

# PERIODIC REPORT



# HEALS

Health and Environment-wide Associations  
based on Large population Surveys

**Grant Agreement number:** 603946

**Project acronym:** HEALS

**Project title:** Health and Environment-wide Associations based on Large population Surveys

**Funding Scheme:** Collaborative project

**Date of latest version of Annex I against which the assessment will be made:**

**Periodic report:** 1<sup>st</sup>  2<sup>nd</sup>  3<sup>rd</sup>  4<sup>th</sup>

**Period covered:** from 1/04/2018 (M55) to 30/06/2019 (M69)

**Name, title and organisation of the scientific representative of the project's coordinator<sup>1</sup>:**

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**Project website<sup>2</sup> address:** <http://www.heals-eu.eu/>

<sup>1</sup> Usually the contact person of the coordinator as specified in Art. 8.1. of the Grant Agreement.

<sup>2</sup> The home page of the website should contain the generic European flag and the FP7 logo which are available in electronic format at the Europa website (logo of the European flag: [http://europa.eu/abc/symbols/emblem/index\\_en.htm](http://europa.eu/abc/symbols/emblem/index_en.htm) logo of the 7th FP: [http://ec.europa.eu/research/fp7/index\\_en.cfm?pg=logos](http://ec.europa.eu/research/fp7/index_en.cfm?pg=logos)). The area of activity of the project should also be mentioned.

## Declaration by the scientific representative of the project coordinator

I, as scientific representative of the coordinator of this project and in line with the obligations as stated in Article II.2.3 of the Grant Agreement declare that:

- The attached periodic report represents an accurate description of the work carried out in this project for this reporting period;
- The project (tick as appropriate)<sup>3</sup>:
  - has fully achieved its objectives and technical goals for the period;
  - has achieved most of its objectives and technical goals for the period with relatively minor deviations.
  - has failed to achieve critical objectives and/or is not at all on schedule.
- The public website, if applicable
  - is up to date
  - is not up to date
- To my best knowledge, the financial statements which are being submitted as part of this report are in line with the actual work carried out and are consistent with the report on the resources used for the project (section 3.4) and if applicable with the certificate on financial statement.
- All beneficiaries, in particular non-profit public bodies, 3rdary and higher education establishments, research organisations and SMEs, have declared to have verified their legal status. Any changes have been reported under section 3.2.3 (Project Management) in accordance with Article II.3.f of the Grant Agreement.

Name of scientific representative of the Coordinator:

**Isabella Annesi-Maesano**



Date: .....18.../ ..X.../....2019....

For most of the projects, the signature of this declaration could be done directly via the IT reporting tool through an adapted IT mechanism and in that case, no signed paper form needs to be sent

<sup>3</sup> If either of these boxes below is ticked, the report should reflect these and any remedial actions taken.

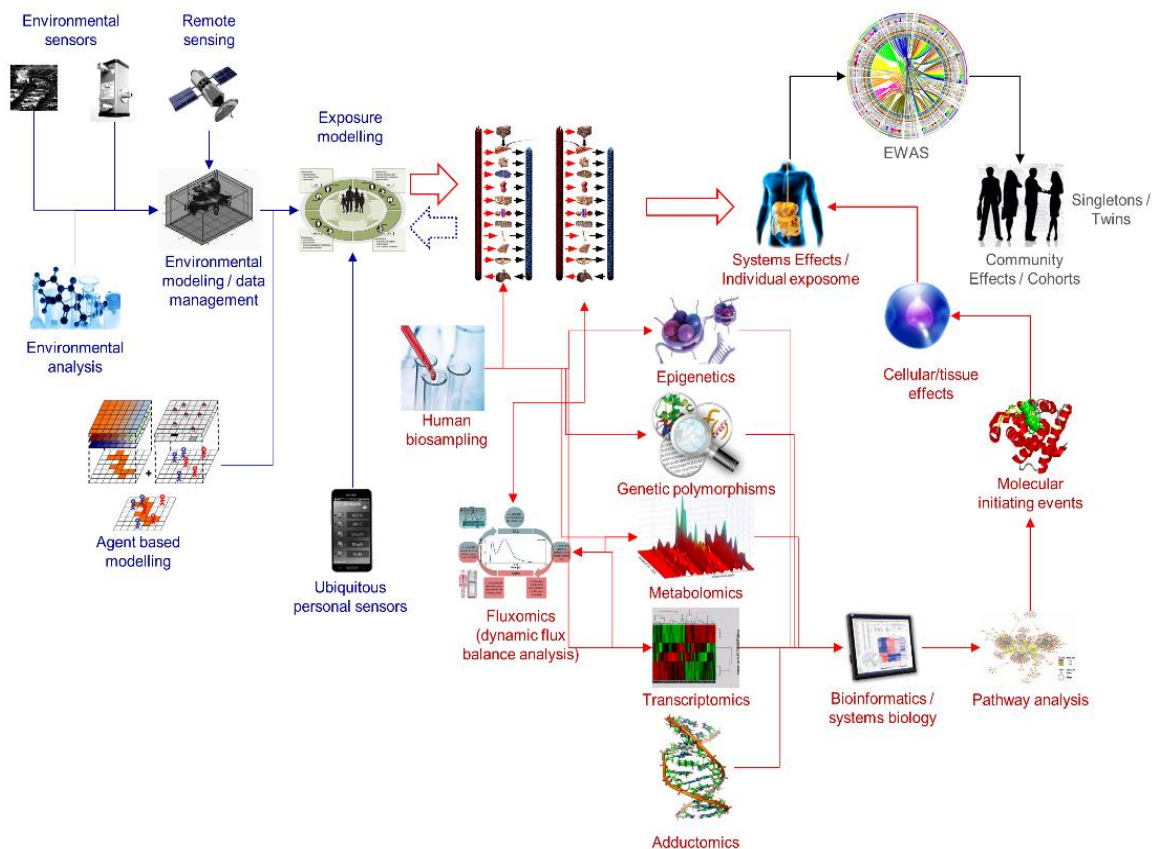
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# 1 Core of the report for the 4<sup>th</sup> period: Project objectives, work progress and achievements, project management

## 1.1 Project objectives for the period

For the period from month 55 to month 69, the **general objective** of the HEALS project continued to be the implementation and the application of the HEALS paradigm (see figure below) in view to explain the development of major health conditions like asthma and allergies, obesity and diabetes, neurodevelopmental disorders, the prevalence of which is elevated in the European population even early in life, and that are increasing.



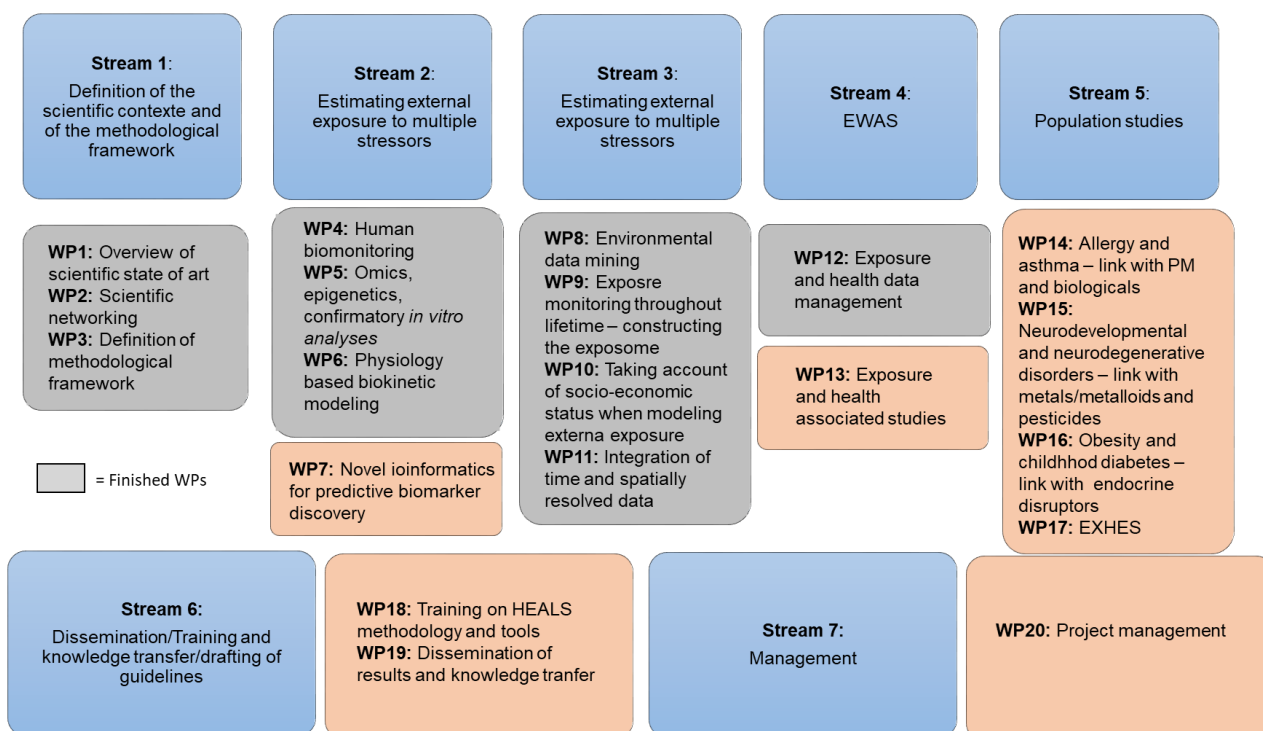
The 4<sup>th</sup> period was consecrated to finish the conduction of the EXposure and Health Examination Survey (EXHES) on the field in 10 countries. In parallel, this period was aimed to continue estimating the individual internal and external exposome, presently, retrospectively and prospectively and to relate it to the considered health outcomes, using data of different nature. At the same time and as a permanent objective of the HEALS project, reporting, networking, disseminating and training was led at the national and international level. For memory, nine additional months without additional costs could be obtained

## 1.2 Work performed and results achieved in the 4<sup>th</sup> period

### 1.2.1. Overview of the progress of the work

As already indicated in the three previous reports, the HEALS project has been structured in 7 streams and 20 work-packages (WPS) (see figure below). In the 4<sup>th</sup> period, the streams that have been particularly active are Streams 4 and 5 from the scientific point of view and Stream 6 for the dissemination. Obviously, all the beforehand mentioned activities have been made possible by a good functioning of the management (Stream 7).

#### The HEALS project workflow (months 55 – 69)



All the obtained progresses allow to HEALS to be a major actor in the health and environment arena. Indeed, even after its official termination, the HEALS consortium that is well established will continue providing results in the field of the exposomic exploration of asthma and allergy, metabolic diseases and neurodegenerative disorders. Due to the obtained findings, alliances are expected with other ongoing projects.

The WP that were still active in the 4<sup>th</sup> period of the HEALS project are:

WP	WP title
7	Novel bioinformatics for predictive biomarker discovery
13	Exposure and health association studies
14	Allergy and asthma - link with particulate matter (PM) and biologicals
15	Neurodevelopmental and neurodegenerative disorders - link with metals/metalloids and pesticides
16	Obesity and childhood diabetes - link with endocrine disruptors
17	Pilot European Exposure and Health Examination Survey (EXHES)
18	Training on HEALS methodology and tools
19	Dissemination of results and knowledge transfer
20	Project management

The specific achieved objectives of the 4<sup>th</sup> reporting period of the HEALS project between months 55 and 69 are expressed by the 13 deliverables, presented in the following table:

#### Deliverables of the HEALS project during the 4<sup>th</sup> period

Number	Deliverable title
<b>D7.2</b>	Report on predictive biomarkers appropriate for environment-wide association health assessments
<b>D13.2</b>	Report on the environment-wide association between exposure data and biological effect data/health outcomes
<b>D14.2</b>	Report on the refined HEALS methodology for estimating the health effects of exposure to multi-pollutant exposure to PM and allergens
<b>D15.2</b>	Final report re-assessing the causal link between external exposure, internal exposure and health outcome as for risk of neurodevelopmental disorders in children within the HEALS framework
<b>D16.2</b>	Report on exposome results and of the environment-wide approach regarding assessment of the environmental determinants of overweight, obesity and diabetes
<b>D17.2</b>	Report on the implementation of EXHES with recruitment and follow-up of, singletons, twins and parents

<b>D17.3</b>	Report on the application of the HEALS environment-wide association approach to EXHES data
<b>D18.4</b>	Learning material for academic curricula
<b>D19.2</b>	HEALS conference: linking Exposome to Human Health?
<b>D19.3</b>	Guidance document on the development and execution of a European Exposure and Health Survey
<b>D19.4</b>	Report of dissemination activities and market analysis from the Knowledge Transfer Secretariat
<b>D19.5</b>	HEALS newsletters and policy briefs
<b>D20.2</b>	Final report on compliance with ethical review requirements

Taking into account the prolongation of the project, no deliverable submission was delayed.

## Main results

Overall, the work organisation has been effective with most of the objectives and technical goals for the 4<sup>th</sup> period that were very satisfactory.

Major achievements of this period consist in the finalisation of the report on predictive biomarkers appropriate for environment-wide association health assessments to be applied to the unique databases of exposures and health at the European level gathered in HEALS using appropriate algorithms, models and statistical methods developed especially for HEALS. First results on EWAS have been obtained in both the pre-existing populations and the new EXHES mother-child birth cohort. Finally, the activities of reporting, networking, disseminating, training have continued in a successful way.

Specific results include:

### Scientific findings

#### *Modeling in view of EWAS*

Methodological advancements consisted in the consolidation of:

- Establishment of the methodological framework for EWAS
- Methodologies for linking omics technologies to population studies
- Review and gathering of methods in bioinformatics for descriptive and predictive data mining
- Development of imputation methods and machine learning have been applied to prevent the consequences of the lack of missing data

#### *EWAS applied to population data*

The finalization of the pilot European Exposure and Health Examination Survey (EXHES) that constitutes one of the milestones of the HEALS project, with around 5,000 families that have accepted to participate to the survey. The children sample include both singletons and twins.

#### *Internal exposome:*

Pathway analysis was completed for the 178 pairs of mother-child samples from PHIME cohort. DNA methylation pre-processing and processing analysis was completed as well

#### *EWAS*

EWAS for neurodevelopmental troubles taking into account both internal and external exposome was conducted in EXHES Spain. EWAS analysis was performed to relate -omics, prenatal exposure and early life (since *in utero*) health outcomes (weight, height, and head circumference, used for neurodevelopment monitoring but also risk factors for asthma and metabolic troubles) data to unravelling the causal links between environmental exposure and the potential risk of the emergence of the aforementioned diseases in the future.

In addition, work has continued on specific research questions that are of utility for the increase of the knowledgement of the considered health outcomes and as intermediate steps in the construction of the exposomic approach of these diseases. Most of these works have been published in a special issue of Environmental Research consecrated to the HEALS project.

#### Dissemination

A huge amount of papers has been finalized and accepted or are presently submitted (see list in the WP and at the end of this document). So far:

- ✓ 177 papers already published in the scientific literature. In journals such as Environmental Health Perspectives, Environment International, Nature Scientific Reports and the Lancet
- ✓ Papers available in open access in the Zenodo database
- ✓ 1280 quotes to date
- ✓ 374 presentations at scientific conferences and meetings
- ✓ One special volume in Environmental Research. 36 papers have been submitted.
- ✓ 8 newsletters

Other papers in preparation and to be submitted to peer-reviewed journals include:

1. The HEALS methodological framework and study design – soon to be submitted in Environmental Health Perspectives.
2. “A critical review of how much of the difference in disease between socio-economic and other social groups can be explained by differences in the “group” exposome”.
3. An overview of results from cohorts/population studies relating adverse health outcomes related to overweight, obesity, diabetes and metabolic disorders to environmental exposures of endocrine disruptors.

The HEALS paradigm and related issues were also presented several times in scientific congresses and meetings and to stakeholders in public events.

Last but not least, the HEALS project is quoted in international publications.



A no additional cost 9-months prolongation was obtained to pursue the work. This allowed HEALS to conclude most of its objectives.

### **1.2.2. HEALS Key facts**

Details on major results achieved in the 3rd reporting period are as follows:

#### **WP7: Novel bioinformatics for predictive biomarker discovery**

Significant amount of the work done in the link between *in vivo* and *in vitro* responses, through the integration of different omics data was finalized. Additional insights in the mechanism associating phthalates exposure to neurodevelopmental disorders have been obtained with the bioinformatics analysis of the data from REPRO\_PL cohort untargeted metabolomics.

#### **WP13: Exposure and health association studies**

Major steps achieved in this WP consisted of:

- Collection of most of data necessary for comprehensive study of the association between environmental exposure and health perturbations. So far, the only data still missing are those from the EXHES study that is still ongoing.
- Update of the literature review of available omics or other biochemical markers of effect for use in population studies with regard to the endpoints of interest in HEALS (allergies and asthma, neurodevelopmental and neurodegenerative disorders, obesity and childhood diabetes) and constitution of related database using HEALS data.
- Identification and application of appropriate statistical analyses in view to perform Environment Wide Association Studies (EWAS) have been developed and implemented.

#### **WP14: Allergy and asthma – link with particulate matter (PM) and biologicals**

Major achievements in this WP are:

- Methods for multipollution analysis were investigated. As a consequence, statistical analyses on the pre-existing single studies databases and on the harmonized HEALS database to assess the effect of the combined exposure to air pollutants and biological allergens on asthma/allergic diseases outcomes and biomarkers at the population level in Europe.
- As a case study on a poorly investigated factor, pooled analyses showed that an increase of 10% in green spaces within 500 m from residential address was significantly associated with greater risks of lifetime wheeze, current wheeze and allergic rhinitis in children of age 3-14 yrs, in particular for coniferous forests exposure. A significant advantage of using Corine land cover classes is that it allows evaluations for separate, coniferous, deciduous and mixed forest, a necessary step towards understanding the health effects of specific vegetation types and untangling the complexities inherent in the interactions between respiratory health and green space. Our desideratum is to

continue to use this data after the natural end of the project to integrate the information about air pollutants exposure estimated at residential address level.

#### **WP15: Neurodevelopmental and neurodegenerative disorders – link with metals/metalloids and pesticides**

A major steps achieved in this WP consisted in the application of the HEALS methodology to HEALS pre-existing population studies.

#### **WP16: Obesity and childhood diabetes – link with endocrine disruptors**

- The environment-wide approach regarding assessment of the link of external environmental determinants and biomarkers of exposure to obesity, diabetes and gestational diabetes at the European level. Major results show the intervention of several pollutants, including Particulate Matter, in these affections after the application of the exposome approach.
- One strategic paper is in press: 1) Association between the exposure to phthalates and adiposity: a meta-analysis in children and adults.
- Another strategic paper is ready to be submitted. The association between environmental exposures to chlordanes, adiposity and diabetes-related features: a systematic review and meta-analysis.

Knowing the link between endocrine disruptors (EDs) and adiposity as a marker of overweight, obesity and diabetes is of great interest in the exposome approach.

#### **WP17: Pilot European Exposure and Health Examination Survey (EXHES)**

The following step has been accomplished:

- EXHES PHASE in 10 countries. Overall, 4,888 families have joined the EXHES mother-child birth cohort by June 2019. As a whole, 5,169 children were included, which comprises 836 twins and 21 triplets. A wide variety of biological material was collected according to standardized sampling procedures in children as well as in their parents. An EXHES biobank has been created. In total, the EXHES biobank included 13,988 different biospecimens collected from the newborns, plus 7,185 and 870 biospecimens collected from their mothers and fathers, respectively. Children and parents are presently followed-up and other biospecimens collected
- Omics also started in EXHES Phase II in urines from Spanish children in order to implement a general model. Main results include relationships between various markers and weight, height, and head circumference.

#### **WP18: Training on HEALS methodology and tools**

The preparation of the training programme and materials on the use of exposure biomarkers and omics for external training continued. Internal training was conducted on both omics and biomarker discovery methods and on the use of exposure biology modeling for internal exposome assessment. A document describing the external training plan and material was elaborated (D18.3).

## **WP19: Dissemination of results and knowledge transfer**

The web-based training and dissemination portal, the Moodle platform, the store for the publications of the Project based on Zenodo database have been updated with recent material. Several papers have already been produced and published. Of note, an entire issue of Environmental Research dedicated to HEALS will be published shortly. It contains almost 40 papers. Most are original papers. The others, meta-analyses and reviews.

Several presentations have been performed to date at national and international congress.. Furthermore, up to twelve meetings have been organized so far by the project partners with stakeholders to report HEALS results.

## **WP20: HEALS management**

Details on HEALS management are provided at the end of the periodic report.

### **1.2.3. Comments**

Activities have been conducted as planned with some exceptions.

The main comment is that HEALS activities have not stopped with the end of the project.

Modeling, omics and epidemiological analyses in the corresponding WPs are still ongoing. Unique databases containing data for internal and external exposome and health have been created. Pre-existing individual data contains up to 50000 records, 5000 of which are geolocalized. EXHES contains almost 5,000 children including 800 twins. Most are being followed-up. The end of the follow-up of 3 years will be finished after the end of the HEALS project. This is due to the fact that the EXHES star was delayed in many countries due local reasons. The related analyses will be postponed too. An official HEALS consortium has been settled to facilitate the work among partners.

**Interesting results on the determinants of the HEALS outcomes were obtained through the exposome approach and will be published shortly in peer-reviewed journal.**

Finally, the worldwide networking with pertinence to the exposome and integrated health risk assessment has continued. Lastly, training and dissemination were warranted. Most deliverables are on time. Only one is slightly delayed.

