-Maesano, Denis Sarigiannis

13:30 – 14:00 “Critical life events” in defining when and how frequently biological samples should be collected to define the exposome (N. Baiz)

14:00 – 14:30 Conclusions from Ljubljana (J. Tratnik)

14:30 – 15:00 Studies relating exposure to particulate matter and biological agents to asthma (G. Viegi)


15:00 – 15:30 Coffee/tea Break

15:30 – 16:00 Gene-environment interactions in asthma and allergies (M. Kabesch)

16:00 – 16:30 Studies relating neurodevelopmental and neurodegenerative disorders to exposure to metals and pesticides (G. Calamandrei)

16:30 – 17:30 Discussion on common mechanisms

19:30 – 21:00 Public lecture: The exposome (David Balshaw) – to be followed by reception

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Tuesday September 16, 2014

9:00 – 9:15 Introduction to the internal and external exposome sessions (Denis Sarigiannis and I. Annesi-Maesano)

Workshop part 1: Internal exposome (Chair: D. Sarigiannis, E. Dogliotti)

9:15 – 9:45 Guidelines for exposure biomarkers in HEALS (D4.2) (N. Steckling)

9:45 – 10:00 Omics technologies in analytical exposure biology (R. Stierum)

10:00 – 10:30 Sample optimization for metabolomics/adductomics for agnostic analysis (Andy Povey /M. Dickinson)

10:30 – 10:45 Genomic profiling – the HEALS SNP array (W. van Workum)

10:45 – 11:15 Coffee/tea break

11:15 – 12:00 Exposure biology workflow integration in HEALS (D. Sarigiannis, R. Stierum)

12:00 – 12:45 Biomarker data integration and systems biology (D. Sarigiannis and all – guided discussion)

12:45 – 13:45 Lunch

Workshop part 2: External exposome (Chair: M. Jerrett, J. Bartzis)

13:45 – 14:00 External exposome – current status (J. Bartzis)

14:00 – 14:30 Remote sensing for exposure assessment – the US experience (M. Jerrett)

14:30 – 15:00 The use of sensor technologies in defining the exposome (M. Loh)

15:00 – 15:30 European data on air pollution (outdoor/indoor) (T. Maggos, E. Oliveira Fernandes)

15:30 -16:00 Coffee/tea break


16:00 – 16:15 European data on water contamination (J. Grimalt, E. Tolis)

16:15 – 16:30 Exposure data assimilation (R. Friedrich)

16:30 – 16:45 The effect of socio-economics on the external exposome (L. Smith)

16:45 – 17:00 Building the HEALS Geodatabase platform (S. Nousiainen)

17:00 – 18:00 Summary and discussion on the external exposome (D. Sarigiannis and I.

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Annesi-Maesano)

20:00

Social dinner

Wednesday September 17, 2014

Chairs: R. Stierum, J. Cherrie

9:00 – 9:45 Ethical issues and the exposome (L. Casteleyn)

9:45 – 10:30 The EXHES study and discussion (I. Annesi-Maesano)

10:30 – 11:00 Coffee break

11:00 – 11:30 Dissemination and training activities in HEALS (M. Schuhmacher, S. Boese O'Reilly)

11:30 – 13:00 General Assembly (I. Annesi-Maesano, D. Sarigiannis)


13:00 – 14:00 Lunch

14:00 – 14:45 Input from the Project Advisory Board (C. Weber, D. Balshaw)

14:45 – 15:30 Final discussion and conclusions (I. Annesi-Maesano, D. Sarigiannis)

15:30 – 16:00 Coffee break

16:00 – 17:30 Management Board meeting

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2 Minutes for each session

2.1 Day 1

Welcome address and Opening of the meeting - John Cherrie

Welcomed delegates to Edinburgh and to the meeting. Administrative arrangements for the meeting were described.

