Annual Report 2017

Environmental Engineering Laboratory

ENVELab

Edited by:

Assoc. Professor

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Welcome message

2017 – A story of success and international expansion

The Environmental Engineering Laboratory (ENVE Lab) was established at the Chemical Engineering department of the Aristotle University of Thessaloniki (AUTH) in the second half of 2011. Its objective is to act as an international center of reference for environmental engineering addressing the interactions between environment and human health and exploiting this knowledge to the design of novel processes and products serving sustainability objectives and the circular economy.

The main scientific foci of ENVE Lab are:

- Environment and health – development of integrated methodologies to assess the impact environmental pollution may have on human health
- Advanced technologies for monitoring environmental pollution and waste management
- Industrial ecology approaches to the design of industrial and urban systems with reduced ecological footprint in order to foster the cyclical economy

Our work paradigm is based on open international collaboration and scientific networking. Within AUTH, ENVE Lab collaborates with several analytical and biochemistry laboratories in the Schools of Engineering, Natural Sciences and Medicine. This collaboration encompasses four international projects running over the last five years.

In Greece ENVE Lab has been providing scientific support to the Ministry of Education, Research and Religious Affairs, the Ministry of Development, the Ministry of Environment, Energy and Climate, and the Ministry of Health. The ENVE Lab Director and staff participate in the permanent Committee on the Environment and several working groups of the Technical Chamber of Greece on air pollution and waste management. We have signed Memoranda of Understanding for on-going collaboration with the National Centre for Scientific Research Demokritos in Athens and the Medical School of the University of Crete. We have working links with the environmental consultancy ENVIROPLAN S.A., the international IT company UPCOM, the largest ceramic tile industry in Greece KEBE and chair the scientific committee of the Citizens' Inspectorate for Sustainable Development (CISD). ENVE Lab supports the long-range research initiative of CEFIC (the European Federation of Chemical Industry) by leading key projects on integrated exposure and risk assessment. In this context, the Lab won the Scientific Innovation Award of the CEFIC-LRI in 2017 with the project DOREMI, focusing on dose-response relationships of chemical mixtures. The Lab is an active member and since 2013 its Director has assumed the Presidency of the Mediterranean Scientific Association for Environmental Protection (MESAEP). In 2017, Prof. Sarigiannis was re-confirmed in Rome as President of MESAEP for the 2017-2019 period.

On a global scale, good collaborative links have been established with the World Health Organization, the European Center for Environment and Health, the US Environmental Protection Agency, the National Institutes for Environmental Health Science and the Schools of Public Health of the University of California at Berkeley and Los Angeles, Emory University, Johns Hopkins University and Harvard University focusing on the development of operational methodologies and novel tools towards unraveling the exposome, i.e. the totality of exposures from conception onwards and its use for assessing the associations between environmental pollution and neurodevelopmental and metabolic disorders.

During 2017, the main challenges included:

(a) leading the Europe-wide effort on the human exposome and contributing to the international debate on rendering the exposome operational for precision prevention in environmental health;

(b) representing Greece at the Program Committee on Climate Action, Environment and Resource Efficiency of Horizon 2020 and contributing to the launching of the European Human Biomonitoring Initiative;

(c) contributing to the Ostrava inter-ministerial meeting of the WHO Europe launching activities on the exposome and on the the link between waste and health;

(d) addressing the risks on neurological development of children from exposure to chemical mixtures;

(e) producing operational tools for addressing multi-hazard risks from combinations of natural and technological hazards affecting chemical plants

(f) addressing risks from chemical and biological terrorism in public indoor spaces on behalf of the Joint Research Centre of the European Commission; and

(g) starting the operation of the HERACLES research centre on Health and the Exposome at the Interdisciplinary Research and Innovation Centre of AUTH

I hope you will enjoy reading our 6th annual report. We would be happy to work with you to roll further back the boundaries of error in our understanding of the world.