### **1.2.4. Expected final results and potential impact and use**

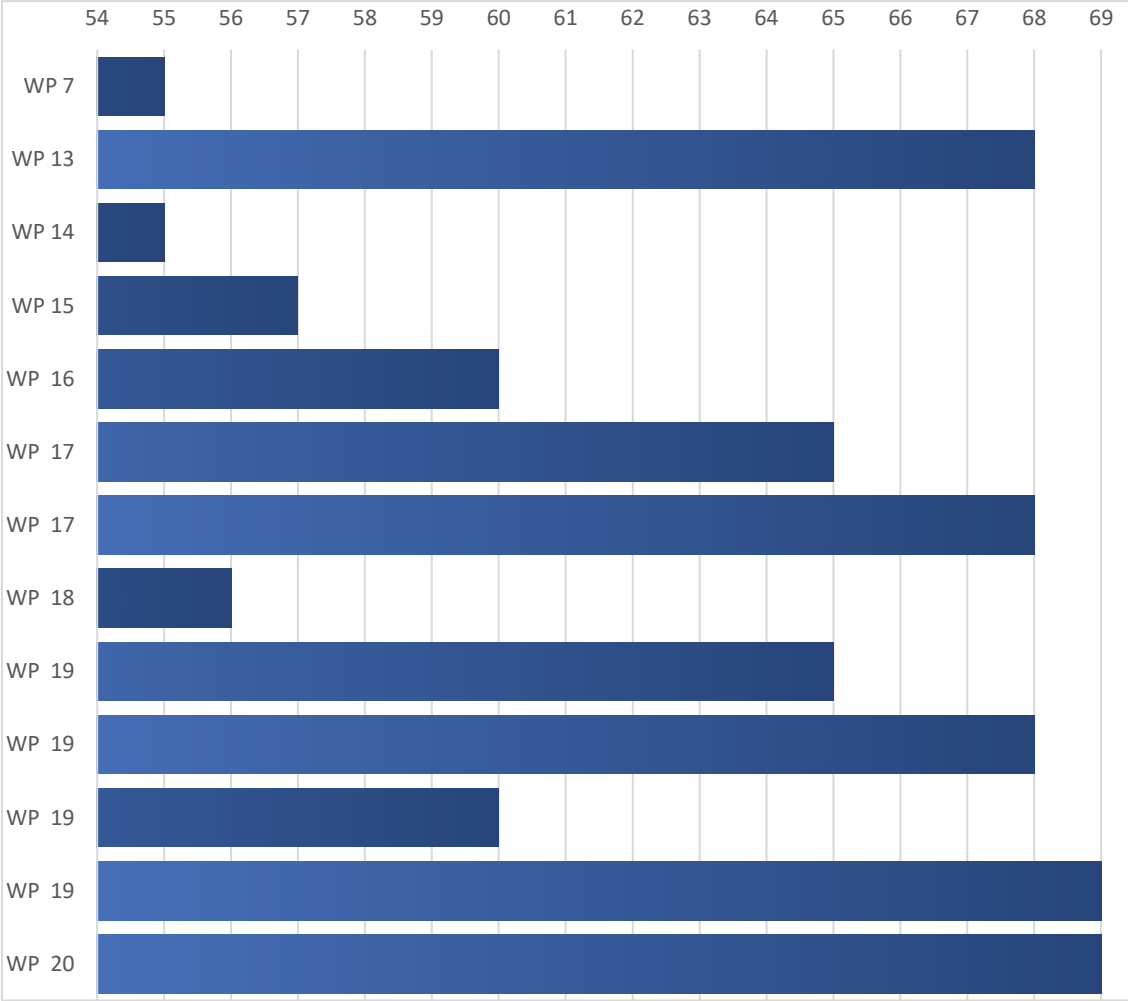
The lessons learned from HEALS will be translated into scientific advice towards the development of protocols and guidelines for the setting up of a larger European environment and health examination survey and for enhancing environmental health risk assessment using the exposome. This will be employed to understand the development of the multifactorial diseases that demand both genetic and environmental exposures to occur. The implemented and developed technologies in HEALS will be available and active technology and knowledge transfer is scheduled to be pursued in the last period of the project. In the long term, this will include screening omics tools and advanced bioinformatics and big data analytics methods

that will be available for usage by the global exposome community in support of the European and the Transatlantic Exposome Initiatives.

### 1.3 Work progress and achievements for each Work Package

## 2 Gantt diagram for the 4<sup>th</sup> period

The below Gantt chart illustrates the HEALS project schedule during the 4<sup>th</sup> period.



- **Conclusions:**

In conclusion, the HEALS project was performant in the last period with many important results most of which are original. It has acquired notoriety becoming “incourtournable” in the exposome arena. It has shown how science and education can be go together.

### **3 Details on WP activities and results for the 4<sup>th</sup> period from 1/04/2018 (M55) to 30/06/2019 (M69)**

In this 4<sup>th</sup> periodic report, are included only the reports of the work packages that are still active, with the exception of WP12 and WP14, which ended in M36.



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## Work package 7 [WP-leader: AUTH]

### Novel bioinformatics for predictive biomarker discovery

#### Report for the 4<sup>th</sup> Period of HEALS

<b>Work Package Number</b>	7		<b>Start date – End date</b>				M1-M55
<b>Work Package Title</b>	Novel bioinformatics for predictive biomarker discovery						
<b>Activity Type</b>	R T						
<b>Participant Number and Short Name</b>	2 AUTH	6 UPD	13 TNO	17 CERETOX	23 URV		
<b>Person-months</b> ( <u>this</u> reporting period / total planned)	2.79/12	6.95/22	6.79/19	0.49/4	0.80/3		
Explanation of deviations between actual and planned person-months per work							

#### Objectives of WP7 for the 4<sup>th</sup> Period

In general, the objectives of WP7 were:

- To understand the biological functions of toxicity pathway interactions in relation to external/internal exposure
- To confirm the causative effect between exposure and disease endpoint through theoretical (computational) and data mining from supportive in vitro models
- To combine mixed data, resulted from various sources, through the utilisation of advanced data mining analysis techniques for biomarker identification
- To provide the methodological tools for integrating multiple biomarkers into a mechanistic description of biological pathways relevant to environment-wide health association studies
- To support the derivation of systems biology models for the internal exposome
- To provide data infrastructure support for storage of data, metadata and analysis pipelines for omics data emerging from cohorts (DIAMONDS and GSCF/dbNP) and integrate this into the HEALS database platform developed in WP12

The specific objective for the 4<sup>th</sup> period was to concretize the work on predictive biomarkers appropriate for environment-wide association health assessments in order to be used in HEALS.

#### Summary of progress of WP7 for the 4<sup>th</sup> Period

Pathway analysis was completed for the 178 pairs of mother-child samples from PHIME cohort. DNA methylation pre-processing and processing analysis was completed as well. Moreover, the deliverable D7.2 was submitted and published.



## Description of Work of WP7 for the 4<sup>th</sup> Period

The work produced by previous tasks was used to build the report on predictive biomarkers appropriate for environment-wide association health assessments.

### **Task 7.1: Descriptive data mining – preprocessing, data clustering and pattern discovery (AUTH, TNO, URV)**

**Aim:** The aim of this task is to provide the data mining – preprocessing, data clustering and pattern discovery, including noise removal, data transformation, data reduction and discretization.

#### **Details of progress and main results:**

This task was completed in a previous reporting period, where the main results were reported.

*If applicable, explain the reasons of any deviation from the Dow (description of work) and the impact on the other tasks, on available resources and planning:*

Not applicable.

*If applicable, explain the reasons for failing to achieve critical objectives and/or not being on schedule and the impact on other tasks as well as on available resources and planning:*

Not applicable.

*If applicable, propose corrective actions:*

Not applicable.

This task has been mainly performed by AUTH.

### **Task 7.2: Predictive data mining – data models design and analysis (AUTH, TNO, CERETOX, UPD)**

**Aim:** The aim of this task is to perform inference on the available combinations of multidisciplinary datasets. Several techniques have been used for that purpose, ranging from typical approaches based on decision trees or k-nearest neighbor algorithms to more sophisticated machine learning approaches including artificial neural networks (ANNs), support vector machines (SVMs) and Bayesian networks (BNs).

#### **Details of progress and main results:**

This task was completed in the 3<sup>rd</sup> period of the project, thus the main results were reported in the 3<sup>rd</sup> periodic report for the WP7.

*If applicable, explain the reasons of any deviation from the Dow (description of work) and the impact on the other tasks, on available resources and planning:*

Not applicable.

*If applicable, explain the reasons for failing to achieve critical objectives and/or not being on schedule and the impact on other tasks as well as on available resources and planning:*

Not applicable.



If applicable, propose corrective actions:

Not applicable.

This task has been mainly performed by AUTH, UPD and CERETOX.

### **Task 7.3: Model integration – biomarkers identification and prediction validation (AUTH, TNO, UPD)**

**Aim:** The aim of this task is the integration of multiple omics biomarkers into a mechanistic description of toxicity pathway interactions, in relation to external/internal exposure.

#### **Details of progress and main results:**

This task was completed in the 4<sup>d</sup> period of the project. The pre-processing of the raw data from cord blood samples (REPRO\_PL) obtained from the DNA methylation analysis including quality control, quintile normalization and cell composition correction, was using the R software package minfi. In addition, a comprehensive bioinformatics analysis on metabolomics results coupled to pathway and EWAS analysis was applied on the PHIME cohort samples. Environmental and social factors were considered while both Bayley Scales of Infant Development (BSID) III and WISC scores were used for neurodevelopment assessment. The final outcome of the pathway analysis performed using the GeneSpring Pathway Architect was a list of 93 unique pathways. Pathway analysis revealed that the most perturbed metabolic pathways from exposure to heavy metals were related to TCA cycle, purine, pyrimidine, phospholipids and carnitine metabolism, and glycolysis. The aforementioned results suggested major disturbances to cells biochemistry, which resulted in the impairment of antioxidant defense mechanisms leading to the clinically observed results in linguistic, motor development and cognitive capacity.

If applicable, explain the reasons of any deviation from the Dow (description of work) and the impact on the other tasks, on available resources and planning:

Not applicable.

If applicable, explain the reasons for failing to achieve critical objectives and/or not being on schedule and the impact on other tasks as well as on available resources and planning:

Not applicable.

If applicable, propose corrective actions:

Not applicable.

This task has been mainly performed by AUTH, UPD, CERETOX and FERA.

### **Task 7.4: Bioinformatics data infrastructure for storage of human cohort study specific metadata in relation to omics and (bio)assay data (TNO, AUTH)**





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**Aim:** The aim of this task is to produce a data infrastructure for storage of human cohort specific metadata.

**Details of progress and main results:**

This task was completed in previous reported period, where the main results were reported.

*If applicable, explain the reasons of any deviation from the Dow (description of work) and the impact on the other tasks, on available resources and planning:*

Not applicable.

*If applicable, explain the reasons for failing to achieve critical objectives and/or not being on schedule and the impact on other tasks as well as on available resources and planning:*

Not applicable.

*If applicable, propose corrective actions:*

Not applicable.

This task has been mainly performed by TNO.

This allowed us to produce deliverable 7.2, the report on predictive biomarkers appropriate for environment-wide association health assessments. The developed comprehensive data processing approach provides the methodological tools for integration of multiple omics biomarkers into a mechanistic description of toxicity pathway interaction, in relation to external/internal exposure.

**List of deliverables in WP7 of HEALS for the 4<sup>th</sup> Period**

No.	Title/objective	Delivery Date	Achieved (Yes/No)	Significant results	Comments [ in progress, delayed..]	If applicable, propose corrective actions
D7.2	Report on predictive biomarkers appropriate for environment-wide association health assessments	4/2019	Yes	The developed comprehensive data processing approach provides the methodological tools for integration of multiple		



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				<p>omics biomarkers into a mechanistic description of toxicity pathway interaction, in relation to external/internal exposure.</p>		
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**List of milestones in WP7 of HEALS for the 4<sup>th</sup> Period**

Not applicable

No.	Title/objective	Delivery Date	Achieved (Yes/No)	Significant results	Comments [ in progress, delayed..]	<u>If applicable,</u> propose <b>corrective actions.</b>
MS1		MXX				
MS2		MXX				
MS3		MXX				
MS4		MXX				
MS5		MXX				



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### Dissemination in WP7 of HEALS for the 4<sup>th</sup> Period

<b>Publications</b>	<b>Title</b>	<b>Authors</b>	<b>In preparation/revision</b>	<b>Submitted (journal / date)</b>	<b>Published (journal / date)</b>	<b>Notes/comments</b>
1	Multi-omics analysis reveals that co-exposure to phthalates and metals disturbs urea cycle and choline metabolism.	Nafsika Papaioanou, Emilie Distel, Eliandre de Oliveira, Catherine Gabriel, Ramón Díaz-Peña, Antonia Odena, Ilias S. Frydas, Ourania Anesti, Eléonore A Attignon, Martine Aggerbeck, Milena Horvat, Robert Barouki, Spyros Karakitsios, Denis A. Sarigiannis	Under revision	Environmental Research, 11-06-2019		
<b>Presentations</b>	<b>Title</b>	<b>Authors</b>	<b>Conference, meeting, workshop (name/ date / place)</b>	<b>Notes/comments</b>		
1	Multi-omics Analysis Reveals that Co-exposure to Phthalates and Metals Disturbs Urea	D.A Sarigiannis, N. Papaioanou, N. Kapretsos, A.	AICHE Annual Meeting, Pittsburgh (PA), USA, 28/10-2/11/2018.			



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	Cycle and Choline Metabolism. 2018	Gabriel, E. Distel, E. De Oliveira, S. Karakitsios, M. Aggerbeck, R. Barouki.				
2	Mechanistic Assessment of the Effect of Phthalates and Heavy Metals on Neurodevelopment.	Dimosthenis Sarigiannis, Nafsika Papaioannou, Maria Fafouti, Mike Dickinson, Kinga Polanska, Wolfgang Hanke, Athanasios Salifoglou, Evangelos Handakas, Catherine Gabriel, Spyros Karakitsios.	AICHE Annual Meeting, Pittsburgh (PA), USA, 28/10-2/11/2018			
3	Multi-omics Analysis Reveals that Co-exposure to Phthalates and Metals Disturbs Urea Cycle and Choline Metabolism	Dimosthenis Sarigiannis, Nafsika Papaioannou, Nikolaos Kapretsos, Catherina Gabriel, Emilie Distel,	EUROTOX, Brussels, Belgium 2-5/9/2018			



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		Eliandre de Oliveira, Spyros Karakitsios, Martine Aggerbeck, Robert Barouki.				
4	Effects of Heavy Metals to Neurodevelopment in a Mother-Infant Cohort Study.	Dimosthenis Sarigiannis, Nafsika Papaionnou, Maria Fafouti, Aikaterina Galonaki, Kinga Polanska, Michael Dickinson, Caterina Gabriel, Spyros Karakitsios.	ICHMET, Athens, Georgia, USA, 22-25/7/2018			
5	Pathway Analysis of Prenatal Exposure to Heavy Metals Related Child Motor Development.	Dimosthenis Sarigiannis, Kinga Polanska, Wojciech Hanke, Athanasios Salifoglou, Nafsika Papaionnou, Evangelos Handakas, Caterina Gabriel, Spyros Karakitsios.	ICHMET, Athens, Georgia, USA, 22-25/7/2018.			



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6	Effects of heavy metals to neurodevelopment in a mother-infant cohort study.	D.A. Sarigiannis, N. Papaioannou, M. Fafouti, A. Galonaki, K. Polanska, M. Dickinson, C. Gabriel, S. Karakitsios.	INCHES, Seoul, South Korea, 27-29/6/2018.			
7	Pathway analysis of prenatal exposure to heavy metals related child motor development.	D.A. Sarigiannis, K. Polanska, W. Hanke, A. Salifoglou, N. Papaioannou, E. Handakas, C. Gabriel, S. Karakitsios.	INCHES, Seoul, South Korea, USA, 27-29/6/2018.			
8	Adverse Outcome Pathway analysis of prenatal combined exposure to heavy metals and phthalates related to child neurodevelopment.	D.A. Sarigiannis, K. Polanska, W. Hanke, A. Gabriel, N. Papaioannou, S. Karakitsios.	PPTOX, Tórshavn, Faroe Islands, 27-30/5/2018.			
<b>Meetings organized with stakeholders</b>	<b>Name</b>	<b>Organizer</b>	<b>Heals participants (name / partners)</b>	<b>Date / Place</b>	<b>Notes/comments</b>	
1						



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2						
3						



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## Work package 13 [WP-leader: UPMC (now SU)]

### Exposure and health association study

#### Report for the 4<sup>th</sup> Period of HEALS

<b>Work Package Number</b>	13		<b>Start date – End date</b>					M9-M68
<b>Work Package Title</b>	Exposure and health association studies							
<b>Activity Type</b>	RTD							
<b>Participant Number and Short Name</b>	1 SU	2 AUTH	8 ISS	11 VTT Oy	15 CSIC	18 IDMEC- FEUP	20 CNR	
<b>Person-months</b> ( <u>this</u> reporting period / total planned)	8.46/18	3.32/6	4.72/1	6.68/10	5/7	xx/4	3.56/3	
Explanation of deviations between actual and planned person-months per work	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	
<b>Participant Number and Short Name</b>	29 UC	31 INEGI						
<b>Person-months</b> ( <u>this</u> reporting period / total planned)	3.59/2	xx/0						
Explanation of deviations between actual and planned person-months per work	n.a.	n.a.						

#### Objectives of WP13 for the 4<sup>th</sup> Period

In general, the objectives of WP13 were:

1. To relate internal and external exposome to health outcomes
2. To identify biomarkers of exposure and effects at the individual level

They were still active during the 4<sup>th</sup> period





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## Summary of progress of WP13 for the 4<sup>th</sup> Period

All the tasks were completed, and the deliverable D13.2 on Report on the environment-wide association between exposure data and biological effect data/health outcomes was submitted.

## Description of Work of WP13 for the 4<sup>th</sup> Period

### **Task 13.2 Environment-wide associations linking environmental exposures to health outcomes (AUTH, UPMC, ISS, VTT, CSIC, CNR, UC)**

**Aim:** The aim of this task is the development of an EWAS approach that allows the export and the investigation of the links between exposure data and effect data/health outcomes.

#### **Details of progress and main results:**

This task was completed during the 4<sup>th</sup> period.

EWAS analysis was applied on the REPRO-PL dataset to find the associations among the exposure to environmental stressors and its impacts on child neurodevelopment. Previously reported work included the results obtained from urinary untargeted metabolomics, while during the last year the dataset was enhanced from the plasma untargeted metabolomics analysis result, and the new results from the aforementioned phthalates analysis. EWAS analysis was also applied to the PHIME completed dataset. Environmental and social factors were considered while both Bayley Scales of Infant Development (BSID) III and WISC scores were used for neurodevelopment assessment.

If applicable, explain the reasons of any deviation from the Dow (description of work) and the impact on the other tasks, on available resources and planning:

Not applicable.

If applicable, explain the reasons for failing to achieve critical objectives and/or not being on schedule and the impact on other tasks as well as on available resources and planning:

Not applicable.

If applicable, propose corrective actions:

Not applicable.

This task has been mainly performed by AUTH, VTT and SU

### **Task 13.3 Identification of differentially expressed biomarkers and biological responses at the individual level (UPMC, AUTH, ISS, CSIC, VTT)**

**Aim:** The aim of this task is the identification of exposure biomarker profiles/biological responses that are differentially expressed in the health examination survey population, thus linking exposure data with health outcomes at the individual level across the EU.



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**Details of progress and main results:**

This task was completed during the 4<sup>th</sup> period.

The previously reported main results were confirmed from the new ones.

If applicable, explain the reasons of any deviation from the Dow (description of work) and the impact on the other tasks, on available resources and planning:

Not applicable.

If applicable, explain the reasons for failing to achieve critical objectives and/or not being on schedule and the impact on other tasks as well as on available resources and planning:

Not applicable.

If applicable, propose corrective actions:

Not applicable.

This task has been mainly performed by AUTH and TNO

The deliverable D13.2 on Report on the environment-wide association between exposure data and biological effect data/health outcomes was submitted.

**List of deliverables in WP13 of HEALS**

No.	Title/objective	Delivery Date	Achieved (Yes/No)	Significant results	Comments [in progress, delayed..]	<u>If applicable</u> , propose corrective actions
D13.2	Report on the environment-wide association between exposure data and biological effect data/health outcomes	M68	Yes	First EWAS to understand the impact of the environment on obesity at the European level		

**List of milestones in WP13 of HEALS**



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Not applicable

<b>No.</b>	<b>Title/objective</b>	<b>Delivery Date</b>	<b>Achieved (Yes/No)</b>	<b>Significant results</b>	<b>Comments [ in progress, delayed..]</b>	<b><u>If applicable,</u> propose corrective actions.</b>
MS1		MXX				
MS2		MXX				
MS3		MXX				
MS4		MXX				
MS5		MXX				



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## Work package 14 [WP-leader: CNR]

### Allergy and asthma – link with particulate matter (PM) and biological

#### Report for the 4<sup>th</sup> Period of HEALS

<b>Work Package Number</b>	14		<b>Start date</b>				M 1- M55			
<b>Work Package Title</b>	Allergy and asthma - link with particulate matter (PM) and biological									
<b>Activity Type</b>	RTD									
<b>Participant Number and Short Name</b>	20 CNR	1 UPMC	2 AUTH	4 USTUT	12 UM	13 TNO	21 FMUP	26 KCL	27 NIPH	28 SDU
<b>Person-months</b>  ( <u>this</u> reporting period / <b>total</b> planned)	3.3/5	7.75/2	2.70/4	2.50/3	0.50/1	1/1	XX/10	0.50/2	4.78/1	0.60/3
<b>Explanation of deviations between actual and planned person-months per work package and per beneficiary</b>	n.a.									

#### Objectives of WP14 for the 4<sup>th</sup> Period

Finalization of the statistical analyses on the harmonized and centralized HEALS database and writing of the Deliverable 14.2.



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### Summary of progress of WP14 for the 4<sup>th</sup> Period

- Finalization of the deliverable 14.2;
- Performing of new statistical analyses using the Corine land cover classes.

### Description of Work of WP14 for the 4<sup>th</sup> Period of HEALS

#### **Task 14.3: Refinement of HEALS methodology to estimate the association of exposure to multi-pollutant mixtures and to allergens in the air (M1-40; UPMC, AUTH, CNR, USTUTT, UM, TNO, FMUP, KCL)**

Aim: The aim of this task is to refine the HEALS methodology in order to estimate the association between exposure to multi-pollutant mixtures and to allergens and adverse health outcomes.

#### Details of progress:

- Few pre-existing studies of the HEALS harmonized database had information about individual exposure to air pollution and allergens; thus, air pollutants exposure data at city level were used in the previous analyses. To overcome this limit, data coming from the Coordination of Information on the Environment (CORINE) program (i.e. land cover classes) were linked to the residential addresses to obtain an analysis at finer resolution. Land cover classes were considered as proxy of exposure to air pollutants and pollens.