Introduction and aims of the meeting - Denis Sarigiannis and Isabella Annesi-Maesano

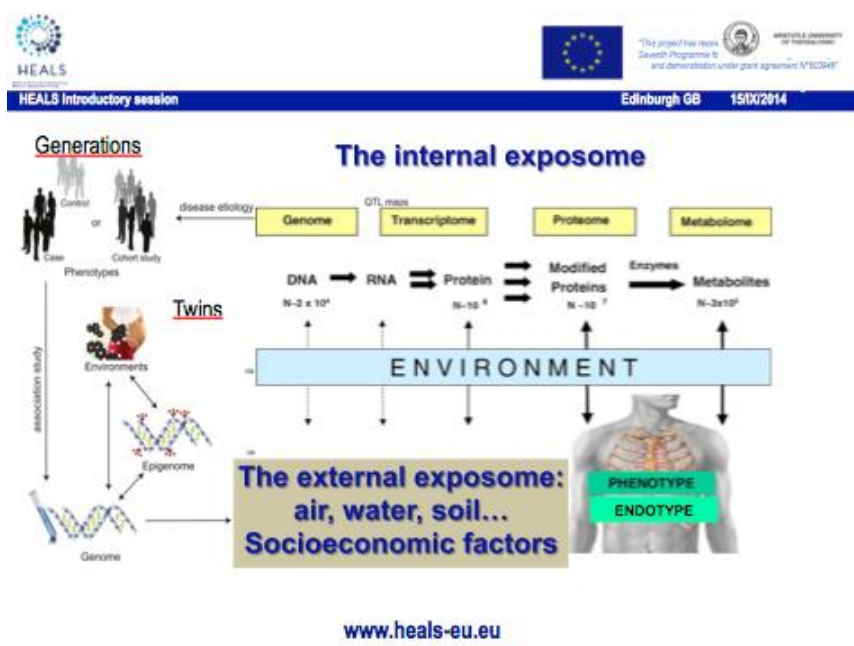
Professor Anesi-Maesano set out the general and specific aims of the meeting.


To contribute to understand links between environmental pressures and health outcomes (asthma/allergies, overweight/diabetes and neurodevelopmental troubles) through the exposomic approach and taking into account recent data.

And specifically during the meeting to:

- Build the exposome related to these diseases;
- Take into account both existing data and data collected in the EXHES study;
- Respond to specific questions in order to assess ad hoc environment stressors and health phenotypes/endotypes in view of understanding their development;
- Build the EXHES in the most efficient way.

The general HEALS approach was outlined, as shown in the following slide.



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Not all perturbations at the level of gene expression should be taken into account because they would result in adaptive, not toxic responses. Thus, gene expression-based molecular response pathways should be coupled to the prevalent pathways identified from bioinformatic analysis of metabolite profiles. Metabolomics data provide a closer link to potential phenotypic/clinical observations. Coupled transcriptomics and metabolomics data analysis will allow us to identify among the perturbed pathways the more likely ones to be associated with adverse outcomes.

Delegates were reminded of the project workflow and the interconnected nature of the various workpackages.


Prof Annesi-Maesano challenged delegates to reflect on “*What do you do in your current research projects that is bringing forward exposome science?*”


The conceptual framework of HEALS and Work Progress – Denis Sariqiannis

Professor Sariqiannis further elaborated the HEALS paradigm, in particular highlighting the way that the study will connect measures of external exposome through a synthesis of data from sensors, measurements, modeled data and questionnaires, to various omic measures. He showed how studies could use untargeted Environment-Wide Association Studies (EWAS) incorporating metabolite profiling and epigenetic measures to develop a disease causation hypothesis that could then be further investigated using targeted omic and biochemical analyses.


“Critical life events” in defining when and how frequently biological samples should be collected to define the exposome - Nour Baiz

Dr Baiz described the results from the review undertaken in WP1 to help identify “Critical life events” and how these should guide the HEALS approach. She described the general methodological approach adopted for the review and explained how the work was guided by knowledge of the developmental timelines in early life and childhood, and developments in later life.



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Definition of critical life periods/stages critical life events



- Periods of time in an individual's lifespan in which:
 - Critical life events occur characterized by changes of the organism status
 - Exposure can have lifelong effects on structure or function that are not modified by later experience (irreversible)
- **Critical life events:** foetus development according to the stage of growth, immune system maturation, organs development, puberty, menopause, ...

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The work also incorporated issues of susceptibility and vulnerability, both innate and acquired, e.g. because of disease or age.

Ten critical life periods were identified as relevant to HEALS, from preconception through to old age, i.e. 80 to 85 years. However, because of ethical considerations, biological specimens will be collected in children recruited in EXHES only twice, at birth and at 2-3 years of age. It was recommended that biological specimens should also be collected from the parents (and eventually grandparents) to address epigenetic considerations. At the other periods, questionnaires will be administered.