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Assoc. Prof. Dimosthenis Sarigiannis

Laboratory director

Scientific Signature

EnvE Lab aims at developing integrated methodologies, knowledge management systems and technologies that can effectively shed light on the interactions between human health and the environment. Our ultimate goal is to generate the knowledge necessary to optimize interventions that protect public and consumer health cost-effectively. These include the design of technological systems that serve sustainability and respect human health.

Our concept brings together beyond-the-state-of-the-art advances in **environmental monitoring**, **human biomonitoring** and **systems biology**, **exposure monitoring** technologies and tools for **computational analyses** of the **exposure-to-health effect continuum**. The above are collated in a novel exposure biology-based methodology supported by an integrated knowledge management system at the core of the "**EnvE Lab Assessment Platform - ELAP**". Expanding the applicability domain of ELAP to a wide variety of environmental stressors is a key prerogative for its scientific soundness and its impact on public policy. Various ELAP modules are put to test through their application in a number of population studies across different exposure settings in Europe and worldwide tackling relevant health endpoints. In addition to technical research and continuous development work, horizontal activities provide the infrastructure necessary for setting ELAP in its proper policy context.

Better understanding of environmental fate, exposure and toxicity mechanisms is required to ensure refined exposure and risk characterization, e.g. the precise quantification of exposure scenarios and circumstances that might set the basis for inducing potential adverse effects on humans. However, social cost increases exponentially as we approach the maximum benefit in terms of exposure reduction; it seems that there is a threshold beyond which social cost increases disproportionally to social benefit. The aim of refining the overall assessment is to identify this optimal point, so as to design cost-effective public health protection policies that foster technical and societal innovation in parallel.

The assessment process focuses on the following: (a) hazard potency of a substance; (b) its uses and mobility in the environment (affecting the amount that the population groups will come into contact); (c) the biologically effective dose of the compound reaching the target tissue; and finally (d) the response of the human body to this dose.

These attributes are influenced strongly by the interaction of the physicochemical properties of the substance(s) under study with biological and physiological characteristics. Thus, well targeted interventions at different stages of the source-to-outcome continuum ensure the optimal management of chemicals in the environment and consumer products. Our final objective is to render this analysis a *sine qua non* tool for guiding new chemical synthesis in industry (Figure 1), in accordance with the "safe by design" principle.

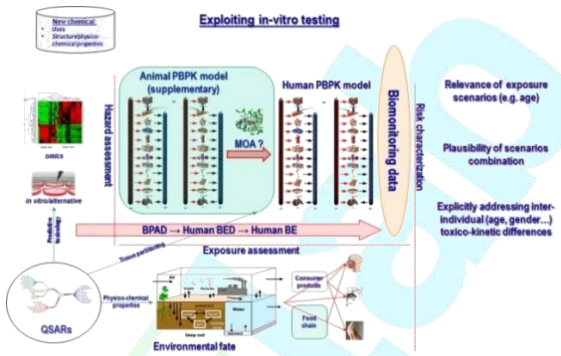

Figure 1. Integrating environmental contamination, human exposure and toxicology for refined risk characterization

The necessity of using ELAP as a novel tool for interpretation of environment and health data in order to better understand the mechanistic relationship between lifelong exposure to environmental stressors and health response has been widely recognized by the scientific, regulatory and chemical industry community; EnvE Lab's resilience in supporting this scientific signature, as well as dedication to a solid work ethics model, was rewarded by the number of different projects granted over the last 5 years, namely:

HEALS – EU FP7 project

CROME – LIFE+ project

ICSHNet – COST Action

BlueHealth – EU Horizon 2020 project

ICARUS – EU Horizon 2020 project

PEC – EU Civil Protection project

HBM4EU – European Human Biomonitoring Initiative

GREEN - GReen INfrastructures for disaster risk reduction protection: evidence, policy instruments and marketability

NEUROSOME - Marie Skłodowska-Curie

DOREMI – (Cefic Lri)

These projects follow the scientific principles described above, while focusing on different aspects of the "source-to-outcome" continuum. Acting synergistically, they contribute to the further development of the holistic EnvE Lab paradigm to exposure science and environmental health management.