#### Main results:

- Data from 8,063 children, aged 3-14, were obtained from nine European population-based studies participating in the project (French EDEN study; Italian Fumane&Mezzane di Sotto, Italian Twin Registry, MUBICOS, PISA2, Turin, Viadana studies; Slovenian PHIME study; Polish REPRO\_PL study); all the children had information about the geographic coordinates of the residential address.

- The individual exposure to air pollutants/pollens was computed using as proxy the land cover data coming from the CORINE program; in particular, the proportion of land cover classes (green, grey, blue, agricultural spaces) within 100m meters, 300m, 500m and 1000m buffers centred on each child's residential address was analyzed.

- The following health outcomes were taking into account: lifetime wheeze, current wheeze, lifetime asthma, current asthma, lifetime allergic rhinitis and eczema.

- To minimize bias from heterogeneity of methodological protocols among studies, a two-stage approach was used. In the first stage, associations of health outcomes with each of the land coverage indicators were estimated within each study using logistic regression models, adjusting for potential confounders available in each study (sex, age, body mass index, parental history of allergy, maternal education, passive smoke exposure). Land-cover main classes (i.e. green, grey, blue, and agricultural) were included in the model as continuous variables and odds ratio were estimated for a 10% increase of land coverage within a 500m buffer. In a sub-analysis, the associations of health outcomes with a binary indicator of presence/absence of forests (any, coniferous, broad-leaf, mixed) within a 500m buffer surrounding the children's home were also evaluated.



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In the second stage, fixed-effects meta-analyses were performed on the estimates calculated for individual studies using the inverse-variance method and overall odds ratio were calculated.

- The following associations were found: pooled analyses showed that an increase of 10% in green spaces within 500m from residential address was significantly associated with greater risks of lifetime wheeze, current wheeze and allergic rhinitis in children of age 3-14 yrs, in particular for coniferous forests exposure.

- A significant advantage of using Corine land cover classes is that it allows evaluations for separate, coniferous, deciduous and mixed forest, a necessary step towards understanding the health effects of specific vegetation types and untangling the complexities inherent in the interactions between respiratory health and green space. Our desideratum is to continue to use this data after the natural end of the project to integrate the information about air pollutants exposure estimated at residential address level.

- This analyses were reported in a manuscript submitted to Environmental Research Journal.

- This task has been mainly performed by CNR, UPMC as partners of WP14; moreover, it was essential the collaboration of other HEALS partners (VTT, ISS, JSI, NIOM, UNIVBRIS (now Aarhus)).

**List of deliverables in WP14 for the 4<sup>th</sup> Period**

No.	Title/objective	Delivery Date	Achieved (Yes/No)	Significant results	Comments [ in progress, delayed..]	If applicable, propose corrective actions
D14.2	Report on the refined HEALS methodology for estimating the health effects of exposure to multi-pollutant exposure to PM and allergens	M56	Yes	Report on the results of the statistical analyses aimed at assessing the relationship between asthmatic/allergic diseases and combined exposure to air pollution and biological allergens.		

**List of milestones in WP14 for the 4<sup>th</sup> Period**

No.	Title/objective	Delivery Date	Achieved (Yes/No)	Significant results	Comments [ in progress, delayed..]	If applicable, propose
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						<b>corrective actions.</b>
M19	Completion of internal exposure assessment	M68	Yes	Land cover classes as proxy of individual exposure at air pollution and biological allergens.		

#### Dissemination in WP14 for the 4<sup>th</sup> Period

<b>Publications</b>	<b>Title</b>	<b>Authors</b>	<b>In preparation/revision</b>	<b>Submitted (journal / date)</b>	<b>Published (journal / date)</b>
1	Influence of residential land cover on childhood allergic and respiratory symptoms and diseases: evidence from 9 European cohorts.	Parmes E et al		Environmental Research, June 11, 2019	
2	Prioritizing research challenges and funding for allergy and asthma and the need for translational research-The European Strategic Forum on Allergic Diseases.	Agache I, Annesi-Maesano I, Bonertz A, Branca F, Cant A, Fras Z, Ingenrieth F, Namazova-Baranova L, Odemyr M, Spanevello A, Vieths S, Yorgancioglu A, Alvaro-Lozano M, Barber Hernandez D, Chivato T, Del Giacco S, Diamant Z, Eguiluz-Gracia I, van Wijk RG,			Allergy. 2019 May 9. 10.1111/all.13856. [E ahead of print] PubMed PMID: 31070805.



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HEALS

		Gevaert P, Graessel A, Hellings P, Hoffmann-Sommergruber K, Jutel M, Lau S, Lauerma A, Maria Olaguibel J, O'Mahony L, Ozdemir C, Palomares O, Pfaar O, Sastre J, Scadding G, Schmidt-Weber C, Schmid-Grendelmeier P, Shamji M, Skypala I, Spinola M, Spranger O, Torres M, Vereda A, Bonini S.			
3	External exposome and allergic respiratory and skin diseases.	Cecchi L, D'Amato G, Annesi-Maesano I.			J Allergy Clin Immunol Mar;141(3):846-857. doi: 10.1016/j.jaci.2018.07.011. Review. PubMed PMID: 29519451.
4	Biomarkers of exposure in environment-wide association studies - Opportunities to decode the exposome using human biomonitoring data.	Steckling N, Gotti A, Bose-O'Reilly S, Chapizanis D, Costopoulou D, De Vocht F, Garí M, Grimalt JO, Heath E, Hiscock R, Jagodic M, Karakitsios SP, Kedikoglou K, Kosjek T, Leondiadis L, Maggos T, Mazej D,			Environ Res. 2018 Jul;164:597-624. doi: 10.1016/j.envres.2018.04.011. Epub 2018 Apr 5. Review. PubMed PMID: 29620000.





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HEALS

		Polańska K, Povey A, Rovira J, Schoierer J, Schuhmacher M, Špirić Z, Stajanko A, Stierum R, Tratnik JS, Vassiliadou I, Annesi- Maesano I, Horvat M, Sarigiannis DA.			
<b>Presentations</b>	<b>Title</b>	<b>Authors</b>	<b>Conference, meeting, workshop (name/ date / place)</b>	<b>Notes/comments</b>	
1	Influence of the proximity of green areas on respiratory symptoms in children. A pan- European study within the HEALS project	Brescianini S et al	Exposome Symposium, May 20-21, 2019, Brescia (Italy)		
<b>Meetings organized with stakeholders</b>	<b>Name</b>	<b>Organizer</b>	<b>Heals participants (name / partners)</b>	<b>Date / Place</b>	<b>Notes/comments</b>
1	New approaches in assessment of environmental exposure effects	Institute of Clinical Physiology, Italian National Research Council	Maio Sara and Sandra Baldacci, partner CNR	April 4, 2019, Pisa (Italy)	Event "IFC50+: The biomedical research society". It was orga to celebrate the 50t Anniversary of Four of the Institute of Cl Physiology



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## Work package 15 [WP-leader: ISS]

### Neurodevelopmental and neurodegenerative disorders – link with metals/metalloids and pesticides

#### Report for the 4<sup>th</sup> Period of HEALS

<b>Work Package Number</b>	15		<b>Start date - End date</b>					M 1 – M68
<b>Work Package Title</b>	<b>Neurodevelopmental and neurodegenerative disorders - link with metals/metalloids and pesticides</b>							
<b>Activity Type</b>	RTD							
<b>Participant Number and Short Name</b>	15 CSIC	10 NIOM	8 ISS	28 SDU	14 FERA	5 JSI	4 USTUTT	
<b>Person-months</b> ( <b>this</b> reporting period / <b>total</b> planned)	3/15	5/33	13.36/8	0/3	0/13	1/6	0,3/3	
<b>Participant Number and Short Name</b>	2 AUTH	1 SU	VTT	TNO	OIKON ZELENA	URV	LMU	
<b>Person-months</b> ( <b>this</b> reporting period / <b>total</b> planned)	1.27/3	0,27/2	0/1	0/1	6/3	0/4	2.40/24	
Explanation of deviations between actual and planned person-months per work package and per beneficiary								

#### Objectives of WP15 for the 4<sup>th</sup> Period of HEALS

According to the DoW the activities carried out in WP15 are organised in 3 major activities in the 4<sup>th</sup> period.....

1. Using data on external exposure assessment to link environmental and health data.
2. Completing the analysis of -omic biomarkers to link environmental and health data in selected samples from existing cohorts.
3. Starting EWAS analysis to validate the HEALS approach exploiting the HEALS database.



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A specific objective was that of applying the EWAS analysis to data bases focused on children's neurodevelopmental scores, as assessment of the association between early life exposome and child neurodevelopment has been scarcely investigated so far.

### **Summary of progress of WP15 for the 4<sup>th</sup> Period of HEALS**

The overall aim of this WP was to quantify the link between exposures to metals, pesticides and chemical compounds with endocrine disrupting activity and neurodevelopmental disorders, by applying the HEALS methodological framework, through both external and internal exposure assessment.

In the 4<sup>th</sup> period of the project the activity of WP15 mainly consisted in completion of activities as foreseen in Task 15.4 "Application of the HEALS methodology to population studies" and they were related to the following aim: Multi-level multi-exposure analyses to model the relative influence of internal and external exposures on neuropsychological outcome.

- Specific analyses have been performed to fill the data gaps and to describe the effect of the interaction between chemicals, other environmental stressors and the outcomes variables focusing on two European birth cohorts, namely REPRO\_PL and PHIME data set. Data harmonisation was completed to develop a model for application of the HEALS methodology to other HEALS data sets. WP15 then performed the integrated statistical analyses of PHIME Slovenia, Croatia and REPRO\_PL data sets to test the usefulness of the EWAS approach; in parallel, multi-platform SNPs, metabolomics and methylomic analyses was carried out and completed in either PHIME or Repro\_PL samples. Furthermore, we completed the assessment of omics biomarkers including metabolomics and SNPs in both REPRO-PL and PHIME available biological samples (cord blood, breast milk, saliva, hair and urine) deriving from mothers and /or children; DNA methylation in REPRO-PL samples.
- In addition, the HERACLES cohort samples and exposure data were analyzed in Greece focusing on the impact of waste management facilities on children's neurodevelopmental health. Similar sampling and analytical protocols as in PHIME and REPRO\_PL were followed in HERACLES with a sample size of n=300 children up to the age of 6. Metabolomics pathway analyses were associated with environmental and dietary exposures linked to residence in the proximity to the largest landfill in Greece (and the 2<sup>nd</sup> largest in Europe) on the one hand, and with results of neurodevelopmental test batteries.

All the generated datafiles are available in the HEALS server and platform.

### **Description of Work of WP15 for the 4<sup>th</sup> Period of HEALS**

**Task 15.4 Application of the HEALS methodology to population studies (ISS, SU, KCL, NIPH, SDU, OIKON ZELENA ,CSIC, URV, FERA, UM, NIOM, AUTH, LMU, USTUTT)**

Laboratory work to fill the data gaps:



- Speciation of Hg in the existing samples from the PHIME cohort (JSI).
- Analysis of urine for organophosphorous pesticide metabolites in the subjects from the PHIME cohort (CSIC).
- Analysis of the samples of REPRO\_PL (250 urine samples were analysed for 21 metabolites of 11 parent phthalates and BPA (LMU and in kind IPS (Institute for Prevention and Occupational Medicine of the German Social Accident Insurance)).
- Analysis of 968 samples of ASGM cohorts (LMU): Hg in blood, urine, hair (LMU) and genotype and (in kind Lund University). Analysis of the samples from REPRO\_PL (about 130) needed to increase sample size for the statistical assessments of the correlation between specific biochemical/omic parameters and neuropsychological outcome (mtDNA/nDNA ratio and total Anti Oxidant Capacity in cord blood) (ISS, AUTH).
- Metabolomics analysis of 175 urine and plasma pair samples of mother-child from PHIME cohort using NMR to increase the metabolites coverage including amino acids (AUTH).

#### Data analysis:

- Re-evaluation of the statistical models describing relationship between prenatal Hg exposure and neurodevelopment, including methyl Hg data and WISC scores, based on the published models, and stratified by the *ApoE* genotype.
- Evaluation of the mentioned relationship stratifying by other genotypes (*BDNF*, *PON1*, *CPOX*).
- Evaluation of distribution of exposure to OP pesticides in mother-child pairs from the PHIME cohort in collaboration with CSIC (Bravo and Grimalt). Evaluation of exposure to organophosphorous pesticides and its association with neurobehaviour (WISC scores).
- Preparation and harmonisation of the variables needed for the analyses related to the impact of exposure to air pollution, phthalate, heavy metals, micronutrients on child neurodevelopment at age of 1, 2 and 7 years (data from REPRO\_PL cohort).
- DNA methylation raw data from cord blood samples (REPRO\_PL) have been processed, quality control, quintile normalization and cell composition correction have been carried out using R software package. association with outcome in process.
- Harmonisation and re-analysis of data of three birth cohorts (Croatia, Slovenia and Poland) to assess consistency of environmental influences on neurodevelopment across European countries differing for geographical, socio-demographic characteristics and levels of chemical exposures to metals and trace elements.
- Analysis of data from REPRO\_PL including new results for phthalates, association with neuro-developmental and general health outcomes at age of 7 years (ISS, NIOM, LMU)
- Analysis of Hg and health data from ASGM cohorts (LMU) with genotype and SNP data (LU) to look for interaction between specific genotype, exposure and neurological performance.
- A comprehensive data processing approach that included the identification of metabolites, the analysis of metabolic pathways and the application of statistical methods and EWAS, to find the associations among the exposure to environmental stressors and its impacts on child neurodevelopment was applied on REPRO-PL dataset. Previously reported work included the results obtained from the urinary untargeted metabolomics, while during the last year the dataset was enhanced from



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the plasma untargeted metabolomics analysis result, and the new results from the phthalates analysis.

- A comprehensive bioinformatics analysis on metabolomics results coupled to pathway and EWAS analysis was applied also on the PHIME cohort samples. Environmental and social factors were considered while both Bayley Scales of Infant Development (BSID) III and WISC scores were used for neurodevelopment assessment.
- A comprehensive bioinformatics analysis on metabolomics results coupled to pathway and EWAS analysis was applied also on the HERACLES cohort samples. Environmental and social factors were considered while both Bayley Scales of Infant Development (BSID) III and WISC scores were used for neurodevelopment assessment similarly to the case of PHIME.

**The Deliverable 15.2 was postponed to M69 due to the delay in omics analyses.**

List of deliverables in WP15 for the 4<sup>th</sup> Period of HEALS

No.	Title/objective	Delivery Date	Achieved (Yes/No)	Significant results	Comments [ in progress, delayed..]	If applicable, propose corrective actions
D15.2		Postponed to 69			Submitted	

List of milestones in WP15 for the 4<sup>th</sup> Period of HEALS

Not applicable

Dissemination in WP15 for the 4<sup>th</sup> Period of HEALS

Dissemination in WP15 in the 4th period of HEALS

Publications	Title	Authors	In preparation/revision	Submitted (journal / date)	Published (journal / date)	Notes/ comments
	Prenatal mercury exposure and child neurodevelopment	Barbone F, Rosolen V, Mariuz M, Parpinel M, Casetta A,			<i>Int J Hyg Environ Health</i> 222 (2019) 9–21, <a href="https://doi.org/10.1016/j.ijheh">https://doi.org/10.1016/j.ijheh</a> .	



	outcomes at 18 months: results from the Mediterranean PHIME cohort.	Sammartano F, Ronfani L, Vecchi Brumatti L, Bin M, Castriotta L, Valent F, Little DL, Mazej D, Snoj Tratnik J, Miklavčič Višnjevec A, Sofianou K, Špirić Z, Krsnik M, Osredkar J, Neubauer D, Kodrič J, Stropnik S, Prpić I, Petrović O, Vlašić-Cicvarić I, Horvat M.				
	Urinary metabolites of organophosphate and pyrethroid pesticides in children from an Italian cohort (PHIME, Trieste).	Bravo N, Grimalt JO, Bocca B, Pino A, Bin M, Brumatti LV, Rosolen V, Barbone F, Ronfani L, Alimonti A, Calamandrei G			<i>Environ Res.</i> 2019 May 29; 176:108508.	
	Lead intoxicated children in Kabwe, Zambia	Bose-O'Reilly S, Yabe J, Makumba J, Schutzmeier P, Ericson B, Caravanos J			<i>Environ Res.</i> 2018;165:420-4.	



	Determinants of phthalate exposure and risk assessment in children from Poland.	Garí M, Koch HM, Pálmke C, Jankowska A, Wesołowska E, Hanke W, Nowak D, Bose-O'Reilly S, Polańska K.			<i>Environ Int.</i> 2019;127:742-753	
	Prenatal and early postnatal phthalate exposure and child neurodevelopment at age of 7 years - Polish Mother and Child Cohort –	Jankowska A, Polańska K, Hanke W, Wesołowska E, Ligocka D, Waszkowska M, Stańczak A, Tartaglione AM, Mirabella F, Chiarotti F, Garí M, Calamandrei G.			<i>Environ Res.</i> 2019 Aug 5;177:108626. doi: 10.1016/j.envres.2019.108626	
	Prenatal and postnatal exposure to air pollution and emotional and aggressive symptoms in children from 8 European birth cohorts	Jorcano A, Lubczyńska MJ, Pierotti L, Altug H, Ballester F, Cesaroni G, Marroun HEL, Fernández-Somoano A. Freire C, Hanke W, Hoek G, Ibarluzea J,			<i>Environment Int</i> 2019; 131:1-10	



		liguez I, Jansen PW, Lepeule J, Markevych I, Polańska K, Porta D, Schikowski T, Slama R, Standl M, Tardon A, Vrijkotte TGM, von Berg A, Tiemeier H, Sunyer J, Guxens M				
	Polymorphisms in potential mercury transporter ABCC2 and neurotoxic symptoms in populations exposed to mercury vapor from goldmining	Kolbinger V, Engstrom K, Berger U, Bose-O'Reilly S.			Environ Res. 2019;176:108512.	
	Prenatal selenium status, neonatal cerebellum measures and child neurodevelopment at the age of 18 months.	Močeni I, Kolić I, Radić Nišević J, Belančić A, Snoj Tratnik J, Mazej D, Falnoga I, Vlašić- Cicvarić I, Štimac T, Špirić Z,			<i>Environ Res.</i> , ISSN 0013-9351, 2019, vol. 176, str. 108529-2-108529-5, doi: <a href="https://doi.org/10.1016/j.envres.2019.108529">10.1016/j.envres.2019.108529</a>	





		Horvat M, Prpić I.				
	Sex-Dependent Impact of Low-Level Lead Exposure during Prenatal Period on Child Psychomot or Functions.	Polanska K, Hanke W, Pawlas N, Wesolowska E, Jankowska A, Jagodic M, Mazej D, Dominowska J, Grzesiak M, Mirabella F, Chiarotti F, Calamandrei			<i>Int. J. Environ. Res. Public Health.</i> <u>2018;15:2263</u>	
	Arsenic metabolites; selenium; and AS3MT, MTHFR, AQP4, AQP9, SELENOP, INMT, and MT2A polymorphisms in Croatian-Slovenian population from PHIME-CROME study	Stajanko A, Šlejkovec Z, Mazej D, France-Štiglic A, Briški AS, Prpić I, Špirić Z, Horvat M, Falnoga I.			<i>Environ Res.</i> 2019 Mar;170:301-319. doi: 10.1016/j.envres.2018.11.045.	
	Sociodemographic, Lifestyle, Environmental and Pregnancy-Related Determinants of	Wesołowska E, Jankowska A, Trafalska E, Kałużny P, Grzesiak M, Dominowska			<i>Int J Environ Res Public Health.</i> 2019 Mar 2;16(5). pii: E754. doi: 10.3390/ijerph16050754	



	Dietary Patterns during Pregnancy.	J, Hanke W, <b>Calamandre i G</b> , Polańska K				
	Mercury speciation in prenatal exposure in Slovenian and Croatian population – PHIME study.	Trdin, A, Snoj Tratnik, J, Mazej, D, Fajon, V, Krsnik, M, Osredkar, J, Prpić, I, Špirić, Z, Petrović, O, Marc, J, Neubauer, D, Kodrič, J, Kobal, A.B, Barbone, F, Falnoga, I, Horvat, M.			Submission in process in <i>Environmental Res.</i>	
	Combined prenatal exposure to mercury and LCPUFA on newborn's brain measures and neurodevelopment at the age of 18 months.	Radić Nišević J, Prpić I, Kolić I, Baždarić K, Snoj Tratnik J, Škarpa Prpić I, Mazej D, Špirić Z, Barbone F, Horvat M			Submission in process in <i>Environmental Res.</i>	
	Pregnancy exposome and child psychomotor development in	Calamandrei G, Ricceri L, Meccia E, Tartaglione AM, Horvat M, Tratnik J,			Submission in process in <i>Environmental Res.</i>	



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	three European birth cohorts.	Mazej D, Špirić Z, Prpić I, Vlašić-Cicvarić I, Neubauer D, Kodrič J, Stropnik S, Janasik B, Kuras R, Mirabella F, Polanska K, Chiarotti F.				
	Neurodevelopmental exposome : the effect of in utero co-exposure to heavy metals and phthalates on child neurodevelopment.	Sarigiannis DA, Papaioannou N, Handakas E, Anesti O, Polanska K, Hanke W, Salifoglou A, Gabrie C, Karakitsios S.			Submission in process in <i>Environmental Res.</i>	
	Phthalate exposure and neurodevelopmental outcomes in early school age children from Poland.	Jankowska A, Polańska K, Koch HM, Pälmeke C, Waszkowska M, Stańczak A, Wesolowska E, Hanke W, Bose O'Reilly S, Calamandrei G, Garí M.			Submission in process in <i>Environmental Res.</i>	



8	Developmental neurotoxicity of endocrine disruptor chemicals: a challenge for behavioral toxicology	G. Calamandrei and L. Ricceri			Advances in Neurotoxicology, 2018	
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**Presentations**