Conclusions from the HEALS Ljubljana meeting - Janja Snoj Tratnik

The workshop on “Internal Exposome Markers in HEALS” was held in Ljubljana, from the 26-28 May 2014. Dr Tratnik provided a summary of the discussions to inform the Edinburgh meeting participants. The workshop represented an important step forward in the implementation of the EWAS and EXHES protocols in HEALS. In particular in relation to:

- Internal exposure assessment and –omics in the context of EWAS (what is needed and who needs to do what)
- How can the existing data and samples support the EWAS?

Studies relating exposure to particulate matter and biological agents to asthma - Giuseppe Sarno

Prof Sarno summarized the available knowledge of indoor and outdoor exposures that are known to be associated with asthma, e.g. Particulate Matter (PM) and biological allergens (house dust, pets, cockroaches, mould/dampness, fungi, pollens). He then described the relevant published epidemiological literature and possible preventative strategies.

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Progress and next steps within WP14 were briefly summarized.

Gene-environment interactions in asthma and allergies - M. Kabesch


A review of the current understanding of gene-environment interactions in relation to asthma and allergies was presented by Prof Kabesch. He presented evidence for possible candidate genes conferring susceptibility for exposure to air pollutants, but he highlighted the importance of epigenetic changes affecting gene expression. In particular, he discussed evidence for DNA methylation “storing” information about early developmental exposures to particulate matter, which then can modify the risk (for asthma measured as FeNO).

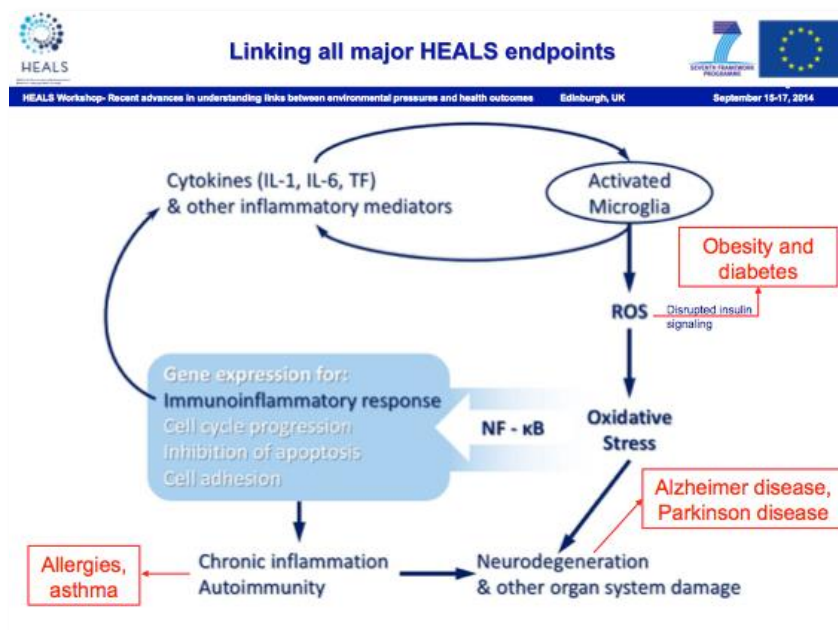
Studies relating neurodevelopmental and neurodegenerative disorders to exposure to metals and pesticides - G. Calamandrei


Dr Gemma Calamandrei spoke about the increasing prevalence of autistic spectrum disorders in the USA and elsewhere, and how only about half of the increase can be attributed to known environmental or diagnostic factors, e.g. parental age. She went on to discuss the work of WP 15, which is focused on exploring potential links between exposures to metals, pesticides and chemical compounds with endocrine disrupting activity (i.e. polyhalogenated aromatic hydrocarbons, phthalates and PCB/PBDE) and neurodevelopmental disorders. The first year work has resulted in an updated understanding of the state of the art and the identification of critical factors, particularly related to measurement of health outcome. Cataloguing the cohorts included in HEALS (5 studies involving about 3000 children) has helped identify similarities, differences, gaps in knowledge.

Discussion on common mechanisms

Prof Sarigiannis led a discussion about common mechanisms for causation of the diseases considered in the HEALS project. He argued for a central role of inflammatory response to environmental factors leading to oxidative stress. The overall concept is shown in the slide below.