Highlights of the year 2017

EnvE Lab Awards

LRI Innovative Science Award

CEFIC (European Chemical Industry Council) launched the annual LRI Innovative Science Award in 2004 to finance outstanding research contributions by early career scientists based in Europe for developing novel approaches to assess the potential impact of chemicals on human health and the environment.

Figure 2. CEFIC LRI 2017 trophy

The award-winning research proposal for the CEFIC LRI award 2017 was the one proposed by EnvE Lab for applying multi-omics analysis to investigate the potential effect of neurotoxic chemical mixtures, such as heavy metals and plasticizers, on children's neurodevelopment. The aim of the DOREMI (DOse REsponse to MIxtures) project is to derive time-dose-response levels for predicting and managing the cumulative exposure to chemicals using a combination of analysis on human biosamples and in vitro models.

iGEM 2017 gold medal

The first undergraduate iGEM team in Greece awarded with the gold medal of the iGEM Competition Competition - an international team competition made up of predominantly undergraduate students interested in the field of synthetic biology. The team was guided by four principal investigators Prof. George Koliakos, Prof. George Mosialos, Prof. Dimitra Dafou, and the director of EnvE Lab Prof. Dimosthenis Sarigiannis. The students set out to develop Pandorra, a biological computer capable of classifying cells based on the expression profile of specific molecules, that exist in all cells but follow different path in each, and expressing a pre-programmed response exclusively in colorectal cancer cells. Finally, the project culminated at the Jamboree on November 9-13 in Boston where the team competed with more than 300 other teams from across the world, presenting their design and results to more than 5000 people.

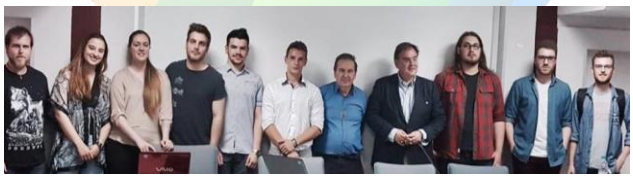

Figure 3. iGEM Team Greece 2017

Advancing neurodevelopmental disorders assessment science

The central nervous system is a common target for many environmental metals and organic compounds. These interact synergistically resulting in effects on neurodevelopment, that are different from the main effects of exposure to each stressor alone. It has also to be noted that metal exposure rarely occurs in isolation and co-exposure to metals and organic chemicals such as phthalates and bisphenols is likely to be the norm. Beyond co-exposure, there is toxicological evidence that metals interact in ways that imply effects greater than additivity, e.g. the mixture of Pb, As and Cd show a greater than additive effect on apoptosis of astrocytes. To better understand the societal cost of exposure to heavy metals, it has been estimated that the monetary cost in the EU associated to reduced IQ as a result of exposure only to Pb, amounts to almost 50 billion euro. At the same time, development of AOPs is continuously gaining ground in modern risk assessment; the latter is a sequence of events initiated by interactions of a stressor with a biomolecule in a target cell or tissue (i.e., a molecular initiating event) progressing through a dependent series of intermediate events, finally resulting in an adverse outcome. The real question is how to quantify the association between combined exposure to environmentally relevant levels of metals and selected plasticizers and neurodevelopmental effects. EnvE Lab answers this question by elucidating the synergistic mechanisms among the toxic metals and plasticizers and developing the respective AOPs relevant to neurodevelopmental disorders. Both of them, involve a combination of human cohorts, advanced *in vitro* models - namely mini brains (Figure 4), multi-omics and advanced bioinformatics.