Title	Authors	Conference, meeting, workshop (name/ date / place)	Notes/comments
Prenatal Methyl Mercury exposure	Trdin, Ajda, Falnoga, Ingrid, Snoj Tratnik, Janja Fajon, Vesna, Mazej, Darja, Osredkar, Joško, Prpić, Igor, Špirić, Zdravko, Horvat, Milena	<i>Prenatal Programming and Toxicity, PPTOX VI: programme and abstract book: Tórshavn, Faroe Islands, May 27-30, 2018</i>	
Low-level mercury exposure, neurodevelopment and the role of genetic polymorphisms: evidence from Slovenian and Croatian birth cohorts.	Snoj Tratnik, Janja, Falnoga, Ingrid, Trdin, Ajda, Mazej, Darja, Prpić, Igor, Špirić, Zdravko, Horvat, Milena	<i>Prenatal Programming and Toxicity, PPTOX VI: programme and abstract book: Tórshavn, Faroe Islands, May 27-30, 2018</i>	
Exposure to mercury during prenatal period	Trdin, Ajda, Snoj Tratnik, Janja, Prpić, Igor, Spirić, Zdravko, Falnoga, Ingrid, Horvat, Milena	<i>Programme and book of abstracts, 1st ISO-FOOD International Symposium on Isotopic and Other Techniques in Food Safety and Quality, Portorož, Slovenia, April 1-3, 2019</i>	



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<p><i>Prisotnost kemikalij v vsakdanjem življenju</i> (eng. Presence of chemicals in the everyday life)</p>	<p>Horvat, Milena</p>	<p>Science on the Street, 14 June 2019, Ljubljana, Slovenia.</p>	<p>Presentation given to the general public</p>
<p>Exposure to metals in susceptible population groups and its role in neurodegeneration</p>	<p>Snoj Tratnik, Janja, Mazej, Darja, Falnoga, Ingrid, Horvat, Milena</p>	<p>Conference of the Hellenic Academy of Neuroimmunology, presentation given within the section "Environmental factors of Neurodegeneration", June 23, 2019, Thessaloniki, Greece</p>	
<p>Impact of micronutrients during pregnancy on children's health and neurodevelopment</p>	<p><a href="#">Hanke W.</a>, <a href="#">Polanska K.</a>, <a href="#">Gromadzinska J.</a>, <a href="#">Kuras R.</a>, <a href="#">Janasik B.</a>, <a href="#">Wasowicz W.</a>, <a href="#">Stelmach,</a> <a href="#">Grzelewski T.</a>, <a href="#">Bobrowska-Korzeniowska M.</a>, <a href="#">Kopka M.</a>, <a href="#">Majak P.</a>, <a href="#">Jerzynska J.</a>, <a href="#">Stelmach W.</a>, <a href="#">Mirabella F.</a>, <a href="#">Chiarotti F.</a>, <a href="#">Calamandrei G.</a></p>	<p>Poster at Prenatal Programming and Toxicity (PPTOX) VI conference. Faroe, May 2018</p>	
<p>Impact of micronutrients during pregnancy on children's health and neurodevelopment</p>	<p><a href="#">Polanska K.</a>, <a href="#">Hanke W.</a>, <a href="#">Gromadzinska J.</a>, <a href="#">Kuras R.</a>, <a href="#">Janasik B.</a>, <a href="#">Wasowicz W.</a>, <a href="#">Stelmach I.</a>, <a href="#">Grzelewski T.</a>, <a href="#">Bobrowska-Korzeniowska M.</a>, <a href="#">Kopka M.</a>, <a href="#">Majak P.</a>, <a href="#">Jerzynska J.</a>, <a href="#">Stelmach W.</a></p>	<p>Poster at The 9<sup>th</sup> International Conference on Children's Health and the Environment: <i>Saving the Children at Risk, Shaping the Future Sustainability.</i> June 2018, South Korea</p>	



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	<a href="#">Mirabella F</a> , <a href="#">Chiarotti F</a> , <a href="#">Calamandrei G</a> .		
	Calamandrei G.	Invited oral presentation within the HEALS Session "Solutions for tackling the link between complex exposures and human health"  International Society for Environmental Epidemiology, Ottawa, Canada, August 26-31 2018	
Health effects of mercury poisoning among miners and families in ASGM	Bose O'Reilly S.	Lecture International Congress on Occupational Health - ICOH 2018; 30th of April 2018; Dublin, Ireland	
Pollutants hinder the development of children [Schadstoffe behindern die Entwicklung von Kindern].	Bose O'Reilly S.	Invited key lecture. Pediatrician Day; Professional Association of Paediatricians e.V.[ BVKJ]; 16th of June 2019; Berlin: Germany	
Extreme weather events and their impact on mental health of children and adolescents. Advance module: Climate change & health: a case for transformation	Bose O'Reilly S.	Invited lecture. 9 <sup>th</sup> of May 2019: Center of International health, Munich, Germany	
Concentrations of Phthalate Metabolites in Children from Poland	Polanska K, Garí M, Hanke W, Koch HM, Pálmke CC, Bose-O'Reilly S.	Lecture. 9th International Conference on Children's Health and the Environment; 27th of June 2018; Seoul / Korea	



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Concentrations of Phthalate Metabolites in Children from Poland (poster)	Polanska K, Garí M, Hanke W, Koch, Holger M. , Pälmeke C, Bose-O'Reilly S.	Poster. ISES - ISEE joint annual meeting - International Society for Environmental Epidemiology; 28th of August 2018; Ottawa, Canada2018.	
Extreme weather events and mental health	Bose-O`Reilly S, Mertes H	Lecture. VAO Symposium 2018; 14th of March 2018; Grenoble, France: Bavarian State Ministry of the Environment and Consumer Protection.	

<b>Meetings organized with stakeholders</b>				
<b>Name</b>	<b>Organizer</b>	<b>Heals participants (name / partners)</b>	<b>Date / Place</b>	<b>Comments</b>
Open day at JSI	Jozef Stefan Institute (JSI)	Anja Stajniko, Ajda Trdin, Janja Snoj Tratnik, Milena Horvat (JSI)	March 24, 2018, Ljubljana, Slovenia	HEALS poster displayed
Meeting of the national research project on interpretation of HBM results	Jozef Stefan Institute (JSI)	Janja Snoj Tratnik, Darja Mazej, Ingrid Falnoga, Milena Horvat	June 6, 2018, Ljubljana, Slovenia	HEALS study was presented to the project partners
Meeting of the national research project NEURODYS	Jozef Stefan Institute (JSI)	Janja Snoj Tratnik, Anja, Stajniko, Darja Mazej, Ingrid Falnoga, Milena Horvat	September 3, 2018, Ljubljana, Slovenia	Results arising from the HEALS were presented to the project partners as a basis to derive study hypothesis for the national exposome study



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## Work package 16 [WP-leader: SU]

### Obesity and childhood diabetes – link with endocrine disruptors

#### Report for the 4<sup>th</sup> Period of HEALS

<b>Work Package Number</b>	16		<b>Start date – End date</b>				M 1 – M60				
<b>Work Package Title</b>	Obesity and childhood diabetes - link with endocrine disruptors										
<b>Activity Type</b>	RTD										
<b>Participant Number and Short Name</b>	1 SU	5 JSI	6 UPD	15 CSIC	33 OIKON ZELENA	21 FMUP	22 NCSR	26 KCL	27 NIPH	28 SDU	
<b>Person-months</b> (this reporting period / total planned)	7.53/15	1.20/6	7/16	6/15	6/3	8/11	9/9	0/2	3/1	0/3	
<b>Explanation of deviations between actual and planned person-months per work package and per beneficiary</b>	n.a.	n.a.	n.a.	n.a.	More work in WP16 but low cost	n.a.	n.a.	n.a.	More work in WP16 but low cost	n.a.	





### **Objectives of WP16 for the 4<sup>th</sup> Period**

The main general objective of WP16 in the 4<sup>th</sup> period was to pursue in the comprehension of the relationships between endocrine disruptors (ED) and obesity/diabetes and metabolic diseases in childhood by exploring the impact of exposome on adiposity, overweight, obesity and diabetes through an environment-wide approach study (EWAS) including ED. To this extent, the specific objectives are:

- To finalize the database using data from the various pre-existing studies of singletons and twins that may contribute to the investigation of the relationship between endocrine disruptors (ED) and overweight, obesity and diabetes taking into account an exposomic approach through EWAS, namely by providing data on overweight, obesity and diabetes on one side and endocrine disruptors and other stressors on other side.
- To start the statistical analyses and in particular EWAS on the harmonized and centralized HEALS database
- As preliminary examples, an EWAS approach was applied to variation in birthweight in 27000 European singletons.

### **Summary of progress of WP16 for the 4<sup>th</sup> Period**

The following intermediate steps to attain the main objective of WP16 have been accomplished:

- 1) The implementation of the HEALS dataset of pre-existing studies of singletons and twins for a total of almost 50000 individuals living in Europe. The sample size is expected to rise as some additional studies are going to contribute but have been stopped temporarily due to the lack of the authorization to provide individual geolocalisation.
- Collaboration with WP14 and WP15 to collect the pre-existing available data from general population samples and twin registries and studies respectively.
    - Implementation of the documents and forms needed to obtain data from the pre-existing available data of singletons and twins from the HEALS partners in a standardized format as well as the official authorization to use them.
    - Databases' collection
    - Unique dataset
  - Harmonization and standardisation of the HEALS dataset collecting the totality of pre-existing datasets
  - Identification of methods for imputation of missing data
  - Identification of statistical analyses in view of the EWAS approach.



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- 2) Two papers based on the relationship between endocrine disruptors (EDs) and markers of overweight, obesity and diabetes of interest in the exposome approach were submitted to Environmental Research that is going to publish a special issue in which HEALS results will be presents.
- 3) One paper based on the relationship of exposome to overweight, obesity overview of cohorts/studies relating adverse health outcomes related to overweight, obesity

One deliverable was expected in this 4<sup>th</sup> period of the project. This is D16.2 Report on exposome results and of the environment-wide approach regarding assessment of the environmental determinants, overweight, obesity overview of cohorts/studies relating adverse health outcomes related to overweight, obesity that is due in M60. A paper to be submitted in a peer-reviewed journal is presently under work.

The scheduled milestone on completion of internal exposure assessment (methodological report) (MS27) is ongoing.

The partners are working to respect the forthcoming deadlines.

#### **Description of Work of WP16 for the 4<sup>th</sup> Period of HEALS**

Establishment of the links between exposome and overweight, obesity and diabetes by applying the HEALS methodology.

##### **Problems encountered:**

A real problem still exists to obtain the geolocalisation of the personal address of the individuals. Of note, in some countries this is because the legislation has changed (see Spain) and that because of privacy. However, special authorizations are looked for. In addition, the target of almost 5000 individuals for whom spatio-time-related and cumulative environmental exposures (air, soil, water, food) to endocrine disruptors based on personal address was reached and it will be employed in EWAS of metabolic disorders that are ongoing.

##### **Forthcoming work:**

The forthcoming objectives include:

1. Complete geolocalisation of individuals
2. Performing further statistical analyses pertaining to WP 14 to WP16. The focus of these analyses is asthma and allergies, metabolic and neurodegenerative disorders caused by exposure to several environmental stressors. The data obtained from the birth-cohorts especially emphasizes on the risk factors for environmental exposure



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in case of mother (or both parents) and their consequent effect on the metabolic and allergic diseases as well as neuro-developmental conditions in their offspring.

3. Performing statistical analyses in the case of twins, which implies the application of methods for non-independent data.
4. Linking with “omics” results (Stream 4 and Task 16.2)
5. Sending of all the collected databases to the WP12 in order to be used for the implementation of the HEALS GeoDatabase platform, which will systematically support the collection of and the access to all the datasets for HEALS environment-wide association studies.

*If applicable, explain the reasons of any deviation from the DoW (description of work) and the impact on the other tasks, on available resources and planning/ If applicable, explain the reasons for failing to achieve critical objectives and/or not being on schedule and the impact on other tasks as well as on available resources and planning /If applicable, propose corrective actions:*

No deviation from the DoW in this task apart the lack of geolocalisation of the individuals' addresses in some studies. **However, there are at least 5000 individuals for whom there exists geocoding of the addresses.**

**List of deliverables in WP16 for the 4<sup>th</sup> Period**

**List of deliverables in WP15 for the 4<sup>th</sup> Period of HEALS**

No.	Title/objective	Delivery Date	Achieved (Yes/No)	Significant results	Comments [ in progress, delayed..]	If applicable, propose corrective actions
D16.2	Report on exposome results and of the environment-wide approach regarding assessment of the environmental determinants overweight, obesity and diabetes			First EWAS for metabolic disorders in European citizens	Submitted	

**List of milestones in WP16 for the 4<sup>th</sup> Period**

Not applicable



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No.	Title/objective	Delivery Date	Achieved (Yes/No)	Significant results	Comments [ in progress, delayed..]	<u>If applicable,</u> propose <b>corrective actions.</b>

### Dissemination in WP16 for the 4<sup>th</sup> Period

<b>Publications</b>						
	Title	Authors	In preparation /revision	Submitted (journal / date)	Published (journal / date)	Notes/ comments
1	MATERNAL SMOKING DURING PREGNANCY AND BIRTH-WEIGHT IN EUROPEAN COHORTS: THE HEALS PROJECT	S. Sanyal, S. Baldacci, H. Barros, M. Horvat, W. Hanke, S. Maio, D. Mazej, K. Polanska, O. Petrovic, I. Prpic, E. Ramos, Z. Spiric, J.S. Tratnik, G. Viegi, I. Annesi-Maesano	In preparation	To be submitted to <a href="#">Int J Environ Res Public Health</a>		
2	APPLYING ENVIRONMENT-WIDE APPROACH TO OVERWEIGHT, OBESITY AND DIABETES IN SINGLETONS	S. Sanyal, S. Baldacci, H. Barros, M. Horvat, W. Hanke, S. Maio, D. Mazej, K. Polanska, O. Petrovic, I. Prpic, E. Ramos, Z. Spiric, J.S.	In preparation	To be submitted to Diabetes		



		Tratnik, G. Viegi, I. Annesi- Maesano				
3	Endocrine disruptors (EDs) and adiposity as a marker of overweight, obesity and diabetes of interest in the exposome approach. Review	E. Ramos, Martine Aggerbeck, E. Diste, R. Barouki, I. Annesi-Maesano	In preparation	Accepted by Environmental Research to which URV has asked to publish a special issue in which HEALS results will be presents		
	Maternal urinary phthalate concentrations after conception related to pregnancy induced hypertension	Soomro MH, Baiz N, Heude B, Bornehag CG, Annesi-Maesano I.	Submitted	J Environ Res Public Health		
	Exposure to heavy metals during pregnancy related to gestational diabetes mellitus in diabetes-free mothers.	Soomro MH, Baiz N, Huel G, Yazbeck C, Botton J, Heude B, Bornehag CG, Annesi-Maesano I.	Published	Sci Total Environ. 2019 Mar 15;656:870-876.		
	Association between the exposure to phthalates and adiposity: a meta-analysis in children and adults	Claudia Ribeiro; Vânia Mendes; Peleteiro Bárbara; Inês Delgado; Joana Araújo; Martine Aggerbeck; Isabella	Accepted		Env Res	



		Annesi-Maesano; Denis Sarigiannis; Elisabete Ramos				
	The association between environmental exposures to chlordanes, adiposity and diabetes-related features: a systematic review and metaanalysis	Vania Mendes; Claudia Ribeiro; Inês Delgado; Bábara Peleteiro; Martine Aggerbeck; Emilie Distel; Isabella Annesi-Maesano; Denis Sarigiannis; Elisabete Ramos	Submitted	Diabetes		
<b>Presentations</b>						
	<b>Title</b>	<b>Authors</b>	<b>Conference, meeting, workshop (name/ date / place)</b>	<b>Notes/ comments</b>		
3	THE ENVIRONMENT-WIDE APPROACH FOR THE ASSESSMENT OF THE EFFECT OF ENVIRONMENTAL STRESSORS ON OVERWEIGHT,	Shreosi Sanyal, Joan O. Grimalt, Milena Horvat, Edward D. Johnstone, Sara Maio,	ISES-ISEE 2018			



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	OBESITY AND DIABETES: A STUDY ON SINGLETONS FOR THE HEALS PROJECT	Kinga Polanska, Elisabete Ramos, Zdravko Spiric, Giovanni Viegi, Dimosthenis A. Sarigiannis, Isabella Annesi-Maesano				
5						
<b>Meetings organized with stakeholders</b>						
	<b>Name</b>	<b>Organizer</b>	<b>Heals participants (name / partners)</b>	<b>Date / Place</b>	<b>Notes/ comments</b>	



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## Work package 17 [WP-leader: UPMC]

### Pilot European Exposure and Health Examination Survey (EXHES)

#### Report for the 4<sup>th</sup> Period of HEALS

<b>Work Package Number</b>	17		<b>Start date - End date</b>				M 1 – M68	
<b>Work Package Title</b>	Pilot European Exposure and Health Examination Survey (EXHES)							
<b>Activity Type</b>	RTD							
Participant Number and Short Name	1 SU	2 AUTH	3 IOM	4 USTUTT	5 JSI	12 UM	31 INEGI	
<b>Person-months</b> ( <u>this</u> reporting period / total planned)	6.84/20	X/10	X/3	x/6	x/50	x/34	x/9	
Explanation of deviations between actual and planned person-months per work package and per beneficiary	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	
Participant Number and Short Name	33 OIKON ZELENA	20 CNR	21 FMUP	26 NCSR	27 UKR	28 KCL	8 ISS	
<b>Person-months</b> ( <u>this</u> reporting period / total planned)	X/26	x/36	x/54	x/46	x/21	x/18.5	x/6	
Explanation of deviations between actual and planned person-months per work package and per beneficiary	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	





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Participant Number and Short Name	10 NIOM	9 LMU					
<b>Person-months</b> ( <u>this</u> reporting period / total planned)	x/38	x/7					
Explanation of deviations between actual and planned person-months per work package and per beneficiary	n.a.	n.a.					

### Objectives of WP17 for the 4<sup>th</sup> Period of HEALS

The overall aim of WP17 during the 4<sup>th</sup> Period of HEALS is to conclude the HEALS pilot European Exposure and Health Examination Survey (EXHES) in 10 countries so to provide relevant harmonized and standardized data to unravel the relationship between body burden from internal and external exposure and the onset/exacerbation of the HEALS health outcomes (i.e. asthma and allergies, neurological disorders, overweight, obesity and diabetes in childhood). Relevant means that we take advantage of the various information system obtained using pre-existing data to be more performant in the conduction of the EWAS approach.

### Summary of progress of WP17 for the 4<sup>th</sup> Period of HEALS

EXHES had started in all the 10 centers of EXHES. Recrutement in the other centres has progressed well. Only 1 center could not start because of legal issues (se below).

The pilot European Exposure and Health Examination Survey (EXHES) constitutes one of the milestones of the HEALS project. It is at the origin of relevant harmonized and standardized data to unravel the relationship between body burden from internal and external exposure and the onset/exacerbation of the health outcomes targeted by HEALS, i.e. asthma and allergies, neurological disorders, overweight, obesity and diabetes in childhood. Overall, 4,888 families have joined the EXHES mother-child birth cohort by June 2019. As a whole, 5,169 children were included, which comprises 836 twins and 21 triplets. A wide variety of biological material was collected according to standardized sampling procedures in children as well as in their parents. In total, the EXHES biobank included 13,988 different biospecimens collected from the newborns, plus 7,185 and 870 biospecimens collected from their mothers and fathers, respectively.



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Children are followed.

## Description of Work of WP17 for the 4<sup>th</sup> Period of HEALS

### Field surveys:

The EXHES population is composed as follows:

**Table 1:** Number of parents and births recruited in the HEALS/EXHES cohort by Country.

	Croatia	France	Germany	Greece	Italy	Poland	Portugal	Slovenia	Spain	UK	Total
<b>Recruitment</b>											
Families	289	328	2492	*	92	390	759	12	179	31	<b>4856</b>
Mothers	289	328	2492	32	92	390	719	12	179	31	<b>4816</b>
Fathers	0	180	1486	*	92	296	95	-	0	-	<b>2149</b>
Total births	289	370	2492	38	12	407	981	11	148	31	<b>5131</b>
<i>Singletons</i>	277	286	2330	30	64	390	485	7	142	5	<b>4296</b>
<i>Twins/Triples</i>	12	84	162	8	56	17	496	4	6	0	<b>837</b>

\*data from Greece haven't been centralized yet.

Children are presently followed.

**Of note: WP5 is greatly contributing to WP17 already in its initial phase.** Beside the analysis on existing cohort samples, in early 2018, it is important to mention that WP5 also succeeded in performing the first LC-MS/MS metabolome analysis on the HEALS EXHES study. AUTH received from URV 154 urine samples, from pregnant women acquired during the three different semesters (S) of the pregnancy: 52 from S1; 53 from S2; 49 from S3. FERA received the first EXHES serum samples from URV: 36 from S1, 33 during delivery and 37 serum samples from child cord blood and has performed LC-MS/MS. Also, AUTH has received (Feb 2018) and analysed 600 urine samples from neonates from the German EXHES (partner UKR). Data acquisition, pre-processing, spectral analysis and pathway analysis is ongoing for UKR and URV samples. Lastly, AUTH has received blood from French EXHES.

**The first results are shown in the deliverable D17.3.**



### **Task 17.3: EXHES Phase II (M12 – M40; SU, AUTH, USTUTT, UM, INEGI, OIKON ZELENA , CNR, FMUP, NCSR, UKR, KCL)**

**Aim:** The aim of this task is to conduct EXHES Phase II according to the established protocol.

#### ***Details of progress and main results:***

- The EXHES PHASE II protocol is completed only in part but will be finalized later so to include almost 2000 individuals.

It contains tools for conducting:

#### **- Omics analyses:**

In close connection with Stream 2 partners, protocols for omics analyses have been elaborated. Analyses will include metabolomics, adductomics, transcriptomics and confirmatory proteomics analyses following the workflow defined in WP5. These samples will be analysed for epigenetic effects of environmental exposures and for genetic variability through SNP profiling.