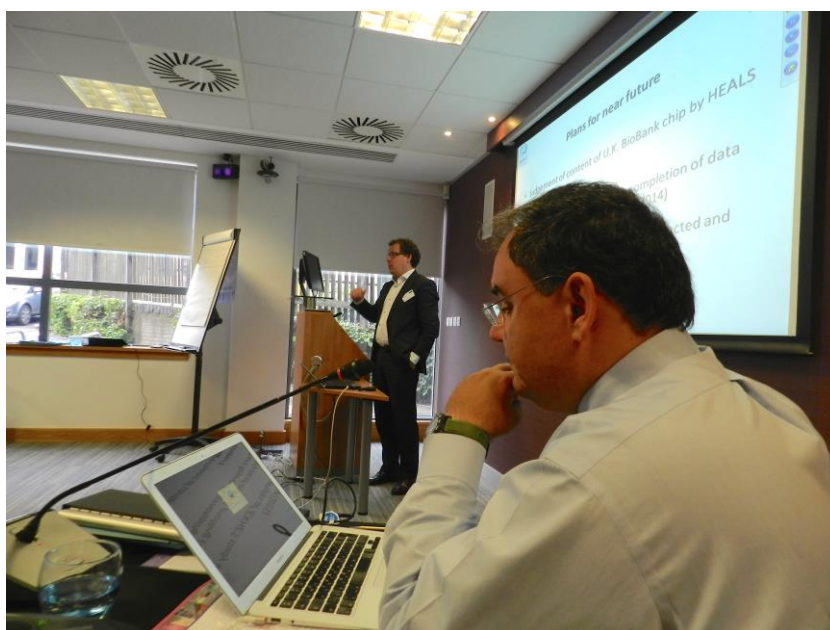
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2.2 Day 2

The meeting began with a series of presentations and discussions about the internal exposome, including Guidelines for exposure biomarkers in HEALS, which included descriptions of the factsheets on specific stressors and associated biomarkers being prepared by WP4 of HEALS. We then discussed the practicalities around using “omics” technologies in the study



Introduction to the internal and external exposome sessions - Denis Sariqiannis and Isabella Annesi-Maesano


Profs Sariqiannis and Annesi-Maesano introduced the sessions scheduled for Day 2.

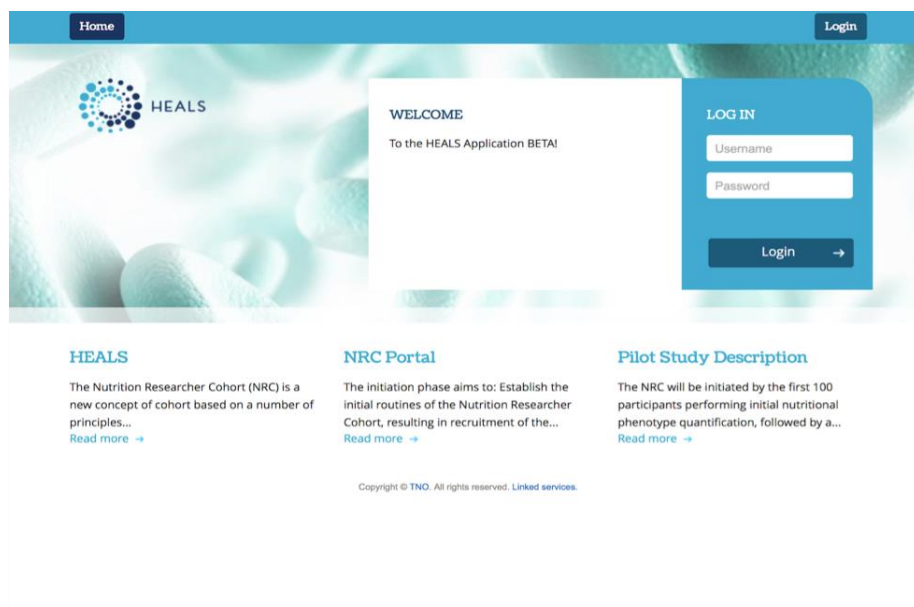
Guidelines for exposure biomarkers in HEALS (D4.2) - N. Steckling

Dr Nadine Steckling presented Deliverable 4.2 on guidelines for biomarker of exposure. The deliverable comprises 51 factsheets for a comprehensive list of biomarkers of exposure plus other stressors with limited/without biomarkers of exposure. The factsheets are intended for the HEALS partners, interested scientists and for the public. They follow a uniform structure and are between 1 and 3 pages in length. Nadine described the rigorous internal peer review process for finalizing the text of each factsheet.