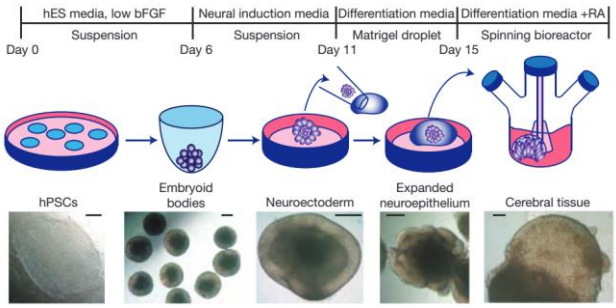

Figure 4. "Mini brains" in vitro model

This type of type comprehensive approach, has been recognized as key for elucidating the complex interplay among environmental, dietary and genetic factors, and has been granted by different stakeholders; EnvE Lab has been granted two scientific highly honorable grants, namely the Cefic Lri Inovation award (project DOREMI) and the Marie Skłodowska-Curie project NEUROSOME.

Exposure science

Exposome

The exposome represents the totality of exposures from conception onwards, simultaneously identifying, characterizing and quantifying the exogenous and endogenous exposures and modifiable risk factors that predispose to and predict diseases throughout a person's life span. The methodology for assessing individual exposome proposed by EnvE Lab brings together a comprehensive array of novel technologies, data analysis and modeling tools that support efficient design and execution of exposome studies.

• Innovations in sensor technology allow us to collect environmental data at unprecedented depth and breadth.

• We propose simulating movement and interaction behaviour using agent-based models (ABM) informed by sensor technologies in order to understand the dynamics of real-world societal and environmental systems.

• Current toxicological state of the art couples estimations of biologically effective dose (BED) with early biological events to derive dose-effect models, which can be used in combination with probabilistic exposure estimates to derive biomarkers of exposure and/or effect. Combined epidemiological, clinical and genetic/epigenetic data analysis will shed light on the effect of risk modifiers such as lifestyle choices and DNA polymorphisms and methylation. Observation of real clinical data and/or results

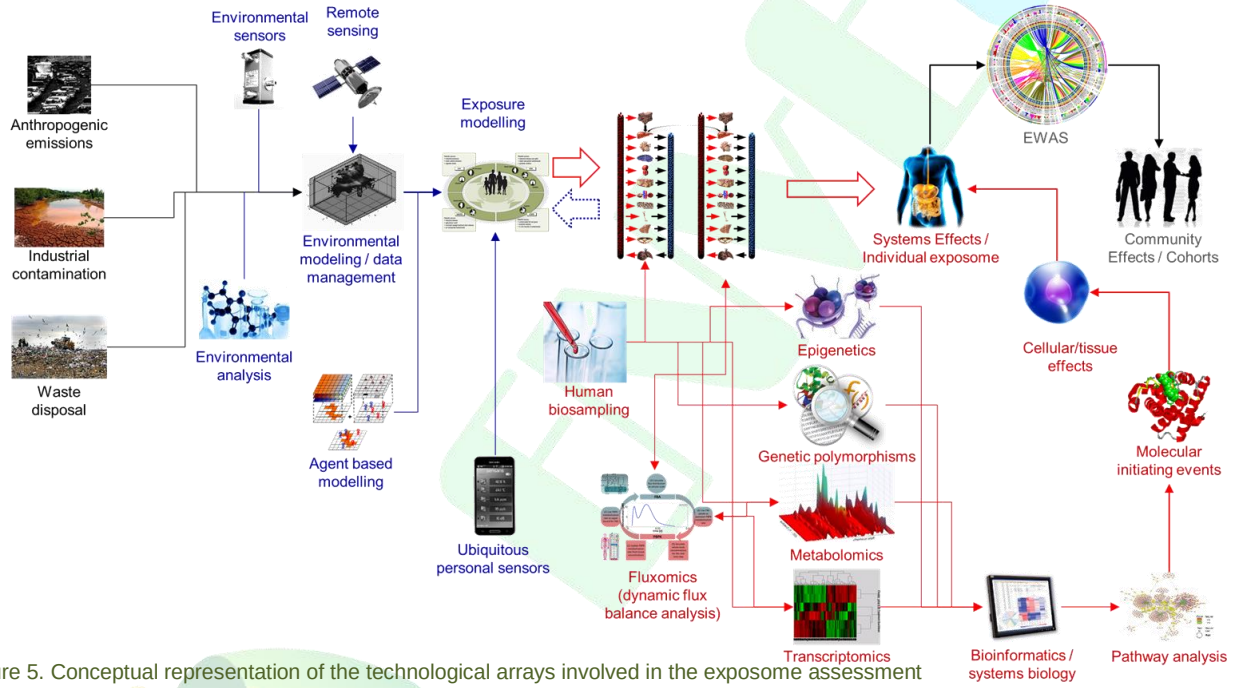

Figure 5. Conceptual representation of the technological arrays involved in the exposome assessment