Concerning the EXHES study, samples were derived from different partners. More specific from the partner URV, AUTH partner received 154 urine samples, coming from pregnant women from the three different semesters of the pregnancy. 52 urine samples from the first semester, 53 urine samples from the second semester and 49 urine samples from the third semester. The samples arrived at AUTH partner in February of 2018 stored immediately at -80 o C and analysed in both positive and negative mode by LC-MS in March of the same year. All the samples had the same volume of the 2ml, and the rest of the samples was storage back to 80 o C for further analysis. FERA partner received from the partner URV, the serum samples respectively. 36 serum samples from the first semester of the pregnancy, 33 serum samples from the delivery and 37 serum samples from cord. The samples arrived at FERA partner in January of 2018 stored immediately at -80 o C and analysed in both positive and negative mode by LC-MS in February of the same year. All the samples had the same volume of the 1 ml, and the rest of the samples was storage back to 80 o C for further analysis. The next step is the downstream bioinformatics analysis, following pathway mapping using the GeneSpring Pathway Architect.

From the partner UKR, AUTH partner received in February of 2018, 600 urine samples from neonates. At the end of March, AUTH partner started the LC-MS analysis of these samples, in both positive and negative mode, and the analysis is still ongoing. Data pre-processing, spectral analysis and pathway analysis from both partners AUTH and FERA for the results of EXHES study are ongoing.

#### **- Ubiquitous exposomic analysis:**

In connection with Stream 3, personal and mobile sensors have been reviewed in order to prepare protocols for external exposure assessment. These sensors will be given to the



mother of the children in this sub-sample to geolocalise the child's position and assess child's exposures during lifespan following the methodology and workflow design developed and optimised in WP9.

**- Indoor air quality assessments:**

To be performed through a detailed checklist and objective assessments of major air pollutants and comfort parameters as prepared by partner 18.

*If applicable, explain the reasons of any deviation from the Dow (description of work) and the impact on the other tasks, on available resources and planning:*

*If applicable, explain the reasons for failing to achieve critical objectives and/or not being on schedule and the impact on other tasks as well as on available resources and planning:*

Not applicable.

*If applicable, propose corrective actions:*

Not applicable.

This task has not started yet due to the delay in the collection of data.

**Task 17.4: Application of the HEALS methodology to EXHES (SU, AUTH, USTUTT, UM, INEGI, OIKON ZELENA , CNR, FMUP, NCSR, UKR, KCL)**

**Aim:** The aim of this task is to perform environment-wide associations studies (EWAS), by combining health, omics and environment data from EXHES PHASE I and PHASE II, so to apply the HEALS approach to perform EWAS studies with adverse health outcomes as defined in WP13. The new data are compared to existing data from both general population studies and pre-existing twin studies and stored for further management in the HEALS database developed in WP12.

***Details of progress and main results:***

This task was conducted with the Spanish EXHES. It is ongoing with the other dataset.

*If applicable, explain the reasons of any deviation from the Dow (description of work) and the impact on the other tasks, on available resources and planning:*

No deviation to report.

*If applicable, explain the reasons for failing to achieve critical objectives and/or not being on schedule and the impact on other tasks as well as on available resources and planning:*

Not applicable.



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If applicable, propose corrective actions:

Not applicable.

**Forthcoming work:**

The forthcoming objectives include:

- . Complete EXHES follow-up.
- . Assess respiratory, overweight and neurodevelopmental troubles in early life.
- . Implement EWAS in the case of HEALS health outcome by combining health, omics and environment data from EXHES PHASE I and PHASE II
- . Perform statistical analyses in the case of twins, which implies the application of methods for non-independent data
- . Compare the new EXHES data to existing data from both general population studies and pre-existing twin studies and stored for further management in the HEALS database developed in WP12.

**List of deliverables in WP17 for the 4th Period of HEALS**

No.	Title/objective	Delivery Date	Achieved (Yes/No)	Significant results	Comments [ in progress, delayed..]	<u>If applicable</u> , propose <b>corrective actions</b>
D17.2	Report on the implementation of EXHES with recruitment and follow-up of, singletons, twins and parents	Postponed to 69			Submitted	
D17.3	Report on the application of the HEALS environment-wide association approach to EXHES data	Postponed to 69			Submitted	

**List of milestones in WP17 for the 4th Period of HEALS**

No.	Title/objective	Delivery Date	Achieved (Yes/No)	Significant results	Comments [ in progress, delayed..]	<u>If applicable</u> , propose
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						<b>corrective actions.</b>
MS28	Completion of external exposure assessment	68	no	Technical report	In progress	
MS29	Completion of internal exposure assessment	68	no	Technical report, scientific papers	In progress	
M30	Completion of EXHES (Twin and singleton Follow-up Study) on use of biomarkers and -omics technologie	68				

#### Dissemination in WP17 for the 4th Period of HEALS

<b>Publications</b>	<b>Title</b>	<b>Authors</b>	<b>In preparation/revision</b>	<b>Submitted (journal / date)</b>	<b>Published (journal / date)</b>	<b>Notes/ comments</b>
<b>Presentations</b>	<b>Title</b>	<b>Authors</b>	<b>Conference, meeting, workshop (name/</b>	<b>Notes/comments. HEALS attendees</b>		



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			date / place)			
<b>Meetings organized with stakeholders</b>	<b>Name</b>	<b>Organizer</b>	<b>Heals participants (name / partners)</b>	<b>Date / Place</b>	<b>Notes/comments</b>	



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## Work package 18 [WP-leader: LMU]

### Training on HEALS methodology and tools

Report for the 4th Period **from 1/04/2018 (M55) to 30/06/2019 (M69)** of HEALS

<b>Work Package Number</b>	18		<b>Start date - End date</b>				M 1 – M68	
<b>Work Package Title</b>	Training on HEALS methodology and tools							
<b>Activity Type</b>	RTD							
<b>Participant Number and Short Name</b>	2 AUTH	3 IOM	5 JSI	9 LMU	10 NIOM	14 FERA	16 UOWM	
<b>Person-months</b> ( <b>this</b> reporting period / <b>total</b> planned)	0/1	xx/4	xx/3	2/14	xx/6	xx/1	xx/2	
<b>Participant Number and Short Name</b>	18 IMEC- FEUP	19 Zelena						
<b>Person-months</b> ( <b>this</b> reporting period / <b>total</b> planned)		3/3						
Explanation of deviations between actual and planned person-months per work package and per beneficiary								

### Objectives of WP18 for the 4th Period **from 1/04/2018 (M55) to 30/06/2019 (M69)** of HEALS

<p>Objectives for the 4<sup>th</sup> period</p> <p>Annual meeting in October 2018 in Thessaloniki / Greece at AUTH</p> <p>Final conference in June 2019 in Paris / France at UPMC and stakeholder meeting in June 2019 in Brussels / Belgium</p>
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Task 18.4 (Development of learning material for Universities and programmes for young scientists (AUTH, UOWM, LMU,ZELENA )

Deliverable D18.4 (Learning material for academic curricula)

### **Summary of progress of WP18 for the 4th Period from 1/04/2018 (M55) to 30/06/2019 (M69) of HEALS**

The overall aim of this WP18 was mostly achieved. The annual meeting for 2018 took place in Thessaloniki in February 2019 and was successful. The final conference 2019 in Paris took place and was successful. The stakeholder conference is still pending. Task 18.4 and deliverable 18.4. were finalized

### **Description of Work of WP18 Report for the 4th Period from 1/04/2018 (M55) to 30/06/2019 (M69) of HEALS**

- The 5<sup>th</sup> annual meeting took place in Thessaloniki on the 13<sup>th</sup> and 14<sup>th</sup> of February 2019. The meeting was titled "EXPOSOME: Advances so far". In the meeting, the Stream Leaders and the Work Package leaders reported what has been done so far, while the next steps were explicitly discussed in order to define "*who does what and who sent what to whom*" for the completion of the more synthetic deliverables of the last months of the project. Various topics regarding data transfer and processing under recent GDPR rules were also discussed. Overall the meeting was well organized.
- The final conference 2019 took place in Paris on the 20<sup>th</sup> of June 2019. It was well organized. The progress being made was presented and discussed.
- Stakeholder conference as described in the DOW is still pending
- Task 18.4 and deliverable 18.4. were finalized . The academic training materials are available on the [www.heals-eu.eu](http://www.heals-eu.eu) website for the interested public audience.
- This deliverable includes educational modules to be developed based on the HEALS techniques, methodology, computational tools and results. These were designed so as to fit within academic curricula in EU Member States and/or be part of international graduate study programs (M.Sc. or PhD).
- NIOM team also cooperating with the existing cohorts like GenerationR, EDEN, ALSPAC and the team involved in LifeCycle project (H2020).
- The moodle website for internal exchange and training was regularly updated with training and educational material from HEALS
- Across all project 27 master or degree students were trained in concept of HEALS project and successfully defended their thesis or end degree projects in their respective universities. In addition 17 PhD students were conducted their research in the framework of HEALS project.
- During the 4th reporting period the UOWM team has performed a training course for the students of the Department of Environmental Engineering and the Department



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of Mechanical Engineering of the University of Western Macedonia. During the course the HEALS Environmental Data Management System (EDMS) was presented to the students, along with information on how to use the provided tools. Also post-processing tools on how to use the EDMS data, were presented to the students

**List of deliverables in WP18 for the 4th Period from 1/04/2018 (M55) to 30/06/2019 (M69) of HEALS**

No.	Title/objective	Delivery Date	Achieved (Yes/No)	Significant results	Comments [ in progress, delayed..]	If applicable, propose corrective actions
D18.4	Learning material for academic curricula	56	Yes	Finalized		

**List of milestones in WP18 for the 4th Period from 1/04/2018 (M55) to 30/06/2019 (M69) of HEALS**

Not applicable

No.	Title/objective	Delivery Date	Achieved (Yes/No)	Significant results	Comments [ in progress, delayed..]	If applicable, propose corrective actions.



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**Dissemination in WP18 for the 4th Period from 1/04/2018 (M55) to 30/06/2019 (M69) of HEALS**

<b>Publications</b>	<b>Title</b>	<b>Authors</b>	<b>In preparation/revision</b>	<b>Submitted (journal / date)</b>	<b>Published (journal / date)</b>	<b>Notes/ comments</b>
	Arsenic metabolites; selenium; and AS3MT, MTHFR, AQP4, AQP9, SELENOP, INMT, and MT2A polymorphisms in Croatian-Slovenian population from PHIME - CROME study	Stajanko, Anja; Šlejkovec, Zdenka; Mazej, Darja; France-Štiglic, Alenka; Sešek Briški, Alenka; Prpić, Igor; Špirić, Zdravko; Horvat, Milena; Falnoga, Ingrid			Environmental Research, Volume 170, March 2019, Pages 301-319 <a href="https://doi.org/10.1016/j.envres.2018.11.045">https://doi.org/10.1016/j.envres.2018.11.045</a>	
	Prenatal selenium status, neonatal cerebellum measures and child neurodevelopment at the age of 18 months	Močenić, Ivona; Kolić, Ivana; Radić Nišević, Jelena; Belančić, Andrej; Snoj Tratnik, Janja; Mazej, Darja; Falnoga, Ingrid; Vlašić-Cicvarić, Inge; Štimac, Tea; Špirić, Zdravko; Horvat, Milena; Prpić, Igor			Environmental Research, Volume 176 September 2019, 108529 <a href="https://doi.org/10.1016/j.envres.2019.108529">https://doi.org/10.1016/j.envres.2019.108529</a>	
	Mercury speciation in prenatal exposure in Slovenian and Croatian population – PHIME study	Trdin, Ajda; Snoj Tratnik, Janja; Mazej, Darja; Fajon, Vesna; Krsnik, Mladen; Osredkar, Joško; Prpić, Igor; Špirić, Zdravko; Petrović, Oleg; Marc, Janja; Neubauer, David; Kodrič, Jana; Kobal, Alfred B; Barbone, Fabio; Falnoga, Ingrid; Horvat, Milena			Environmental Research; Volume 177, October 2019, 108627 <a href="https://doi.org/10.1016/j.envres.2019.108627">https://doi.org/10.1016/j.envres.2019.108627</a>	
	Combined prenatal exposure to mercury and LCPUFA on newborn's brain	Radić Nišević, Jelena; Prpić, Igor; Baždarić, Ksenija; Snoj Tratnik, Janja; Škarpa Prpić, Ingrid; Mazej, Darja;			Environmental Research, Volume 178, November 2019, 108682	



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	measures and neurodevelopment at the age of 18 months	Špirić, Zdravko; Horvat, Milena				
	Determinants of phthalate exposure and risk assessment in children from Poland.	Garí M, Koch HM, Pálmke C, Jankowska A, Wesolowska E, Hanke W, Nowak D, Bose-O'Reilly S, Polańska K.			Environ Int. 2019;127:742-753.	
	Prenatal and early postnatal phthalate exposure and child > neurodevelopment at age of 7 years - Polish Mother and Child Cohort	Jankowska A, Polańska K, Hanke W, Wesolowska E, Ligocka D, Waszkowska M, Stańczak A, Tartaglione AM, Mirabella F, Chiarotti F, Garí M, Calamandrei G.			Environ Res. 2019;177:108626. doi: 10.1016/j.envres.2019.108626.	
	Sex-Dependent Impact of Low-Level Lead Exposure during Prenatal Period on Child Psychomotor Functions.	Polanska K, Hanke W, Pawlas N, Wesolowska E, Jankowska A, Jagodic M, Mazej D, Dominowska J, Grzesiak M, Mirabella F, Chiarotti F, Calamandrei G.			Int. J. Environ. Res. Public Health. 2018;15;2263	
	Pregnancy exposome and child psychomotor development in three European birth cohorts.	Calamandrei G, Ricceri L, Meccia E, Tartaglione AM, Horvat M, Tratnik J, Mazej D, Špirić Z, Prpić I, Vlašić-Cicvarić I, Neubauer D, Kodrič J, Stropnik S, Janasik B, Kuras R, Mirabella F, Polanska K, Chiarotti F.			Environmental Res. <sup>§</sup>	
	Phthalate exposure and neurodevelopmental outcomes in early school age children from Poland.	Jankowska A, Polańska K, Koch HM, Pálmke C, Waszkowska M, Stańczak A, Wesolowska E, Hanke W, BoseO'Reilly S, Calamandrei G, Garí M.			Environmental Res.	
	Neurodevelopmental exposome: the effect of in utero co-	Sarigiannis DA, Papaioannou N, Handakas E, Anesti O, Polanska K, Hanke W,			Environmental Res.	

<sup>§</sup> Environmentam Research= paper submitted to the special issue reporting HEALS results



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	exposure to heavy metals and phthalates on child neurodevelopment.	Salifoglou A, Gabrie C, Karakitsios S.				
	Lead intoxicated children in Kabwe, Zambia.	Bose-O'Reilly S, Yabe J, Makumba J, Schutzmeier P, Ericson B, Caravanos J.			Environ Res. 2018;165:420-4.	
	Polymorphisms in potential mercury transporter ABCC2 and neurotoxic symptoms in populations exposed to mercury vapor from goldmining.	Kolbinger V, Engstrom K, Berger U, Bose-O'Reilly S.			Environ Res. 2019;176:108512.	
	Biomarkers of exposure in environment-wide association studies - Opportunities to decode the exposome using human biomonitoring data..	Steckling N, Gotti A, Bose-O'Reilly S, Chapizanis D, Costopoulou D, De Vocht F, et al.			Environ Res. 2018;164:597-624	
	Environmental data treatment to support exposome studies: The statistical behavior for NO2, O3, PM10 and PM2.5 air concentrations in Europe.	John G. Bartzis, Krystallia K. Kalimeri, Ioannis A. Sakellaris	Revision		Environmental Research, Special Issue "Unraveling Exposome"	
	Investigation on PM2.5, NO2 and O3 exposure differentiation due to the indoor environment.	Krystallia K. Kalimeri, John G. Bartzis, Ioannis A. Sakellaris, Eduardo de Oliveira Fernandes	Revision		Environmental Research,	
	Phthalate exposure and neurodevelopmental outcomes in early school age	Jankowska A, Polańska K, Koch HM, Pálmke C, Waszkowska M, Stańczak A,	Revision		Environmental Research, Special Issue "Unraveling Exposome"	



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	children from Poland	Wesołowska E, Hanke W, Bose-O'Reilly S, Calamandrei G, Garí M.				
	The influence of residential and workday population mobility on exposure to air pollution in the UK.	Reis, et al.			Environment International 2018, (121). pp.803-813	
	Comparison of Methods for Converting Dylos Particle Number Concentrations to PM2.5 Concentrations.	Franken, R., Maggos, T., Stamatelopoulou, A., Loh, M., Kuijpers, E., Bartzis, J., Steinle, S., Cherrie, JW., Pronk, A.			Indoor Air, 2019, <a href="https://doi.org/10.1111/ina.12546">https://doi.org/10.1111/ina.12546</a>	
	Neurodevelopmental exposome: the effect of in utero co-exposure to heavy metals and phthalates on child neurodevelopment	Denis A. Sarigiannis, Nafsika Papaioannou, Evangelos Handakas, Ourania Anesti, Kinga Polanska, Wojciek Hanke, Athanasios Salifoglou, Catherine Gabriel, Spyros Karakitsios	Under revision	Environmental Research, 11-06-2019		
	Multi-omics analysis reveals that co-exposure to phthalates and metals disturbs urea cycle and choline metabolism.	Nafsika Papaioannou, Emilie Distel, Eliandre de Oliveira, Catherine Gabriel, Ramón Díaz-Peña, Antonia Odena, Ilias S. Frydas, Ourania Anesti, Eléonore A Attignon, Martine Aggerbeck, Milena Horvat, Robert Barouki, Spyros Karakitsios, Denis A. Sarigiannis	Under revision	Environmental Research, 11-06-2019		
<b>Presentations</b>	<b>Title</b>	<b>Authors</b>	<b>Conference, meeting, workshop (name/ date / place)</b>	<b>Notes/ comments. HEALS</b>		



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				<b>attend ers</b>		
	Extreme weather events and their impact on mental health of children and adolescents. Advance module: Climate change & health: a case for transformation	Bose O'Reilly S.	Invited lecture. 9th of May 2019: Center of International health, Munich, Germany			
	Concentrations of Phthalate Metabolites in Children from Poland	Polanska K, Garí M, Hanke W, Koch HM, Pálmke CC, Bose-O'Reilly S.	Lecture. 9th International Conference on Children's Health and the Environment ; 27th of June 2018; Seoul / Korea			
	Concentrations of Phthalate Metabolites in Children from Poland (poster)	Polanska K, Garí M, Hanke W, Koch, Holger M. , Pálmke C, Bose-O'Reilly S.	Poster. ISES - ISEE joint annual meeting - International Society for Environmental Epidemiology; 28th of August 2018; Ottawa, Canada2018			
	Extreme weather events and mental health	Bose-O`Reilly S, Mertes H	Lecture. VAO Symposium 2018; 14th of March 2018; Grenoble, France: Bavarian State Ministry of the Environment			



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			and Consumer Protection.			
	Child neurology	Jasna Jančić, Igor Prpić, Nataša Cerovac	Adriatic Neurology Forum, 22-26 may 2019, Budva, Monte Negro <a href="http://www.astakos.com/wp-content/uploads/I-poziv-AF-2019-8-ENGLESKI.pdf">http://www.astakos.com/wp-content/uploads/I-poziv-AF-2019-8-ENGLESKI.pdf</a>			
	Genetic testing of children with epilepsy in clinical practice	Igor Prpić	Adriatic Neurology Forum, 22-26 may 2019, Budva, Monte Negro <a href="http://www.astakos.com/wp-content/uploads/I-poziv-AF-2019-8-ENGLESKI.pdf">http://www.astakos.com/wp-content/uploads/I-poziv-AF-2019-8-ENGLESKI.pdf</a>			
		Igor Prpić	Serbian pediatric school, 22 seminar, Zlatibor, Jun 2019, Serbia			
		Igor Prpić	Adriatic Neurology Forum, 23-27 may 2018, Monopoli, Italy, <a href="http://www.astakos.com/wp-content/uploads/Adriatic-Neurology-">http://www.astakos.com/wp-content/uploads/Adriatic-Neurology-</a>			





			Forum-program.pdf			
	Impact of micronutrients during pregnancy on children's health and neurodevelopment	Hanke W, Polanska K, Gromadzinska J, Kuras R, Janasik B, Wasowicz W, Stelmach, Grzelewski T, Bobrowska-Korzeniowska M, Kopka M, Majak P, Jerzynska J, Stelmach W, Mirabella F, Chiarotti F, Calamandrei G.	Poster at Prenatal Programing and Toxicity (PPTOX) VI conference. Faroe, May 2018			
	Impact of micronutrients during pregnancy on children's health and neurodevelopment	Polanska K, Hanke W, Gromadzinska J, Kuras R, Janasik B, Wasowicz W, Stelmach I, Grzelewski T, Bobrowska-Korzeniowska M, Kopka M, Majak P, Jerzynska J, Stelmach W, Mirabella F, Chiarotti F, Calamandrei G.	Poster at The 9th International Conference on Children's Health and the Environment : Saving the Children at Risk, Shaping the Future Sustainability. June 2018, South Korea			
	Health effects of mercury poisoning among miners and families in ASGM	Bose O'Reilly S.	Lecture International Congress on Occupational Health - ICOH 2018; 30th of April 2018; Dublin, Ireland			
	Pollutants hinder the development of children [Schadstoffe behindern die Entwicklung von Kindern].	Bose O'Reilly S.	Invited key lecture. Pediatrician Day; Professional Association of Paediatricians e.V.[ BVKJ]; 16th of June			



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			2019; Berlin: Germany			
	HEALS: Bringing together comprehensive array of technologies and data analysis modelling tools to measure the overall "exposome" and its impact on health	Michael Dickinson	United Nations World Environment Day presentation for Capita Plc. Online Webinar, 5/6/2019			
	"Air Pollution and Health in the Era of the Exposome."	Loh, M..	Institute of Biological Chemistry, Biophysics, and Bioengineering Seminar, Heriot-Watt University. 5 December 2018			
	"The Exposome and Work."	Cherrie, J.	Lane Lecture 2018, Centre for Occupational and Environmental Health, University of Manchester			
	"Current and Future Trends in Exposure Science."	Cherrie, J.	Keynote at the Annual Meeting of the European Chapter of the International Society for Exposure Science, Bilthoven, Netherlands, 2019.			
	Use of Sensors in Occupational	Cherrie, J.	EPICOH/X2 016 ,			