Omics technologies in analytical exposure biology - Rob Stierum

Dr Stierum briefly described the concepts behind the omics analysis in HEALS and the planned work in WP5. He detailed around a dozen different technologies that could be applied to undertake these analyses, and how the team have been working towards a set of Standard Operating Protocols for use in the EXHES. He also described work to develop a software platform that could contain omics and other data for the HEALS project, i.e. from WP9.

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Sample optimization for metabolomics/adductomics for agnostic analysis (Andy Povey /M. Dickinson)

Drs Povey and Dickinson provided an update of work within the HEALS project on adductomics, which has mostly been involved in exploring appropriate sample preparation and analysis methods. They described how a targeted approach for detecting and identifying adducts using LC-MS had been shown to work well for O6-MetG. Other adducts from a known list in the literature have been confirmed using dual MS approach. The next steps are to further develop this approach for untargeted analyses.

Genomic profiling – the HEALS SNP array - W. van Workum


The work being undertaken by the partner ServiceXS set out to design a targeted SNP profiling tool relevant to the EXHES, which could contribute to the establishment of the exposome. A list of relevant SNPs related to metal toxicity and neurological endpoints was produced along with a list of 384 SNPs identified from a literature review. However, it is difficult and time consuming to find relevant SNPs for targeted genotyping and a 'whole-genome' approach would allow identification of new susceptibility markers. Options to achieve this goal were described.

Exposure biology workflow integration in HEALS - D. Sarigiannis and R. Stierum

The proposed data workflow for omics data generated within HEALS was described by Prof Sarigiannis. Existing commercial databases were identified and the advantages of such approaches were discussed. Prof Sarigiannis went on to describe how novel biomarkers can be discovered through protein interaction networks analysis. The group discussed how this approach can be developed within HEALS.

Biomarker data integration and systems biology - D. Sarigiannis and all – guided discussion

The group discussed the issues raised during the morning session.

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External exposome – current status - John Bartzis

Progress in Stream 3 was summarized by John Bartzis. Good progress has been made in gathering relevant environmental data within WP8 and this is being added to the online database at <http://heals.uowm.gr/>. Deliverable 8.1, a report on quality assessment and quality control of environmental data collected, was described. WP9 has completed a pre-pilot study to test the practicality of some of the sensors that will be used in the main work, and has made good progress in developing the protocol for the main pilot. WP10 is making good progress in the state-of-the art of the relationship between socio-economic status (SES) and exposure. A review has been conducted, the preliminary findings suggesting that the majority of published work focuses on the associations between exposure and psychological factors, ethnicity, and access to health services. It was reported that WP11 is about to begin its work with a kick-off meeting to be held in Edinburgh immediately after the Annual Meeting.

Remote sensing for exposure assessment – the US experience - Mike Jerrett

Prof Jerrett presented the results from a study that compared the effects of seven different PM_{2.5} exposure estimates on survival in the United States based on the American Cancer Society Cohort Cancer Prevention II Study. They evaluated four basic approaches:


- U.S. EPA Hierarchical Bayesian model (atmospheric chemistry model fused to ground with approximately 36 km resolution)
- Remote sensing model (approx. 9.8 km resolution – 3 separate models evaluated)
- Bayesian Maximum Entropy (BME) Space-time kriging models (approx. 9.8 km resolution)
- Hybrid models (Land Use Regression BME with approx. 100 m resolution)