This approach brings together and organizes environmental, socio-economic, exposure, biomarker and health effect data; in addition, it includes all the procedures and computational sequences necessary for applying advanced bioinformatics coupling advanced data mining, biological and exposure modeling so as to ensure that environmental exposure-health associations are studied comprehensively. The following are key components of the EnvE Lab paradigm towards unraveling the individual exposome:

• Human biomonitoring (HBM) and biobanking are seen as a central theme.

• Understanding of the interaction between HBM and exposure modeling (EM) or estimation is another key factor for elucidating the exposome.

• Lifestyle/behaviour patterns (such as time-activity-location, food consumption, use of consumer products, etc.) are needed to understand individual and population-based geospatial lifelines.

of biomonitoring coupled with exposure/effect biomarker discovery systems, will produce predictive biomarkers allowing estimations of individual response to toxic insults. Metabolomics and adductomics are key to this analytical and data interpretation process. They will be functionally integrated with transcriptomics and proteomics to provide the mechanistic underpinning for establishing causality in the association between health status and exposure to environmental stressors.

Health and Environment-wide Associations based on Large population Surveys (HEALS)

The concept

Health and Environment-wide Associations based on Large population Surveys (HEALS - www.heals-eu.eu) is the most important FP7 project funded by the European Union on environment and health. EnvE Lab co-coordinates the project providing scientific leadership and coordinating the scientific strategy and ethical aspects of the project.

Assessing the exposome in order to encompass life-course internal and external environmental exposures, from preconception onwards in order to explain the development of asthma and allergies, overweight, obesity and diabetes, as well as neurodevelopmental and neurodegenerative disorders is the first challenge taken up by HEALS. HEALS will disentangle the "internal exposome" by developing and validating biological markers using data from European pre-existing and new population-based studies and their bio-banks. This will allow detecting signals in body fluids through proteomics, metabolomics and transcriptomics permitting to characterize exposures to environmental contaminants and identify intermediate markers that lead to chronic diseases. To be exhaustive other "omics" technologies and measures in relation to external exposures (namely heavy metals, POPs, etc.) as well as the investigation of DNA adducts in relation to a number of exposure types are being conducted.

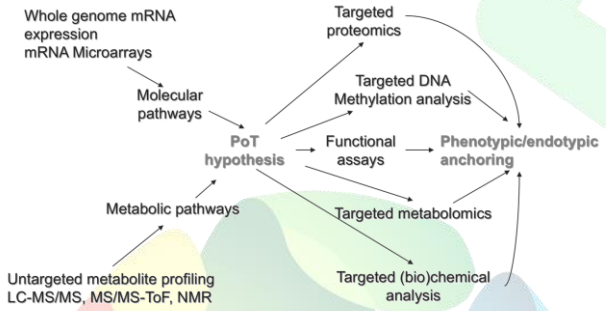

Figure 6. Analytical exposure biology workflow according to the HEALS paradigm

Research on the "external exposome" includes analysis of data from lifetime exposures to environmental pollutants in air, food, water, physical activity, medications, homes and daily stressors.