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	Exposure Assessment		Barcelona, Spain, 2019.			
	“Does greenspace mitigate air pollution and motivate physical activity?: A case study of four European cities.”	W. Mueller, S. Steinle, J. Pärkkä, E. Parmes, H. Liedes, E. Kuijpers, D. Sarigiannis, D. Chapizanis, T. Maggos, M. Stamatelopoulou, P. Wilkinson, J. Milner, S. Vardoulakis, M. Loh.	Presented at the World Conference on Forests for Public Health, Athens, Greece from 8 to 11 May 2019			
	Examining the role of greenspace to mitigate air pollution and motivate physical activity in four European cities”	W. Mueller, S. Steinle, J. Pärkkä, E. Parmes, H. Liedes, E. Kuijpers, D. Sarigiannis, D. Chapizanis, T. Maggos, M. Stamatelopoulou, P. Wilkinson, J. Milner, S. Vardoulakis, M. Loh	Presented at the UK and Ireland Occupational and Environmental Epidemiology Meeting, 1 April 2019			
	Linking administrative data with modelled pollution fields to improve estimates of population exposure to air pollution	Tomas Liska	Joseph Black Conference – 30th May 2019. Oral presentation.			
	Multi-omics Analysis Reveals that Co-exposure to Phthalates and Metals Disturbs Urea Cycle and Choline Metabolism. 2018	D.A Sarigiannis, N. Papaioannou, N. Kapretsos, A. Gabriel, E. Distzel, E. De Oliveira, S. Karakitsios, M. Aggerbeck, R. Barouki.	AICHE Annual Meeting, Pittsburgh (PA), USA, 28/10-2/11/2018.			
	Mechanistic Assessment of the Effect of Phthalates and Heavy Metals on Neurodevelopment.	Dimosthenis Sarigiannis, Nafsika Papaioannou, Maria Fafouti, Mike Dickinson, Kinga Polanska, Wolfgang Hanke, Athanasios Salifoglou, Evangelos Handakas, Catherine Gabriel, Spyros Karakitsios.	AICHE Annual Meeting, Pittsburgh (PA), USA, 28/10-2/11/2018			
	Multi-omics Analysis	Dimosthenis Sarigiannis, Nafsika	EUROTOX, Brussels,			



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HEALS

	Reveals that Co-exposure to Phthalates and Metals Disturbs Urea Cycle and Choline Metabolism	Papaioannou, Nikolaos Kapretsos, Catherina Gabriel, Emilie Distel, Eliandre de Oliveira, Spyros Karakitsios, Martine Aggerbeck, Robert Barouki.	Belgium 2-5/9/2018			
	Effects of Heavy Metals to Neurodevelopment in a Mother-Infant Cohort Study.	Dimosthenis Sarigiannis, Nafsika Papaioannou, Maria Fafouti, Aikaterina Galonaki, Kinga Polanska, Michael Dickinson, Caterina Gabriel, Spyros Karakitsios.	ICHMET, Athens, Georgia, USA, 22-25/7/2018			
	Pathway Analysis of Prenatal Exposure to Heavy Metals Related Child Motor Development.	Dimosthenis Sarigiannis, Kinga Polanska, Wojciech Hanke, Athanasios Salifoglou, Nafsika Papaioannou, Evangelos Handakas, Caterina Gabriel, Spyros Karakitsios.	ICHMET, Athens, Georgia, USA, 22-25/7/2018.			
	Effects of heavy metals to neurodevelopment in a mother-infant cohort study.	D.A. Sarigiannis, N. Papaioannou, M. Fafouti, A. Galonaki, K. Polanska, M. Dickinson, C. Gabriel, S. Karakitsios.	INCHES, Seoul, South Korea, 27-29/6/2018.			
	Pathway analysis of prenatal exposure to heavy metals related child motor development.	D.A. Sarigiannis, K. Polanska, W. Hanke, A. Salifoglou, N. Papaioannou, E. Handakas, C. Gabriel, S. Karakitsios	INCHES, Seoul, South Korea, USA, 27-29/6/2018.			
	Adverse Outcome Pathway analysis of prenatal combined exposure to heavy metals and phthalates related to child neurodevelopment.	D.A. Sarigiannis, K. Polanska, W. Hanke, A. Gabriel, N. Papaioannou, S.Karakitsios.	PPTOX, Tórshavn, Faroe Islands, 27-30/5/2018.			



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## Work package 19 [WP-leader: CSIC]

### Dissemination of results and knowledge transfer

Report for the 4th Period **from 1/04/2018 (M55) to 30/06/2019 (M69)** of HEALS

<b>Work Package Number</b>	19		<b>Start date - End date</b>				M 1 – M69
<b>Work Package Title</b>	<b>Dissemination of results and knowledge transfer</b>						
<b>Activity Type</b>	RTD						
<b>Participant Number and Short Name</b>	1 UPMC	2 AUTH	3 IOM	5 JSI	9 LMU	14 FERA	15 CSIC
<b>Person-months (this reporting period / total planned)</b>	2.63/7	1/8	2.73/4	0.5/2	1/3	0/2	3/8
<b>Explanation of deviations between actual and planned person-months per work package and per beneficiary</b>	7/7 No deviation	9/7 This partner made a strong effort with the web page	4/4 No deviation	2/2 No deviation	5/3 This partner was the chairman of WP18 which involved a close interaction with WP19	0/2 Limited contribution	13.25/8 This partner was the chairman of this WP which involved a strong dedication (more than initially anticipated)



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<b>Participant Number and Short Name</b>	16 UOWM	18 IDMEC-FEUP	19 OIKON	23 URV	25 SXS		
<b>Person-months</b> <b>(this reporting period / total planned)</b>	1/2	0.9/3	1/1	2/6	2/3		
<b>Explanation of deviations between actual and planned person-months per work package and per beneficiary</b>	1/2 Less contribution than scheduled	3/3 No deviation	6/1 This partner performed a lot of presentations	8/6 This partner was the coordinator of the whole stream which involved a lot of dedication to WP9	3/3 No deviation		

**Objectives of WP19 for the 4th Period from 1/04/2018 (M55) to 30/06/2019 (M69) of HEALS**

- Maintenance of the web site for internal and external communication of the HEALS results.
- Dissemination of the heals results to the wide public and stakeholders
- Maintenance of the platform for reporting the HEALS publications (Zenodo)
- Commercialization of the HEALS results Market analysis and Business Planning
- Generation of Guidance to strengthen the European Research Area in Environment and Health
- Presentation of Milestones and Deliverables

**Summary of progress of WP19 for the 4th Period from 1/04/2018 (M55) to 30/06/2019 (M69) of HEALS**

The web site (<http://www.heals-eu.eu/>), the Zenodo platform (<https://zenodo.org/communities/heals/>) for reporting the HEALS publications in open access and the Moodle platform for training are fully operative. Renewal and maintenance of these platforms has been performed every time that new information had to be added.



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Several Stream 6 meetings have been celebrated by GotoMeeting for discussion of the dissemination strategy and other promotional issues. Eight technical newsletters describing the on-going results of the project have been published.

Since the beginning of the project, HEALS participants have already presented results and technical aspects related with exposome assessment methods in international scientific workshops, meetings and conferences. Three hundred and seventy-four presentations have been performed to date (ninety-four in the fourth reporting period). One hundred and seventy-seven papers have already been published in the international scientific literature (which acknowledgement to HEALS). Some of them in Environmental Health Perspectives, Environment International, Nature Scientific Reports and the Lancet. In this fourth period fifty-one papers have been published. In addition, a special volume of the journal "Environmental Research" has been prepared with papers reporting HEALS work. This volume received almost 40 manuscripts, therefore the final number of HEALS papers will increase. All published papers have already been quoted in the scientific literature one thousand two-hundred and eighty times (Scopus database, 30<sup>th</sup> August 2018) which shows that the results of the HEALS project have a strong impact in the scientific community. This audience will be useful for development of the guidelines to strengthen the European Research Area in Environment and Health.

A stakeholders list was elaborated. It is periodically updated with new information. As a result of the HEALS activities and dissemination of the HEALS progress into exposome characterization several meetings with top political representatives have been performed. These have included organizations from Italy, China and Barcelona. The main topics of these meetings have essentially concerned effects of environmental exposure on human health (including aspects such as the effects of dioxin exposure in urban populations as consequence of urban incineration plants and advantages and drawbacks of the reintroduction of DDT for fighting against malaria).

Concerning commercialization of the HEALS achievements, public organizations, several companies, private associations and lobbies have already approached HEALS partners for discussion of the project results. The areas of activity in which the interested organizations are involved encompass studies of health effects of environmental pollutants, impact of new compounds or technologies on human health and impact of industrial activities on human health and environmental distribution of pollutants. As consequence of these interviews six contracts have already been implemented. Some of them involving field analysis and technical assessment (City Hall of Barcelona, Metropolitan Area of Barcelona and Health Agency of Barcelona) and others were related to training (Panama, Chile, Nepal).

**Bullets:**

- ✓ 177 papers already published in the scientific literature. In journals such as Environmental Health Perspectives, Environment International, Nature Scientific Reports and the Lancet
- ✓ Papers available in open access in the Zenodo database
- ✓ 1280 quotes to date
- ✓ 374 presentations at scientific conferences and meetings
- ✓ One special volume in Environmental Research. 36 papers have been submitted.
- ✓ 8 newsletters



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- ✓ Contracts for studies of health effects of environmental pollutants, impact of new compounds or technologies on human health, impact of industrial activities on human health, environmental distribution of pollutants and capacity building.
- ✓ Website for communication of the results to the broad audience

## Description of Work of WP19 for the 4th Period from 1/04/2018 (M55) to 30/06/2019 (M69) of HEALS

### Task 19.1: Development and maintenance of HEALS website (AUTH, UPMC)

*Aim:* An active collaborative website with public and non-public parts was set up early in the project as first point of access for all interested scientific and business parties in order to enlarge awareness of the HEALS results on the broadest possible international scale (public parts), and as the integral HEALS knowledge base for the consortium members.

*Details of progress:* The HEALS website (<http://www.heals-eu.eu/>) is operational and updated periodically. AUTH is taking care of the regular maintenance. This activity includes regular updating with the latest news, deliverables, newsletters (seven issues published, the eighth in preparation), upcoming events etc. Links to the Zenodo and to the Moodle training platforms were also created so that users may access them from the HEALS web site. Videos (HEALS interviews) are uploaded.

This task has been mainly performed by **AUTH and CSIC**

### Task 19.2: Development of a dissemination strategy, market analysis and business planning for knowledge transfer (CSIC, URV, LMU, AUTH, UPMC, FERA, UOWM, IDMEC-FEUP)

*Aim:* The aim of this task is to produce a dissemination plan.

*Details of progress:* - Dissemination strategic plan was elaborated (Milestone 35, Month 12).

- Strong success in communication of the results to stakeholders and the private sector (see details in the lists at the end of this report). Examples:

--In the reporting period there have been several meetings with representatives of the City Hall of Barcelona, the management agency of the Metropolitan area of Barcelona and the Health Agency of Barcelona for discussion of health problems associated with pollutant emissions of traffic and emissions from a waste incineration plant in Barcelona. Some of these meetings have also included presentations to the inhabitants living nearby this incineration plant.

This task has been mainly performed by **CSIC**

### Task 19.3: Organisation of stakeholder and user workshops (URV, IDMEC-FEUP, UoWM, AUTH, IOM, LMU, UPMC)

*Aim:* A list of public agencies and stakeholders within Europe is maintained. These organizations are kept aware of the progress of HEALS and the knowledge accumulated





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within this project. EU authorities and officers and stakeholders included in the list receive periodic information on the relevant results obtained from the development of the project.

*Details of progress:* There has been a periodic updating of the lists of public agencies and stakeholders to be kept aware of the progress of HEALS and the knowledge accumulated within this project.

This task has been mainly performed by **CSIC, URV and LMU**

#### **Task 19.4: Organisation of final HEALS Conference.**

*Aim:* Organization of a final HEALS Conference.

*Details of progress:* This conference was organized in Paris, on June 20, 2019.

This task has been mainly performed by **UPMC**

#### **Task 19.5: Scientific publications and presentations in conferences and EU events (LMU, URV, AUTH, UoWM, IOM, UPMC)**

*Aim:* Coordination and planning of publications and participation in conferences and other regular/or and well-attended European events.

*Details of progress:* Three hundred and thirty-nine presentations have been performed to date (thirty-five in the first reporting period and one hundred, twenty-three in the second, eighty-four in the third and eighty-nine in the fourth). One hundred and fifty papers have already been published in the international scientific literature (which acknowledgement to HEALS). Some of them in Environmental Health Perspectives, Environment International, Nature Scientific Reports and the Lancet. In this fourth period fifty-one papers have been published. In addition, a special volume of the journal "Environmental Research" has been prepared with papers reporting HEALS work. This volume received thirty-six manuscripts for evaluation which involves that the final list of published HEALS papers will increase considerably. So far, one thousand two-hundred and eighty times (Scopus database, 30th August 2018) which shows that the results of the HEALS project have a strong impact in the scientific community.

This task has been mainly performed by **CSIC, AUTH, IOM, UPMC, LMU, JSI and OIKON**

#### **Task 19.6: Dissemination of results to the public (URV, AUTH, LMU, IOM, FERA)**

*Aim:* Production of information material such as leaflets, fact sheets, a technical newsletter and other condensed information material for communication of results to policy makers and the general public.

*Details of progress:* Eight technical newsletters describing the on-going results of the project have been published. A flyer and a poster presenting HEALS was prepared and has been presented at several international conferences.

a) Problems related with mercury in the Mediterranean Sea:



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Radio: IB3 (Balearic Islands)

b) Problems related with atmospheric pollution: SER (Spain).

c) General description of activities related to HEALS.

The book mentioned in the previous report (3<sup>rd</sup>) with the conclusions of the meeting in Rio de Janeiro (Brasil) on Human health and Environmental Problems in Big cities (13-16 July 2017) that was edited in Spanish (April 2018; La Catarata ed.), has been translated into Italian (Libreria Editrice Vaticana. Città del Vaticano) and Catalan (Claret Publishing Group, Barcelona). A translation into Portuguese is planned. HEALS members are authoring some chapters.

This task has been mainly performed by **CSIC, URV, AUTH, LMU, IOM, UPMC, ISS and JSI**

#### **Task 19.7: Development of an environmental health survey at the European level (UPMC, CSIC, FERA)**

*Aim:* Development and implementation of methodology for standardization and harmonization of exposure assessment methods.

*Details of progress:* - May 14, 2018 and May 28, 2019. Participation board meetings of the International Panel on Chemical Pollution (Brussels, Belgium) in which J.O. Grimalt described the goals of Heals and explained the main results achieved.

This task has been mainly performed by **CSIC**

#### **Task 19.8: Commercialization of technical developments and exposome outcomes (SXS, OIKON, UPMC, CSIC, AUTH)**

*Aim:* Development and implementation of a methodology for standardization and harmonization of exposure assessment methods.

*Details of progress:*

- There have been several meetings with the EPPA lobbying firm (Brussels) and the Tobacco Vapor Electronic Cigarette Association.
- There have also been meetings with the City Hall of Barcelona, the Management Organization of the Metropolitan Area of Barcelona, the Health Agency of the Barcelona and the Department of Environmental Quality of the Catalan Government.
- Also with associations of farmers (Sucs, Catalonia) and NGO (Aire Net and Forum Narcis Monturiol in Barcelona)
- As consequence of these meetings several contracts have been created for implementation of some of the HEALS results in the private and public sectors.

This task has been mainly performed by **CSIC**



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**List of deliverables in WP19 for the 4th Period from 1/04/2018 (M55) to 30/06/2019 (M69) of HEALS**

No.	Title/objective	Delivery Date	Achieved (Yes/No)	Significant results	Comments [ in progress, delayed..]	If applicable, propose corrective actions
D19.2	HEALS conference "linking Exposome to Human Health"	65	Yes	Celebrated in Paris, June 20, 2019	completed	
D19.3	Guidance document on the development and execution of a European Exposure and Health Survey	68	Yes	The upgrade of the Heals provides the model for the Health Survey at European level	completed	
D19.4	Report of dissemination activities and market analysis from the Knowledge Transfer Secretariat	60	Yes	Several products have been identified as available for commercialization	completed	
D19.5	HEALS newsletters and policy briefs	69	Yes	Eight newsletters were published. Several leaflets reporting HEALS activities were elaborated and distributed.	completed	

**List of milestones in WP19 for the 4th Period from 1/04/2018 (M55) to 30/06/2019 (M69) of HEALS**

No.	Title/objective	Delivery Date	Achieved (Yes/No)	Significant results	Comments [ in progress, delayed..]	If applicable, propose corrective actions.
MS36	HEALS Publications	60	Yes	150 scientific papers published. 339	completed	



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				scientific presentations reported. One special volume in "Environmental Research"		
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**Dissemination in WP19 for the 4th Period from 1/04/2018 (M55) to 30/06/2019 (M69) of HEALS**

<b>Publications</b>	<b>Title</b>	<b>Authors</b>	<b>In preparation/revision</b>	<b>Submitted (journal / date)</b>	<b>Published (journal / date)</b>	<b>Notes/comments</b>
1	Review on crosstalk and common mechanisms of endocrine disruptors: Scaffolding to improve PBPK/PD model of EDC mixture.	Sharma RP, Schuhmacher M and Kumar V			Environment International 99: 1-14 (2017)	
2	Landrigan PJ, Fuller R, et al.		The Lancet Commission on pollution and health.		Lancet, 391: 10119 (2017)	
3	Low cadmium exposure in males and lactating females-estimation of biomarkers.	Stajniko A, Falnoga I, et al.			Environmental research, 152: 109-119 (2017)	
4	Assessing the impact of hazardous waste on children's health: the exposome paradigm.	Sarigiannis D			Environmental Research, 158: 531-541 (2017)	
6	Informatics and data	Manrai AK, Cui Y, et al.			Annual Review of Public Health, 38: 279-294 (2017)	



	analytics to support exposome-based discovery for public health,					
7	Gut microbial diversity is associated with lower arterial stiffness in women.	Menni C, Lin C, et al.			Eur Heart J. 39(25):2390-2397 (2018)	
8	Glycosylation Profile of Immunoglobulin G Is Cross-Sectionally Associated With Cardiovascular Disease Risk Score and Subclinical Atherosclerosis in Two Independent Cohorts.	Menni C, Gudelj I, et al.			Circ Res.,122(11):1555-1564 (2018)	
9	External exposome and allergic respiratory and skin diseases.	Cecchi L, D'Amato G, and Annesi-Maesano I.			J Allergy Clin Immunol.,141(3):846-857 (2018)	
10	Steps forward reduction of environmental impact on children's health.	Grimalt JO, Böse-O'Reilly S and van den Hazel P			Environmental Research 164: 184-185 (2018)	
11	Development of a human physiological	Sharma RP, Schuhmacher			Toxicology Letters 296:152-162 (2018)	



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	y based pharmacokinetic (PBPK) model for phthalate (DEHP) and its metabolites: A bottom up modeling approach.	M, and Kumar V				
12	Differential protein expression of hippocampal cells associated with heavy metals (Pb, As, and MeHg) neurotoxicity: Deepening into the molecular mechanism of neurodegenerative diseases.	Karri V, Ramos D, et al.			Journal of Proteomics, 187: 106–125 (2018)	
13	Comparing dietary and non-dietary source contribution of BPA and DEHP to prenatal exposure: A Catalonia (Spain) case study.	Martínez MA, Rovira J, et al.			Environmental Research, 166: 25–34 (2018)	
14	Vitamins A and E during Pregnancy and Allergy Symptoms in	Gromadzinska J, Polanska K, et al			International Journal of Environmental Research and Public Health, 15(6), E1245 (2018)	



	an Early Childhood-Lack of Association with Tobacco Smoke Exposure.					
15	Main components of PM10 in an area influenced by a cement plant in Catalonia, Spain: Seasonal and daily variations.	Rovira J, Sierra J, Nadal M, Schuhmacher M, and Domingo JL			Environmental Research, 165: 201–209 (2018)	
16	Urinary bisphenol A in children, mothers and fathers from Slovenia: Overall results and determinants of exposure.	Snoj Tratnik J, Kosjek T, et al.			Environmental Research, 168: 32–40 (2018)	
17	Gestational weight gain charts for different body mass index groups for women in Europe, North America, and Oceania.	Santos S, Eekhout I et al.			BMC Medicine, 16(1): 201 (2018)	
18	Sex-Dependent Impact of Low-Level Lead Exposure	Polanska K, Hanke W, et al.			Int. J. Environ. Res. Public Health, 15: 2263 (2018)	





	during Prenatal Period on Child Psychomotor Functions.					
19	Origin of polycyclic aromatic hydrocarbons and other organic pollutants in the air particles of subway stations in Barcelona.	van Drooge BL, Prats RM, et al.			Science of the Total Environment, 642: 148–154 (2018)	
20	The influence of residential and workday population mobility on exposure to air pollution in the UK.	Reis S, Liška T, et al.			Environment International, 121: 803-813 (2018)	
21	An effective and low cost carbon based clean-up method for PCDD/Fs and PCBs analysis in food.	Kedikoglou K, Costopoulou D, Vassiliadou I, Bakeas E, and Leondiadis L.			Chemosphere, 206: 531-538 (2018)	
22	Assessing and enhancing the utility of low-cost sensors in exposure studies.	Asimina S, Chapizanis D, et al.			Environmental Monitoring and Assessment, 190: 155 (2018)	



23	Addressing complexity of health impact assessment in industrially contaminated sites via the exposome paradigm.	Sarigiannis DA and Karakitsios SP			Epidemiologia e prevenzione 42(5-6S1): 37-48 (2018).	
24	Drivers of maternal accumulation of organohalogen pollutants in Arctic areas (Chukotka, Russia) and 4,4'-DDT effects on the newly born.	Bravo N, Grimalt JO, Chashchin M, Chashchin VP, and Odland JO			Environment International, 124: 541–552 (2019)	
25	Influence of electronic cigarette vaping on the composition of indoor organic pollutants, particles and exhaled breath of bystanders.	van Drooge BL, Marco E, Perez N, and Grimalt JO			Environmental science and pollution research, 26(5):4654-4666 (2019)	
26	Comparison of Methods for Converting Dylos Particle Number Concentrations to PM2.5 Concentrations.	Franken R, Maggos T, et al.			Indoor Air, 29: 450–459 (2019)	