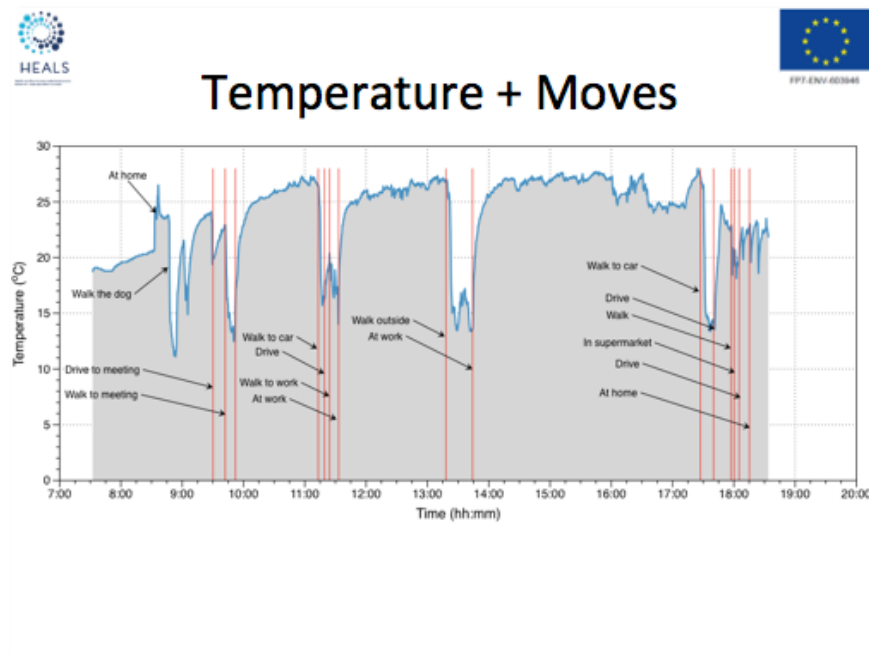
The correlation between the model estimates ranged from 0.56 to 0.94.

The study showed associations between all of the exposure metrics and mortality, although the risk estimates were higher for models with ground data and for those models that reflect small-area variation in traffic density.

The use of sensor technologies in defining the exposome - Miranda Loh

Progress in the use of sensor technologies in defining the external exposome was presented by Dr Miranda Loh. She reviewed the available measurement technologies and the modeling approaches that can be used. There has been considerable progress with small low-cost environmental sensors, which where practicable, will be incorporated into HEALS, although this depends on the technology being robust and reliable. Most promising were location and activity sensors, e.g. using smartphones.

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Dr Loh presented the results from a small preliminary pilot study undertaken by WP9. Criteria for the selection of environmental sensors for HEALS WP9 were outlined and the evaluation for use in HEALS was presented. She also described a software portal being developed in WP9 to manage the sensor deployment (also described earlier by Dr Stierum).


European data on air pollution (outdoor/indoor) - T. Maggos and E. Oliveira Fernandes

Dr Maggos spoke about the environmental data mining on air quality data being undertaken in WP8. He presented a catalogue of available outdoor air pollution concentration data throughout Europe, e.g. AirBase. In addition an inventory of air emission data sources was also presented.

Work on indoor air quality data mining being undertaken within WP8 was described by Prof Eduardo de Oliveira Fernandes. He provided an introduction to the key scientific concepts involved and then provided an inventory of indoor air databases.

European data on water contamination - Joan Grimalt and E. Tolis

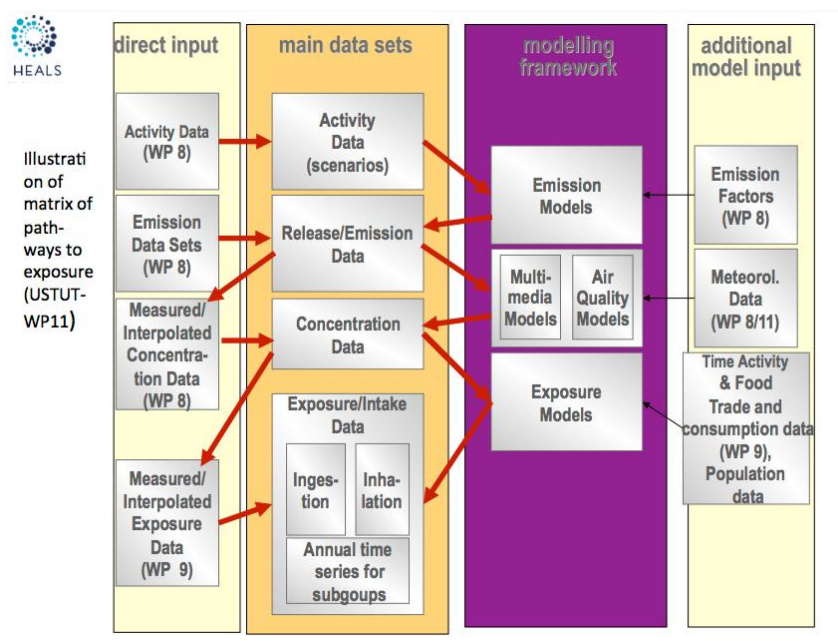
This presentation continued the description of work being undertaken in WP8 on the available data on chemical contamination in water. Conceptual models for the transfer of pollutants within the environment were presented and the importance of the large-scale meteorology across Europe was demonstrated in terms of variation in pollutants in groundwater. It was stressed that contamination in public drinking water is strictly regulated throughout Europe. Data sources have been identified. Finally, the presentation discussed contaminants found in swimming pools, particularly trihalomethanes (THM).