To this aim HEALS completed a pre-pilot study in seven cities in Europe where four participants per city were asked to carry for one week several personal sensors to track position, movement and activity. The successive step was to extend the variables measured by using other personal sensors in a second pilot study involving 50 households in four European cities aiming at defining an exposure assessment protocol to be implemented in the Exposure and Health Examination Survey (EXHES) study. This is the prospective cohort study through new cohorts of singletons and twins that are being to be recruited in 2016 in 10 EU Member States since in utero life and followed-up for 3 years and of their parents that best suits the "exposomics" approach. This study design gives us the opportunity to perform repeated sampling of questionnaires, clinical data and biological specimens in a longitudinal mode. Because monozygotic twins develop from a single fertilized egg, they have the same genome any differences between twins are due to their environments. Recent studies have shown that many environmentally induced differences are reflected in the epigenome. The available large-scale epigenetic studies of monozygotic and dizygotic twins in HEALS will provide data useful to the understanding of how genetic and environmental factors impact through an individual's lifespan upon epigenetics, and how epigenetics impacts on complex traits underlying disease onset and/or exacerbation.

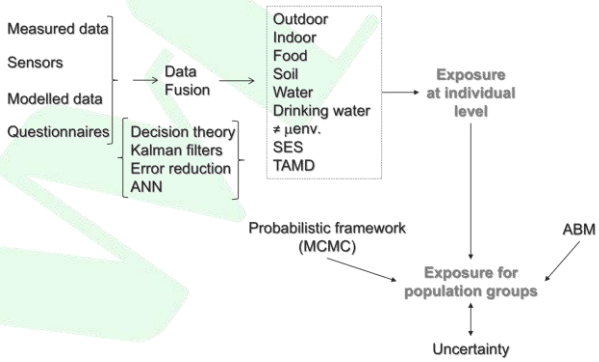

Figure 7. Workflow of external exposome assessment according to the HEALS paradigm

Developing reliable tools for assessing a complete exposure history is the second challenge taken up by HEALS. Data mining will be used to extract information from the large data set obtained, transform it into an understandable structure for further analyses and discover patterns in the environment-wide associations (EWAS) underlying diseases. The HEALS approach will be a mechanistic one, based not only on data associations but coupling bionformatics analysis with mechanistic modeling to ensure that causal associations between exposures and health outcomes are elucidated.

Dissemination, communication and training were key activities last year. International scientific workshops were organized to disseminate the project outcomes to the scientific community and EnvE lab scientists took part in major international Conferences (ISEE, SETAC, ICCA-LRI), gave one of the first lectures at the US-NIEHS webinar series on the exposome, and published in the peer-reviewed literature.

Sensors - Advancing personal and population exposure assessment

Technological advances in the recent years have produced sophisticated monitoring devices which can be carried or worn by a person during their regular daily routine allowing for personal exposure to be monitored explicitly.

Smartphone apps, wireless devices and the downsizing of monitoring technologies and costs make it possible for various environmental stressors and exposure factors to be measured more easily and frequently, thus providing a more reliable "time–geography of exposure" shifting the current paradigm from a population to an individual level.

From an operational point of view personal sensors can be grouped according to the type of data they can provide: passive pollution measuring sensors which can measure the pollution levels encountered in the different locations where users spend their days, tracking location and physical activity sensors which provide information about the spatial patterns of user location and physical activity. Direct reading monitors are used to identify whether peak exposures are more important than average exposure values, identify specific exposure pathways that dominate in critical time windows over an individual's lifetime, and finally build individual exposure profiles.

Combining information on individual position with spatially resolved pollution levels allows us to assign pollutant concentrations to a person as they move through different microenvironments. Moreover, information on individual physical activity as tracked by personal sensors allows the estimation of the breathing rates during different activities which in turns translated into inhaled dose. This novel and promising approach gives us access to an unprecedented amount of "individualized exposure data", which could greatly improve our understanding of exposure and health associations but which are worthless without interpretation (e.g. human behaviour recognition). This requires statistical advances, sophisticated data mining techniques, computing power as well as a careful sharing of data sources while also maintaining privacy protections for personal data. Big data is difficult to be used with classical relational databases, desktop statistics and traditional visualization packages. What is common for big data treatment is that it is not just about storing huge amounts of data; it is the ability to mine and integrate data, extracting new knowledge from it.