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27	Early-life intake of major trace elements, bisphenol A, tetrabromobisphenol A and fatty acids: Comparing human milk and commercial infant formulas,	Martínez MA, Castro I, et al.			Environmental Research, 169: 246-255 (2019)	
28	Prenatal exposure to PFOS and PFOA in a pregnant women cohort of Catalonia, Spain.	Rovira J, Martínez MA, et al.			Environmental Research, 175: 384-392 (2019)	
29	Human biomonitoring to evaluate exposure to toxic and essential trace elements during pregnancy. Part A. concentrations in maternal blood, urine and cord blood.,	Bocca B, Ruggieri F, et al.			Environmental Research, 177: 108599 (2019)	
30	Effects of PM, TVOCs and comfort parameters on indoor air quality of	Stamatelopoulou A, Asimakopoulos DN, and Maggos T			Building and Environment 150: 233-244 (2019)	



	residences with young children.					
31	Preliminary assessment of general population exposure to perfluoroalkyl substances through diet in Greece.	Kedikoglou K, Costopoulou D, Vassiliadou I, Bakeas E, Leondiadis L			Environmental Research, 177: 108617 (2019)	
32	Prenatal selenium status, neonatal cerebellum measures and child neurodevelopment at the age of 18 months.	Močenić I, Kolić I, et al.			Environmental research, 176: 108529 (2019)	
33	Mercury speciation in prenatal exposure in Slovenian and Croatian population – PHIME study.	Trdin A, Snoj Tratnik J, et al.			Environmental Research, 177: 108627 (2019)	
34	Combined prenatal exposure to mercury and LCPUFA on newborn's brain measures and neurodevelopment at the age of 18 months.	Radić Nišević J, Prpić I, et al.			Environmental Research, 178: 108682 (2019)	



35	Analytical Quality Requirements in Human Biomonitoring Programs: Trace Elements in Human Blood.	Snoj Tratnik J, Mazej D, and Horvat M.			Int. J. Environ. Res. Public Health, 16:, 2287 (2019)	
36	Urinary bisphenol A in children, mothers and fathers from Slovenia : overall results and determinants of exposure.	Snoj Tratnik, J., Kosjek, et al.			Environmental research, 168: 32-40 (2019)	
37	Risk characterization of bisphenol-A in the Slovenian population starting from human biomonitoring data.	Sarigiannis DA, Snoj Tratnik J, et al.			Environmental research, 170: 293-300 (2019)	
38	Arsenic metabolites; selenium; and AS3MT, MTHFR, AQP4, AQP9, SELENOP, INMT, and MT2A polymorphisms in Croatian-Slovenian population	Stajniko A, Šlejkovec Z, et al.			Environmental research, 170: 301-319 (2019)	



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	from PHIME-CROME study.					
39	Prenatal mercury exposure and child neurodevelopment outcomes at 18 months: results from the Mediterranean PHIME cohort.	Barbone F, Rosolen V, et al.			Int J Hyg Environ Health, 222: 9–21 (2019)	
40	Urinary metabolites of organophosphate and pyrethroid pesticides in children from an Italian cohort (PHIME, Trieste).	Bravo N, Grimalt JO, et al.			Environ Res., 176: 108508 (2019)	
41	Determinants of phthalate exposure and risk assessment in children from Poland.	Garí M, Koch HM, et al.			Environ Int., 127: 742-753 (2019)	
42	Prenatal and early postnatal phthalate exposure and child neurodevelopment at age of 7 years - Polish Mother and Child	Jankowska A, Polańska K, et al.			Environmental Res., 177: 108626 (2019)	



	Cohort – accepted for publication in					
43	Prenatal and postnatal exposure to air pollution and emotional and aggressive symptoms in children from 8 European birth cohorts.	Jorcano A, Lubczyńska MJ, et al.			Environment Int., 131: 1-10 (2019)	
44	Environmental and health inequalities.	Sarigiannis DA			Fresenius Environmental Bulletin 28(2): 516-517 (2019)	
45	Advancing chemical risk assessment through human physiology-based biochemical process modelling.	Sarigiannis DA and Karakitsios S			Fluids, 4(1): 4 (2019)	
46	<u>A model for estimating the lifelong exposure to PM2.5 and NO2 and the application to population studies, Environmental Research</u>	Li N, Maesano CN, et al.			Environmental Research 177, 108629 (2019)	
47	Exposure to heavy metals during pregnancy related to	Soomro, M.H., Baiz, N., et al.			Science of the Total Environment, 656: 870-876 (2019)	



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	gestational diabetes mellitus in diabetes-free mothers.					
48	The Exposome	Annesi-Maesano I			ISES - ISEE joint annual meeting - International Society for Environmental Epidemiology; 28th of August 2018; Ottawa, Canada2018.	
49	Global Burden of Disease of Mercury used in Artisanal Small-Scale Gold Mining.	Steckling N, Tobollik M, et al.			Annals of Global Health. 83(2):234-247 (2017)	
50	Integrated assessment of infant exposure to persistent organic pollutants and mercury via dietary intake in a central western Mediterranean site (Menorca Island)	Junqué E, Garí M, et al.			Environmental Research 156: 714–724 (2017)	
51	Down-regulation of the expression of alcohol dehydrogenase 4 and CYP2E1 by the combination of $\alpha$ -endosulfan	Attignon EA, Distel E, et al.			Toxicology in vitro S0887-2333(17):30185-6 (2017)	





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HEALS

	and dioxin in HepaRG human cells.					
52	Modelling spatial patterns of correlations between concentrations of heavy metals in mosses and atmospheric deposition in 2010 across Europe	Nickel, S., Schröder, W., Schmalfluss, R., Saathoff, M., Harmens, H., Mills, G., Frontasyeva, M.V., Barandovski, L., Blum, O., Carballeira, A., de Temmerman, L., Spiric, Z. et al.			Environmental Sciences Europe, 30 (2018), 53; 1-17 doi:10.1186/s12302-018-0183-8	
<b>Presentations</b>	<b>Title</b>	<b>Authors</b>	<b>Conference, meeting, workshop (name/date / place)</b>	<b>Notes/comments. HEALS attenders</b>		
<b>1</b>	Sensor Technologies and Data for a Healthy Environment	Loh, M.	DorsaVi sponsored event: Panel discussion on the topic of wearable technology in the workplace and how it can help us create safer environments and a healthier workforce,			



			London, UK, February 23, 2017.			
2	Sensor Technologies and the Exposome.	Loh, M.	Presented at the Centre for Occupational and Environmental Health, University of Manchester, February 27, 2017.			
3	Particle Deposition in the Lung of Mothers and their children in residential environments	A. Stamatelopoulou, M. Pilou, C. Housiadas, D.N. Asimakopoulos, D. Sarigiannis, T. Maggos,	European Aerosol Conference (EAC), Zurich, 27 August-1 September, 2017.			
4	Maternal diet and lifestyle, levels of selected elements and fatty acid composition in maternal milk from two different areas in Slovenia	M. Jagodic, J. Snoj Tratnik, D. Mazej, A. Stajko, L. Kononenko, D. Potočnik, N. Ogrinc, M. Horvat	9th Jožef Stefan International Postgraduate School Students' Conference and 11th Young researchers' Day, 19.-20. April 2017, Ljubljana, Slovenia.			
5	Research for "Precision prevention. Setting research priorities in environment and health	D.A. Sarigiannis.	WHO, Bonn, Germany, 29-30/11/2017			



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6	Exposomics – based association of environmental exposures and neurodevelopmental disorders.	K. Tsioka, N. Papaioannou, E. Handakas, C. Gabriel, S. Karakitsios, O. Anesti, D.A. Sarigiannis.	68th Congress of the Hellenic Society of Biochemistry and Molecular Biology, Athens, Greece, 10-12/11/2017			
7	Oxidative stress induced by ambient air PMx: Which are the Main Sources?	D. Sarigiannis, S. Karakitsios, M. Kermenidou	AIChE Annual Meeting, Minneapolis (MN), USA, 29/10-3/11/2017.			
8	Exposure reconstruction of multiple chemicals from human biomonitoring data using Markov chain and differential evolution Monte Carlo	D.A. Sarigiannis, E. Handakas, A. Gotti, S. Karakitsios	AIChE Annual Meeting, Minneapolis (MN), USA, 29/10-3/11/2017.			
9	Integrated use of Agent Based Modelling with sensor webs for personal exposure assessment.	D. Chapizanis, S. Karakitsios, D.A. Sarigiannis.	27th Annual Meeting of Exposure Science (ISES), North Carolina, USA, 15-19/10/2017			
10	Assessing the impact of hazardous waste on children's health: the	D.A. Sarigiannis.	19th International Symposium on Environmental			



	Exposome paradigm.		Pollution and its Impact on Life in the Mediterranean Region (MESAEP), Rome, Italy, 4-6/10/2017.			
11	Assessment of public health risk from arsenic using biomarkers and biokinetics modeling.	I. Furxhi, D. Sarigiannis, S. Karakitsios.	2017 19th International Symposium on Environmental Pollution and its Impact on Life in the Mediterranean Region (MESAEP), Rome, Italy, 4-6/10/2017.			
12	Emerging methodologies for personal exposure assessment: coupling portable sensors data and agent based modelling (ABM).	D. Chapizanis, S. Karakitsios, D. Sarigiannis.	19th International Symposium on Environmental Pollution and its Impact on Life in the Mediterranean Region (MESAEP), Rome, Italy, 4-6/10/2017.			
13	Human exposure assessment to multiple chemicals using biomarkers.	D.A. Sarigiannis, Handakas, A. Gotti, S. Karakitsios.	19th International Symposium on Environmental Pollution and its Impact on			



			Life in the Mediterranean Region (MESAEP), Rome, Italy, 4-6/10/2017.			
14	Modeling of elimination half – life for environmental chemicals.	K. Papadaki, S. Karakitsios, D. Sarigiannis.	19th International Symposium on Environmental Pollution and its Impact on Life in the Mediterranean Region (MESAEP), Rome, Italy, 4-6/10/2017.			
15	Pathway analysis of prenatal combined exposure to heavy metals and phthalates related child motor development.	D.A. Sarigiannis, K. Polanska, W. Hanke, A. Salifoglou, A. Gabriel, N. Papaioannou, E. Handakas, S. Karakitsios.	19th International Symposium on Environmental Pollution and its Impact on Life in the Mediterranean Region (MESAEP), Rome, Italy, 4-6/10/2017.			
16	Generation of oxygen species is linked to ambient air PMx sources.	D. Sarigiannis, S. Karakitsios, M. Kermenidou.	19th International Symposium on Environmental Pollution and its Impact on Life in the Mediterranean Region			



			(MESAEP), Rome, Italy, 4-6/10/2017.			
17	Pathway analysis of neurodevelopment toxicity due to prenatal combined exposure to heavy metals and phthalates.	D.A. Sarigiannis, K. Polanska, W. Hanke, A. Salifoglou, A. Gabriel, N. Papaioannou, E. Handakas, S. Karakitsios.	53rd Congress of the European Societies of Toxicology, Bratislava, Slovakia, 10-13/09/2017			
18	Advanced modeling of adipose: blood partition coefficient for environmental chemicals.	D. Sarigiannis, K. Papadaki, S. Karakitsios.	6th International Conference on Environmental Management, Engineering, Planning & Economics (CEMEPE) and SECOTOX, Thessaloniki, Greece, 25-30/06/2017			
19	Assessing the impact of hazardous waste on children's health: the exposome paradigm	D. Sarigiannis.	6th International Conference on Environmental Management, Engineering, Planning & Economics (CEMEPE) and SECOTOX, Thessalonik			



			i, Greece, 25-30/06/2017			
20	Assessment of public health risk from arsenic using biomarkers and biokinetic modelling. 2017 6th International Conference on Environmental Management, Engineering, Planning & Economics (CEMEPE) and SECOTOX, Thessaloniki, Greece, 25-30/06/2017.	D. Sarigiannis, S. Karakitsios, I. Furxhi.	6th International Conference on Environmental Management, Engineering, Planning & Economics (CEMEPE) and SECOTOX, Thessaloniki, Greece, 25-30/06/2017			
21	D. Chapizanis, S. Karakitsios, D. Sarigiannis. Can Agent Based Modelling, coupled with sensors data, be used for personal exposure assessment?		6th International Conference on Environmental Management, Engineering, Planning & Economics (CEMEPE) and SECOTOX, Thessaloniki, Greece, 25-30/06/2017			
22	Exposure assessment of multiple	D.A. Sarigiannis, Handakas, A.	6th International Conference			



	chemicals starting from biomonitoring data.	Gotti, S. Karakitsios	on Environmental Management, Engineering, Planning & Economics (CEMEPE) and SECOTOX, Thessaloniki, Greece, 25-30/06/2017.			
23	Sources of oxidative induced by ambient air PMx.	D. Sarigiannis, S. Karakitsios, M. Kermenidou.	6th International Conference on Environmental Management, Engineering, Planning & Economics (CEMEPE) and SECOTOX, Thessaloniki, Greece, 25-30/06/2017.			
24	Assessing the impact of hazardous waste on children's health: the Exposome paradigm	D.A. Sarigiannis.	11th Panhellenic Research Congress of Chemical Engineering, Thessaloniki, Greece, 25-27/05/2017.			
25	Emerging methodologies for personal exposure assessment:	D. Sarigiannis, D. Chapizanis, S. Karakitsios	11th Panhellenic Research Congress of Chemical Engineering			





	coupling portable sensors data and agent based modelling (ABM)		, Thessaloniki, Greece, 25-27/05/2017			
26	Exposure assessment of multiple chemicals starting from biomonitoring data.	D.A. Sarigiannis, Handakas, A. Gotti, S. Karakitsios.	11th Panhellenic Research Congress of Chemical Engineering , Thessaloniki, Greece, 25-27/05/2017			
27	Modelling the adipose: blood partition coefficient for environmental chemicals.	D. Sarigiannis, K. Papadaki, S. Karakitsios.	11th Panhellenic Research Congress of Chemical Engineering , Thessaloniki, Greece, 25-27/05/2017			
28	Pathway analysis of prenatal combined exposure to heavy metals and phthalates related child motor development.	D.A. Sarigiannis, K. Polanska, W. Hanke, A. Salifoglou, A. Gabriel, N. Papaioannou, E. Handakas, S. Karakitsios	11th Panhellenic Research Congress of Chemical Engineering , Thessaloniki, Greece, 25-27/05/2017			
29	Sources of oxidative induced by ambient air PMx.	D. Sarigiannis, S. Karakitsios, M. Kermenidou	11th Panhellenic Research Congress of Chemical Engineering ,			



			Thessalonik i, Greece, 25- 27/05/2017 .			
30	Emerging methodologie s for environmenta l exposure assessment at a personal level.	D. Sarigiannis, D. Chapizanis, S. Karakitsios.	6th Environme ntal Conference of Macedonia, Thessalonik i, Greece, 5- 7/05/2017.			
31	Reactive oxygen species generation associated with sources of atmospheric particulate matter in ambient air of Thessaloniki	D. Sarigiannis, S. Karakitsios, M. Kermenidou.	6th Environme ntal Conference of Macedonia, Thessalonik i, Greece, 5- 7/05/2017.			
32	Combined exposure to EDCs resulting in neurodevelop mental disorders.	D.A. Sarigiannis, K. Polanska, W. Hanke, A. Salifoglou, A. Gabriel, N. Papaioannou, E. Handakas, S. Karakitsios.	SETAC, 27th Annual Meeting, Brussels, Belgium, 7- 11/05/2017 .			
33	Exposure to heavy metals, contaminated soil, diet and children neurodevelop ment.	D.A. Sarigiannis, A. Gotti, V. Handakas, S. Karakitsios.	SETAC, 27th Annual Meeting, Brussels, Belgium, 7- 11/05/2017 .			
34	Internal dosimetry metrics for risk assessment of	D.A. Sarigiannis, S.P. Karakitsios, E. Handakas, A. Gotti.	SETAC, 27th Annual Meeting, Brussels, Belgium, 7-			



	endocrine disruptors – the case of bisphenol A.		11/05/2017			
35	Air Pollution and Health in the Era of the Exposome.	Loh, M.	Institute of Biological Chemistry, Biophysics, and Bioengineering Seminar, Heriot-Watt University. 5 December 2018.			
36	The Exposome and Work.	Cherrie, J.	Lane Lecture 2018, Centre for Occupational and Environmental Health, University of Manchester			
37	Environmental benefits and threats of life in the cities.	J.O. Grimalt	Central Organization of CSIC in Barcelona. Barcelona, Catalonia. 18th February 2018.			
38	Drivers of the accumulation of measured organochlorine pollutants in Mediterranean lean fish and dietary significance.	J.O. Grimalt et al.	PPTOX Conference . Torshavn, Faroe Islands. 28th-31st May 2018.			
39	Temporal trends of	M. Garí et al.	PPTOX Conference . Torshavn,			



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	organochlorine compounds and PBDEs from utero until 4 years of age in the Asturias INMA birth cohort		Faroe Islands. 28th-31st May 2018.			
40	Human exposure to organophosphate and pyrethroid pesticides in occupational and general populations in Catalonia and Galicia (Spain)	M. Garí et al.	PPTOX Conference . Torshavn, Faroe Islands. 28th-31st May 2018.			
41	Three decades of research on the environmental Health effects associated to chlor-alkali plants	J.O. Grimalt	Institut d'Estudis Catalans. Barcelona, Catalonia. 6th June 2018.			
42	Advantages and disadvantages of life in big cities.	J.O. Grimalt	Cervantes Institute. El Cairo, Egypt. 16 <sup>th</sup> July 2018.			
43	Life in big cities. Advantages and drawbacks.	J.O. Grimalt	International University Menendez y Pelayo. Santander, Spain. 23th July 2018.			
44	Air immission measurement	J.O. Grimalt	Public Health Agency of			



	s of dioxins in Barcelona.		Barcelona. Barcelona, Catalonia. 22nd October 2018.			
45	Empowering society by creating healthy urban environments	Gabriel M, Mourão Z, Oliveira Fernandes E.	World Health Organization (WHO) International Healthy Cities Conference . 1-4 October 2018, Belfast, N. Ireland, U.K.			
46	Prenatal Methyl Mercury exposure Prenatal Programming and Toxicity	A. Trdin, I. Falnoga, J. Snoj Tratnik, V. Fajon, D. Mazej, J. Osredkar, I. Prpić, Z. Špirić, M. Horvat	PPTOX Conference . Torshavn, Faroe Islands. 28th-31st May 2018.			
47	Low-level mercury exposure, neurodevelopment and the role of genetic polymorphisms : evidence from Slovenian and Croatian birth cohorts.	J. Snoj Tratnik, I. Falnoga, A. Trdin, D. Mazej, I. Prpić, Z. Špirić, M. Horvat	PPTOX Conference . Torshavn, Faroe Islands. 28th-31st May 2018.			
48	Prenatal Methyl Mercury exposure. Prenatal Programming and Toxicity,	Trdin, Ajda, Falnoga, Ingrid, Snoj Tratnik, Janja Fajon, Vesna, Mazej, Darja, Osredkar, Joško, Prpić, Igor, Špirić,	PPTOX Conference . Torshavn, Faroe Islands. 28th-31st May 2018.			



		Zdravko, Horvat, Milena.				
49	Low-level mercury exposure, neurodevelopment and the role of genetic polymorphisms: evidence from Slovenian and Croatian birth cohorts.	Snoj Tratnik, Janja, Falnoga, Ingrid, Trdin, Ajda, Mazej, Darja, Prpić, Igor, Špirić, Zdravko, Horvat, Milena.	PPTOX Conference . Torshavn, Faroe Islands. 28th-31st May 2018.			
50	Impact of micronutrients during pregnancy on children's health and neurodevelopment.	Hanke W, Polanska K, Gromadzinska J, Kuras R, Janasik B, Wasowicz W, Stelmach, Grzelewski T, Bobrowska-Korzeniowska M, Kopka M, Majak P, Jerzynska J, Stelmach W, Mirabella F, Chiarotti F, Calamandrei G.	PPTOX Conference . Torshavn, Faroe Islands. 28th-31st May 2018.			
51	Impact of micronutrients during pregnancy on children's health and neurodevelopment.	Polanska K, Hanke W, Gromadzinska J, Kuras R, Janasik B, Wasowicz W, Stelmach I, Grzelewski T, Bobrowska-Korzeniowska M, Kopka M, Majak P, Jerzynska J, Stelmach W, Mirabella F, Chiarotti F, Calamandrei G.	9th International Conference on Children's Health and the Environment: Saving the Children at Risk, Shaping the Future Sustainability. June 2018, South Korea			



52	Lifelong exposure of population subgroups with PM2.5	Naixin Li, Rainer Friedrich, Christian Schieberle	International Society for Environmental Epidemiology, Ottawa, Canada, 26-31/8/2018.			
53	Improved assessment of personal exposure to chemicals using Agent Based Modelling (ABM) coupled with multi-sensors networks.	D. Chapizanis, S. Karakitsios, D. Sarigiannis	18th AICHE Annual Meeting, Pittsburgh, USA, 28/10-2/11/2018.			
54	Mechanistic Assessment of the Effect of Phthalates and Heavy Metals on Neurodevelopment.	D. Sarigiannis, N. Papaioannou, M. Fafouti, A. Galonaki, M. Horvat, J. Snoj Tratnik, M. Dickinson, C. Gabriel, S. Karakitsios.	18th AICHE Annual Meeting, Pittsburgh, USA, 28/10-2/11/2018.			
55	Multi-omics Analysis Reveals that Co-exposure to Phthalates and Metals Disturbs Urea Cycle and Choline Metabolism.	D.A. Sarigiannis, N. Papaioannou, N. Kapretsos, C. Gabriel, E. Distel, E. Oliveira, S. Karakitsios, M. Aggerbeck, R. Barouki.	EUROTOX 2018, Brussels, Belgium, 2-5/9/2018.			
56	QSAR modeling for predicting elimination half-life of environmental	K. Papadaki, S. Karakitsios, D. Sarigiannis.	EUROTOX 2018, Brussels, Belgium, 2-5/9/2018.			