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Exposure data assimilation - R. Friedrich

Prof Friedrich provided an update of plans for WP11. This WP will provide the integration of external exposure assessments for both the existing cohort studies and for the EXHES pilot study.

For each pollutant and each population subgroup, a combination of methods ('pathways to exposure') will be chosen, that transforms the available information/data into external exposures.




A meeting of the team members participating in WP11 was scheduled to take place immediately after the Annual Meeting.

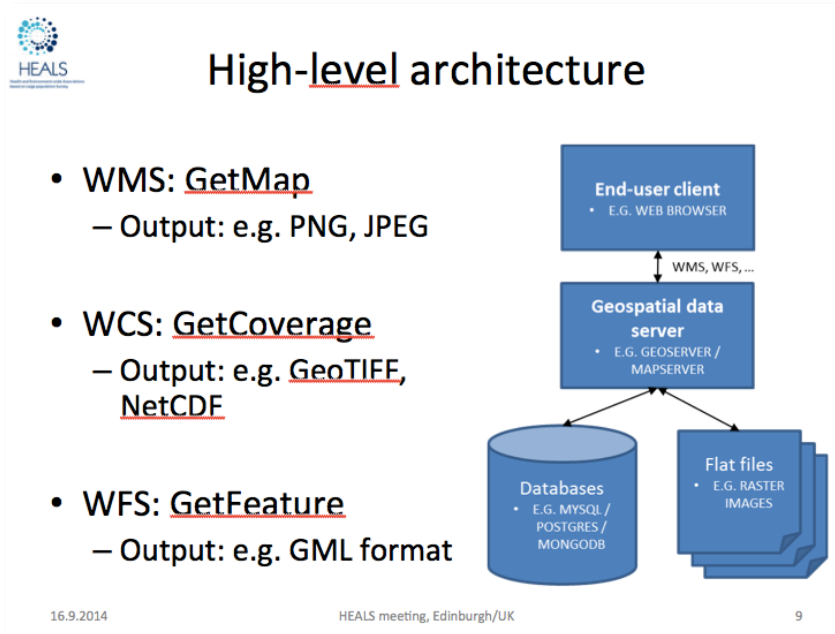
The effect of socio-economics on the external exposome - Lauren Smith

Dr Smith presented work being undertaken in relation to the importance of socio-economic status and vulnerable groups such as those with pre-existing disease or the elderly (WP10). The working group have embarked on a literature review to inform future work within HEALS. In addition, planned work was outlined that will use geospatial analysis methods to distribute our exposure estimates (from WP9) across all sectors of society at a local neighbourhood scale, for all of Europe.

Building the HEALS Geodatabase platform - S. Nousiainen

Work to build the HEALS Geodatabase platform in WP12 was described by Dr Nousiainen. The conceptual issues involved in the database development were discussed and the classes of data identified in the talk.

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The INSPIRE Directive requirements (i.e. for spatial information in Europe to support Community environmental policies) were discussed and the high-level architecture of the planned database was described.


Summary and discussion on the external exposome - D. Sarigiannis and I. Annesi-Maesano

The wealth of information about HEALS and the scientific backdrop for the project that had been presented on Day 2 of the conference were summarized and delegates had the opportunity to ask questions.

2.3 Day 3

Ethical issues and the exposome - Virgilia Toccaceli

The final day of the meeting began with a very interesting and informative presentation about ethical issues involved in studying the exposome given by Prof Toccaceli. It was unfortunate that Prof Toccaceli could not be present in Edinburgh but she was able to deliver her talk using the GoToMeeting facility.