As part of the HEALS project, during 2016, larger scale measurements have been initiated that include a series of commercially available location tracking and physical activity sensors together with pollution measuring sensors. Data was captured based on both in-home and personal monitoring. In more than 25 households a series of devices was placed, such as: a) the *Dylos*, a small, noiseless PM sensor that captures particles concentration in 2 size ranges >0.5 um and >2.5 um diameter, b) the *Netatmo*, which measures indoor air temperature, humidity, CO_2 and noise and c) *Radiello*® passive diffusive air samplers that capture aldehydes and benzene, toluene, ethylbenzene, and xylenes (BTEX). Participants' location and activity data was captured with physical activity sensors and smartphone apps. Specifically, the *Fitbit Flex* fitness monitor captured motion and intensity of activity, *Moves* app tracked location and activity, *WideNoise Plus* app tracked noise and *FatSecret* app tracked nutrition patterns. In addition, participants were asked to fill in a time activity diary and to answer to a series of questionnaires with the aim to capture further information regarding their personal exposure to potential sources of pollution, household conditions, SES and preferences/frequency of usage of consumer products. Occasionally in-house exposure assessment experiments took place with additional high accuracy equipment such as a) the AQ Expert Indoor Air Quality Monitor, that tracks CO_2, CO, tVOC, CH_2O, O_2, NO_2, O_3, SO_2, H_2S, NO/NO_x, relative humidity, temperature, barometric pressure and air velocity and b) Aerocet-531S Mass Particle Counter, that tracks six mas ranges and four particle sizes.

Wider scale sensors campaigns (HEALS – EXHES) will soon take place. This approach is a characteristic of *exposome* studies, where data is being gathered with the aim to do exploratory analyses to discover associations that lead to further, more targeted hypothesis driven research.

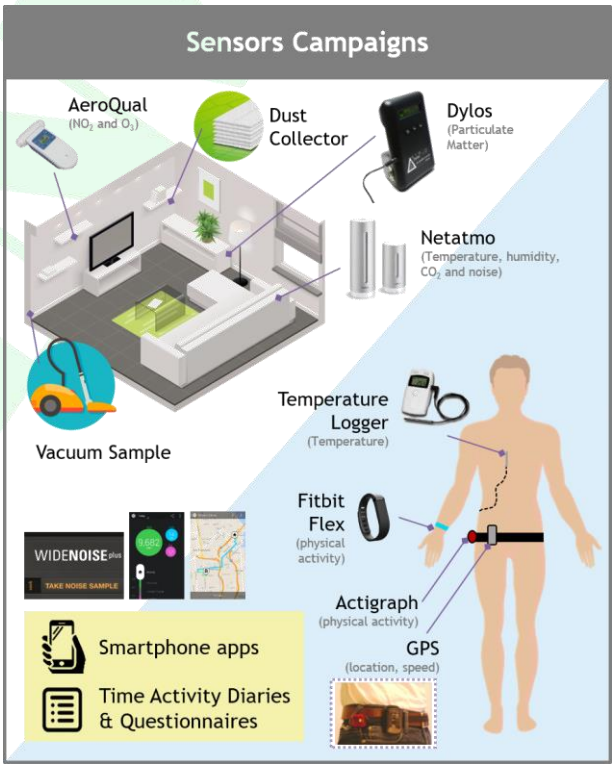

Figure 8. Overview of the personal sensors used during the preliminary trial campaign.

Personal exposure assessment using portable sensors data and Agent Based Modelling (ABM).

As already mentioned, innovations in sensor technology create possibilities to collect environmental data at unprecedented depth and breadth. Measuring, though, personal exposure directly requires a large number of people and therefore is often not feasible due to time and financial constraints. Considering the substantial hurdles involved in collecting personal exposure data for whole populations, a decision has been made to simulate human movement and interaction behaviour using Agent Based Modelling (ABM), a simulation technique that enables a better understanding of the behaviour of individuals and populations in social and evolutionary settings. This approach can produce data that could fill in gaps that exist in traditional datasets, taking into account different activity patterns and Socioeconomic Status (SES) data.