	I chemical compounds.					
57	Simplexity in Complex Environmental Health Problems Using the Exposome.	D. Sarigiannis.	Invited oral presentation within the HEALS Session "Solutions for tackling the link between complex exposures and human health". International Society for Environmental Epidemiology, Ottawa, Canada, 26-31/8/2018.			
58	Waste impact on children's health: the exposome paradigm.	D. Sarigiannis	International Society for Environmental Epidemiology, Ottawa, Canada, 26-31/8/2018.			
59	Effects of Heavy Metals to Neurodevelopment in a Mother-Infant Cohort Study.	D. Sarigiannis, N. Papaioannou, M. Fafouti, A. Galonaki, M. Horvat, J. Snoj Tratnik, M. Dickinson, C. Gabriel, S. Karakitsios.	2018 International Conference on Heavy Metals in the Environment, Athens, GA USA, 22-25/7/2018.			
60	Effects of Heavy Metals to Neurodevelopment in a Mother-Infant Cohort Study.	D. Sarigiannis, K. Polanska, W. Hanke, A. Salifoglou, N. Papaioannou, E. Handakas, C. Gabriel, S. Karakitsios.	2018 International Conference on Heavy Metals in the Environme			





			nt, Athens, GA USA, 22-25/7/2018.			
61	Effects of heavy metals to neurodevelopment in a mother-infant cohort study.	D.A. Sarigiannis, N. Papaioannou, M. Fafouti, A. Galonaki, K. Polanska, M. Dickinson, C. Gabriel, S. Karakitsios.	9th International Conference on Children's Health and the Environment: Saving the Children at Risk, Shaping the Future Sustainability. June 2018, South Korea			
62	Pathway analysis of prenatal exposure to heavy metals related child motor development.	D.A. Sarigiannis, K. Polanska, W. Hanke, A. Salifoglou, N. Papaioannou, E. Handakas, C. Gabriel, S. Karakitsios.	9th International Conference on Children's Health and the Environment: Saving the Children at Risk, Shaping the Future Sustainability. June 2018, South Korea			
63	A generic PBPK model for assessing in utero toxicokinetics: application on bisphenol A and evaluation of placental $\beta$ -	D.A. Sarigiannis, A. Gotti, S. Karakitsios.	PPTOX Conference . Torshavn, Faroe Islands. 28th-31st May 2018.			



	glucuronidase activity.					
64	The HERACLES Waste study: unraveling the associations between prenatal exposure to metals, post-natal exposure to environmental and dietary factors and child cognitive capacity.	D.A. Sarigiannis, A. Gotti, S. Karakitsios.	PPTOX Conference . Torshavn, Faroe Islands. 28th-31st May 2018.			
65	Adverse Outcome Pathway analysis of prenatal combined exposure to heavy metals and phthalates related to child neurodevelopment.	D.A. Sarigiannis, K. Polanska, W. Hanke, A. Gabriel, N. Papaioannou, S.Karakitsios	PPTOX Conference . Torshavn, Faroe Islands. 28th-31st May 2018.			
66	Current and Future Trends in Exposure Science.	Cherrie, J	Keynote at the Annual Meeting of the European Chapter of the International Society for Exposure Science, Bilthoven,			



			Netherlands, 2019.			
67	Use of Sensors in Occupational Exposure Assessment	Cherrie, J.	EPICOH/X2016, Barcelona, 2019.			
68	“Does greenspace mitigate air pollution and motivate physical activity?: A case study of four European cities.”	W. Mueller, S. Steinle, J. Pärkkä, E. Parmes, H. Lienes, E. Kuijpers, D. Sarigiannis, D. Chapizanis, T. Maggos, M. Stamatelopoulou, P. Wilkinson, J. Milner, S. Vardoulakis, M. Loh.	World Conference on Forests for Public Health, Athens, Greece from 8 to 11 May 2019.			
69	Examining the role of greenspace to mitigate air pollution and motivate physical activity in four European cities	W. Mueller, S. Steinle, J. Pärkkä, E. Parmes, H. Lienes, E. Kuijpers, D. Sarigiannis, D. Chapizanis, T. Maggos, M. Stamatelopoulou, P. Wilkinson, J. Milner, S. Vardoulakis, M. Loh.	UK and Ireland Occupational and Environmental Epidemiology Meeting, 1 April 2019.			
70	Prenatal exposure to PFOS and PFOA in a Catalan pregnant women cohort	J. Rovira, M.Á. Martínez, T. Espuis, R.P. Sharma, M. Nadal, V. Kumar, D. Costopoulou, I. Vassiliadou, L. Leondiadis, J.L. Domingo, M. Schuhmacher.	SETAC 29th annual Meeting. Helsinki 26-30 May.			
71	Tarragona mother-child risk exposure assessment to wide spread	M. A. Martínez, J. Rovira, V. Kumar, M. Schuhmacher	SETAC YES. Ghent.5-10February 2019.			



	endocrine disruptors (eds) and in vitro eds exposure effects on adipogenesis.					
72	Development and implementation of a user-friendly IAQ checklist for ensuring healthy households for children.	Gabriel M, Felgueiras F, Mourão Z, Oliveira Fernandes E.	International Conference on Integrated Problem-Solving Approaches to Ensure Schoolchildren's Health. 23-24 May 2019, Budapest, Hungary.			
73	Towards a better management of early-life exposures through the enhancement of the knowledge on air pollution in households.	Gabriel M, Felgueiras F, Ramos E, Mourão Z, Oliveira Fernandes E.	International Societies of Exposure Science (ISES) and Indoor Air Quality and Climate (ISIAQ) joint conference. 18-22 August 2019, Kaunas, Lithuania.			
74	Exposure to mercury during prenatal period	A. Trdin, J. Snoj Tratni, I. Prpić, Z. Špirić, I. Falnoga, M. Horvat	1st ISO-FOOD International Symposium on Isotopic and Other Techniques in Food Safety and Quality, Portorož, Slovenia,			



			April 1-3, 2019			
75	Presence of chemicals in the everyday life)	M. Horvat, Prisotnost kemikalij v vsakdanjem življenju	Science on the Street, 14 June 2019, Ljubljana, Slovenia.			
76	Exposure to metals in susceptible population groups and its role in neurodegeneration	J. Snoj Tratnik, D. Mazej, I. Falnoga, M. Horvat	Conference of the Hellenic Academy of Neuroimmunology, June 23, 2019, Thessaloniki, Greece			
77	Exposure to mercury during prenatal period.	Trdin, Ajda, Snoj Tratnik, Janja, Prpić, Igor, Spirić, Zdravko, Falnoga, Ingrid, Horvat, Milena.	1st ISO-FOOD International Symposium on Isotopic and Other Techniques in Food Safety and Quality, Portorož, Slovenia, April 1-3, 2019			
78	Presence of chemicals in the everyday life.	Horvat, Milena. Prisotnost kemikalij v vsakdanjem življenju	Science on the Street, 14 June 2019, Ljubljana, Slovenia.			
79	Exposure to metals in susceptible population groups and its role in neurodegeneration.	Snoj Tratnik, Janja, Mazej, Darja, Falnoga, Ingrid, Horvat, Milena.	Conference of the Hellenic Academy of Neuroimmunology, June 23, 2019, Thessaloniki, Greece			
80	Impact on the human HepG2 cell metabolome	Cédric Caradeuc, Béatrice Le-Grand, Aude	French society for toxicology (STCM)			



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	of exposure to a mixture of 2 persistent organic pollutants.	Catalayud, Adama K, Martine Aggerbeck, Gildas Bertho, Etienne Blanc.	which stands for Société de Toxicologie Cellulaire et Moléculaire (former SPTC) June 13-14th 2019, Paris, France			
81	Advancing chemical risk assessment through human physiology based biochemical process modeling.	S. Karakitsios, D.A. Sarigiannis.	12th Panhellenic Research Congress of Chemical Engineering , Athens, Greece, 29-31/05/2019 .			
82	Advancing chemical risk assessment through human physiology based biochemical process modeling.	S. Karakitsios, D.A. Sarigiannis.	Seventh International Conference On Environmental Management, Engineering , Planning And Economics (CEMEPE 2019) And SECOTOX Conference , Mykonos, Greece, 19-24/5/2019.			
83	Advancing chemical risk assessment through human physiology based biochemical	S. Karakitsios, D.A. Sarigiannis.	Seventh International Conference On Environmental Management, Engineering			



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	process modeling.		, Planning And Economics (CEMEPE 2019) And SECOTOX Conference , Mykonos, Greece, 19-24/5/2019.			
84	Exposome science for public health protection and innovation.	D.A. Sarigiannis	Seventh International Conference On Environmental Management, Engineering , Planning And Economics (CEMEPE 2019) And SECOTOX Conference , Mykonos, Greece, 19-24/5/2019.			
85	How environmental pollutants influence human health.	J.O. Grimalt	University Pompeu Fabra. Barcelona. 19 December 2018			
86	Environmental pollution in big cities.	J.O. Grimalt	Palau Macaya. La Caixa Foundation. Barcelona. 4 March 2019			
87	Impact and potential effects of DDT reintroduction in newborns and scholars.	J.O. Grimalt	Guangzhou Institute of Geochemistry. Guangzhou. China. 26 Abril 2019			



88	Plaguicides and human effects.	J.O. Grimalt	Catalan Academia. 16 May 2019			
89	The Environment-Wide Approach for the Assessment of the Effect of Environmental Stressors on Overweight, Obesity and Diabetes: A Study on Singletons for the Heals Project	Sanyal, S., Grimalt, J.O., Horvat, M., Johnstone, E., Maio, S., Polanska, K., Ramos, E., Špirić, Z., Viegi, G., Sarigiannis, D.A.; Annesi-Maesano, I.	The ISES-ISEE 2018 Joint Annual Meeting; Abstract book / Johnson, Markey; Zidek, Angelika; Smargiassi, Audrey (ur.). Ottawa, Canada: 2018. International Society of Exposure Science + International Society for Environmental Epidemiology, 1516-1516			
90	How much do dietary and non-dietary sources contribute to prenatal exposure to BPA and DEHP? A Catalonia (Spain) case study.	M.A. Martínez, J. Rovira, R.P. Sharma, M. Nadal, V. Kumar, M. Schuhmacher	SETAC 29th annual Meeting. Helsinki 26-30 May. 2018 Oral presentation.			
91	Do the principals analogs of bisphenol A have	M.A. Martínez, J. Blanco, J. Rovira, V.	SETAC 29th annual Meeting. Helsinki 26-30 May.			





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	endocrine activity? In vitro case study.	Kumar, M. Schuhmacher.	2018 Poster.			
92	Exposure to persistent organic pollutants and risk of metabolic syndrome in the population of Catalonia (Poster).	M. Garí et al.	3rd Early Career Researchers Conference on Environmental Epidemiology. Munich, Germany. 19th-20th March 2018.			
93	Urinary concentrations of organophosphate and pyrethroid metabolites from two Spanish populations (Poster).	M. Garí et al.	3rd Early Career Researchers Conference on Environmental Epidemiology. Munich, Germany. 19th-20th March 2018.			
94	Mercury accumulation in Mediterranean Sea lean fish.	J.O. Grimalt, E. Junque, M. Capodiferro, E. Marco	SETAC. Helsinki. Oral presentation. 27 May 2019			
<b>Meetings organized with stakeholders</b>	<b>Name</b>	<b>Organizer</b>	<b>Heals participants (name / partners)</b>	<b>Date / Place</b>	<b>Notes/comments</b>	
1	Final Heals Scientific Conference : "Linking	Isabella Annesi-Maesano	All	20th June 2019		



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	exposome to Human Health”					
<b>2</b>	Diverse activities have been organized in schools of Catalonia to show the results of Heals	Joan O. Grimalt and Marta Schuhmacher	The whole groups of CSIC and University Rovira i Virgili	2018-2019	These activities have involved schools of Tarragona, Barcelona, Puigcerda and other sites.	
<b>3</b>	Meeting with the gynecologists and medical doctors of the Hospital	Marta Schuhmacher and Joaquim Rovira	The whole group of the University Rovira I Virgili	October 2018		



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## 4 Project management during the period

### Work package 20 [WP-leader: UPMC (now SU)]

#### **WP20: Management**

**Partner responsible:** UPMC (now SU (Sorbonne Université))

**Reporting period:** from month 55 to 69

**Efforts planned (M1 – M69):** Efforts reported (M55 – M69)

**Actual progress:** 100 %

**Partners involved:** All partners

#### **1.4.1. Consortium management tasks and achievements**

During the 4<sup>th</sup> reporting period, the Project Office at UPMC (SU) took care of the daily management work.

- **HEALS annual meetings**  
HEALS annual meeting was held in Thessaloniki, Greece (13-14 February 2019).
- **HEALS annual meetings**  
HEALS final meeting was held in Paris, France (20 June 2019).
- **Management Board**  
Management board (MB) meeting are held almost every 4 months.

The Project office has been in charge of preparing and circulating the minutes of all MB meetings to all MB members for approval and then to the consortium by mail. Members of the consortium are granted to right to appeal against any decision taken during the MB meetings. All minutes of both MB were made available to the partners via HEALS platform (intranet). Management Board members are stream leaders in charge of Work Packages and managing Work Package Leader. Therefore, all information discussed during the management board was communicated through the Stream Leaders to Work Package leaders thanks to email or personal phone calls. It allowed regular feedbacks from Stream leaders' part of the MB to all other Stream and WP leaders, in order to ensure scientific integration of the information about the project and coherence within and across different Streams.



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- **Coordination, communication between beneficiaries**

The coordination of the scientific aspect of the project has included a regular exchange with all stream and WP leaders about the progress made. Coordination has been ensured by the Project Coordination Team (PCT).

The PCT has also been in regular contact with WP leaders in order to keep track of the work progress, of any news related to delay in progress made, problems and challenged observed, as well as to define interfaces between WPs. Communication among HEALS partners has transited mainly through meetings with WP leaders, emails and phone call. During the first period, WP leaders have also organized several internal WP meetings. The PCT has been very active in the organization of the final reporting.

Besides, the HEALS communication platform has been developed to facilitate internal communication. Partners use the tool for sharing important documents related to the project, internal report, deliverables, and presentations and communicate information related to WP meetings. The Project office has been centralizing all of these documents in order to check whether instructions and templates were followed, especially for deliverables, before being uploaded on the European Commission platform. In addition, all MB minutes, as well as minutes of every meetings and workshops and deliverables have been uploaded to HEALS platform.

- **General Assembly (GA)**

It is regularly held during the annual meetings.

- **Co-operation with other projects**

During the 4<sup>th</sup> reporting period of the project, liaisons with external projects dealing with the exposome were kept either in Europe or in USA.

- **Dissemination to other scientists from other projects**

Since, the beginning of the project, technical newsletters describing the on-going results of the project have been published and were communicated to the community during international conferences. A flyer and a poster presenting HEALS was prepared and has been presented at several international conferences.

- **Management problems which have occurred and how they were solved or envisaged solutions**



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No major issue at the management level occurred. All minor issues were solved by organising teleconferences and by communication with the partners by phone and emails.

- **Change in consortium**

The change of UPMC in Sorbonne University was mentioned in the 3<sup>rd</sup> periodic report.

As a results of the HEALS project, the creation of an HEALS consortium has been officially formalized. This will work on HEALS data and will seek for funding from public bodies, EC... to go further in the analyses.

#### **1.4.2. List of project meetings, dates and venues**

Time	Title of the meeting	Date	Venue
M63	HEALS Ewas Meeting	17-18 January 2019	Paris (France)
M64	EXPOSOME: Advances so far	13-14 Febbraury 2019	Thessaloniki (Greece)
M69	HEALS Final Meeting	20 June 2019	Paris (France)

In addition, it is planned a meeting in Brussels to convene stakeholders and researchers from related study areas to discuss the results and forthcoming activities.



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### **1.4.3. Project planning and status**

Delay in WP17 had knock-on effects resulting in delays in other WPs. EXHES is now concluded and has provided biospecimens for omics analysis (Task 17.3) and for implementing the final dataset (Task 13.2) and EWAS (Task 13.3). These analyses will be continued in the forthcoming in the frame of the HEALS consortium. The final goal is to unravel the exposome of major chronic diseases to be presented in a final meeting.

### **1.4.4. Impact of possible deviations from the planned milestones and deliverables**

No major deviation from the planned milestones and deliverables has been reported during the 4<sup>th</sup> period.

### **1.4.5. Development of the Project website**

The HEALS public web site which presents general project information has been constantly updated with news about the project, events organized, technical newsletters, videos and other dissemination and communication material. The last video concerns the HEALS final meeting in Paris.

Both public and internal e-learning materials for training have been regularly uploaded and are accessible from the Heals web site.

## **5 Discussion**

So far, the HEALS strategy has been implemented satisfactorily and has been innovative.

There are strengths in the project. HEALS constitutes a reference in terms of health and exposure databases. HEALS propose several relevant technologies for implementing EWAS at several steps. One good example is provided by Progress in WP11 consisted in the development of a novel external exposure modelling framework which supports the objectives of HEALS. The approach makes use of data and models collected within Stream 3 as a whole following a life-course approach of external exposome characterization. For the first time such methodology was applied to a group of ~550 individuals (twins) and showcased the applicability of the methodology to existing studies. This allows to associate and link different life-long multi-stressor exposure profiles to specifics of individuals. Furthermore, this may allow to draw policy-relevant conclusions about population groups of society. HEALS is also innovating with its multidisciplinary.



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However, there have been some drawbacks in HEALS. Obtaining personal address of the individuals included in the pre-existing studies has been difficult. We are still trying to obtain them. The resolution for some hazards is not good, which can bring to exposure misclassification. The problem of missing data in previous datasets has been overcome through imputation methodology and machine learning. Biospecimens in the pre-existing study are not all of good quality. However, new fresh biospecimens are collected in EXHES.



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## 6 HEALS deliverables and milestones to be accomplished during the 4<sup>th</sup> reporting period

DELIVERABLES										
Del. no.	Deliverable name	Version	WP no.	Lead beneficiary	Nature	Dissemination level <sup>5</sup>	Delivery date from Annex I (project month)	Actual / Forecast delivery date (project month)	Status Not submitted/ Submitted	Comments
D7.2	Report on predictive biomarkers appropriate for environment-wide association health assessments	1	7	ARISTOTELIO PANEPISTIMIO THESSALONIKIS	Other	PU	M30 M55 after the prolongation	M55	Received	

<sup>5</sup> **PU** = Public  
**PP** = Restricted to other programme participants (including the Commission Services).  
**RE** = Restricted to a group specified by the consortium (including the Commission Services).  
**CO** = Confidential, only for members of the consortium (including the Commission Services).  
**Make sure that you are using the correct following label when your project has classified deliverables.**  
**EU restricted** = Classified with the mention of the classification level restricted "EU Restricted"  
**EU confidential** = Classified with the mention of the classification level confidential " EU Confidential "  
**EU secret** = Classified with the mention of the classification level secret "EU Secret "





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<b>D14.2</b>	Report on the refined HEALS methodology for estimating the health effects of exposure to multi-pollutant exposure to PM and allergens	1	14	CNR	Report	PU	M40 M55 after the prolongation	M55	Accepted	
<b>D15.2</b>	Final report re-assessing the causal link between external exposure, internal exposure and health outcome as for risk of neurodevelopmental disorders in children within the HEALS framework	1	15	ISS	Report	PU	M48 M57 after the prolongation	M69	Received	
<b>D16.2</b>	Report on exposome results and of the environment-wide approach regarding	1	16	UPMC (SU)	Report	PU	M40 M60 after the prolongation	M62	Accepted	



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	assessment of the environmental determinants overweight, obesity and diabetes									
<b>D17.2</b>	Report on the implementation of EXHES with recruitment and follow-up of, singletons, twins and parents		17	UPMC (SU)			M40 M60 after the prolongation	M69	Received	
<b>D17.3</b>	Report on the application of the HEALS environment-wide association approach to EXHES data		17	UPMC (SU)			M54 M68 after the prolongation	M69	Received	
<b>D18.4</b>	Learning material for academic curricula		18	LUDWIG-MAXIMILIANS-UNIVERSITAET MUENCHEN			M56	M69	Received	



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<b>D19.2</b>	HEALS conference ?linking Exposome to Human Health?		19	AGENCIA ESTATAL CONSEJO SUPERIOR DE INVESTIGACIONES CIENTIFICAS			M56 M65 after the prolongation	M69	Received	
<b>D19.3</b>	Guidance document on the development and execution of a European Exposure and Health Survey		19	AGENCIA ESTATAL CONSEJO SUPERIOR DE INVESTIGACIONES CIENTIFICAS			M58 M68 after the prolongation	M69	Received	
<b>D19.4</b>	Report of dissemination activities and market analysis from the Knowledge Transfer Secretariat		19	AGENCIA ESTATAL CONSEJO SUPERIOR DE INVESTIGACIONES CIENTIFICAS			M60	M69	Received	
<b>D19.5</b>	HEALS newsletters and policy briefs		19	AGENCIA ESTATAL CONSEJO SUPERIOR DE			M60 M69 after the	M69	Received	



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				INVESTIGACIONES CIENTIFICAS			prolongation			
<b>D20.2</b>	Final report on compliance with ethical review requirements		20	UPMC (SU)			M60 M69 after the prolongation		Received	



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<b>MILESTONES</b>							
<b>Milestone no.</b>	<b>Milestone name</b>	<b>Work package no</b>	<b>Lead beneficiary</b>	<b>Delivery date from Annex I dd/mm/yyyy</b>	<b>Achieved Yes/No</b>	<b>Actual / Forecast achievement date dd/mm/yyyy</b>	<b>Comments</b>
<b>MS28</b>	Completion of external exposure assessment	17	1	M68	Ongoing	In progress	Extended: because it depends on implementation of EXHES
<b>MS29</b>	Completion of internal exposure assessment	17	1	M68	Ongoing	In progress	Extended: because it depends on implementation of EXHES
<b>M30</b>	Completion of EXHES (Twin and singleton Follow-up Study) on use of biomarkers and – omics technology	17	1	M68	Ongoing	In progress	



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<b>MS33</b>	Materials on use of biomarkers and – omics technologies for external training	18	9	M60	Ongoing	In progress	Exposure biomarkers and omics for external training
<b>MS36</b>	HEALS Publications	19	15	M69	Ongoing	In progress: 100 papers already published	To date, these publications have been quoted 489 times (Scopus)