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The importance of balancing the collective needs of society to understand the causes of disease to help prevent future ill-health and the rights of the individual are at the heart of the ethical debate. The main areas of ethical concern for exposome studies are:

- Information to individuals (e.g. informed consent);
- Vulnerability of individuals (e.g. new-borns);
- Data sharing (e.g. confidentiality, privacy, security, harmonization of national legal requirements);
- Biological material use (use and re-use, rights of individuals);
- Interpretation and Communication of results.

Strategies to appropriately manage the ethical (and legal compliance) challenges were outlined and Prof Toccaceli and she expressed a commitment on the part of the HEALS Ethics Advisory Board to support the project in effectively manage these issues.

The EXHES study and discussion - I. Annesi-Maesano

Prof Annesi-Maesano set out the detailed vision for the EXHES trans-generational study within HEALS. The basis design involves 150 twins per country and 450 singletons (150 matched) plus their parent in a 3 year follow-up. The study will be undertaken in Croatia, France, Germany, Greece, Italy, Portugal, Slovenia, Spain, Poland and the United Kingdom.

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Prof Annesi-Maesano further described the two phases of the work: the Core Protocol and the Enlarged Protocol, which will involve a more intensive data collection.

The potential use of measures of trans-epidermal water loss (TEWL) on children using the hand-held AquaFlus monitor was discussed.


The EXHES nested case-control study will involve 140 twins per country/70 singletons.

Details were provided about the SOPs being developed for EXHES, including recruitment and data recording. The plans for further development of these procedures were outlined. It was announced that there will be a meeting with the TWINS Registers in November (London) and EXHES Training in December (Paris or Munich).

Dissemination and training activities in HEALS - M. Schuhmacher and S. Boese O'Reilly

Dr Stephan Böse-O'Reilly and Prof Marta Schuhmacher provided an update of HEALS activities on training and dissemination (WP18 and 19). Several deliverables have been successfully produced during the first year of the project, including the HEALS website, the Moodle platform, and a brochure about the project. A poster about the project has been presented at a number of scientific meetings to raise the profile of the work. A list of publications from the HEALS project is managed by CSIC (J. Grimalt) within the bibliographic dataset Zenodo (<https://zenodo.org/collection/user-heals>).

The HEALS Dissemination Strategic Plan is available on the project website.

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General Assembly - I. Annesi-Maesano and D. Sarigiannis

The HEALS General Assembly was held and minutes of the meeting are available separately.

Input from the Project Advisory Board - C. Weber and D. Balshaw

The Project Advisory Board provided very helpful and incisive advice for the project team. In particular they highlighted:


- The need to define clear go/no-go criteria for each stream and WP, in particular they identified the need to come to a final decision about sensor performance/usability for WP9 and the EXHES, along with sample and data acquisition / recruitment for the existing studies and EXHES;
- Hold a workshop on modeling and data integration (which is planned for year 2);
- Prioritization of analytes for external exposure/biomonitoring, with the specific question “How many targeted analyses makes an untargeted assessment?”;
- Hold a workshop on implications for risk assessment and health impact
 - What is added value for public health?
 - What is added value for EU policy?

Concerning the latter recommendation the Advisory Board identified the lack of an economist, plus policy and legal expertise on the project team and challenged the HEALS team as to how they could address issues in these areas.

Several challenges were highlighted for the team to address:


- Poor availability of previous data, in particular on clinical exposure;
- Limited biobanked material (not easily released);
- Lack of repeated sampling: spot biological samples □ lack of in-depth exposure assessment;
- Effects of long-term storage of bio-samples;
- Representativeness of existing data (and possible missclassifications);
- Type of available samples: blood, rarely urine (which the Board considered may be better e.g. for metabolomics analysis);
- Poor cover of lifetime: none of the existing cohorts allow life-course epidemiology;
- Ethical issues;
- Potential problems of low statistical power;
- High costs for omics analyses;
- Need to develop novel biostatistical approaches, data mining in view of causal interpretation.

Finally, the Advisory Board identified the necessity for strong governance in the project, in particular to coordinate well across Streams and WPs, to adhere to go/no-go decision points and to have a strong vision across the whole consortium.

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Final discussion and conclusions - I. Annesi-Maesano and D. Sarigiannis

Delegates had an opportunity to make final comments and to ask questions.


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	WP2	Security:	
	Author(s): J Cherrie, M Loh	Version: 1	24/26

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