A spatially explicit ABM platform was established, modelling the city of Thessaloniki. The model can feed into a population-based exposure assessment without imposing prior bias, but rather basing its estimations onto emerging properties of the behaviour of the computerised autonomous decision makers (agents) that compose the modelled system (city). City's population data, vehicles fleet information, road and buildings networks were transformed into human, vehicle, road and building agents respectively. Particular emphasis is being given in the case of in-model incorporation of SES data. Time – use survey outputs with data on lifestyle/behavioural patterns were associated with human agent behavioural rules, aiming to model representative to real world conditions.

At the end of a model run, activity patterns can be determined for every human agent, as an outcome of the prevalence of specific preferences and decision-making throughout the simulated time of experiment. Different human agents based on different characteristics (age, gender, SES indicators) will express different behaviours and this could lead to a different exposure profile. It is then possible to extract human agents' trajectories on a GIS format together with a database that contains their coordinates and activities in time through different locations/microenvironments. The GIS layer can then be superposed onto Air Quality maps. In this model, individual exposure to PM concentration is deduced via superimposing the human agent's trajectory on daily average PM10 concentration maps, modelled for urban Thessaloniki. These maps are the outcome of data fusion from ground observations, pollutants dispersion modelling and satellite images. The high spatial resolution map allows us to calculate exposure at the level of building block. For the cases where human agents are located indoors, indoor concentration is estimated using the INTERA computational platform. Personal exposure, expressed as inhalation-adjusted exposure to air pollutants is then evaluated by assigning pollutant concentrations to an agent based on his/her coordinates, activities and the corresponding inhalation rate.

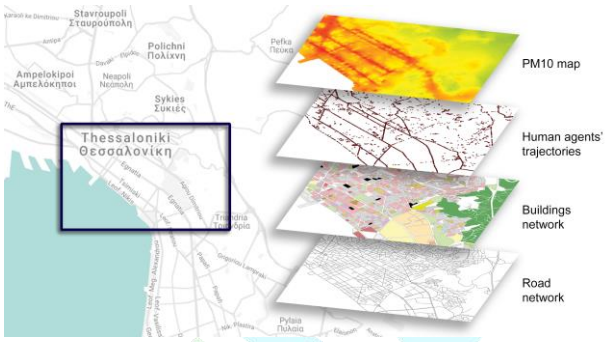

Figure 9. Personal exposure assessment using Agent Based Modelling (ABM).

The ABM model can be validated against real "time-geography" of exposure data, retrieved by exposure assessment campaigns, like the Thessaloniki sensors campaign (*mentioned in a previous chapter)*. Virtual time-activity data and exposure profiles of human agents can be compared to and be validated against the real data of campaign participants with a similar sociodemographic background.

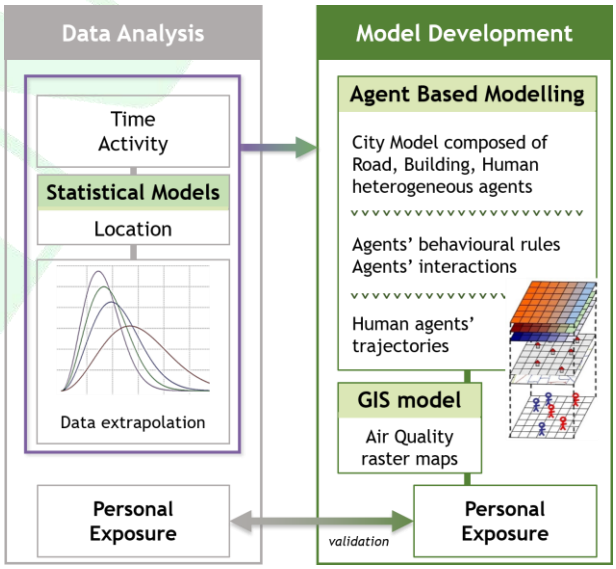

Figure 10. From sensors data to a personal exposure model.

An example of the ABM derived exposure profiles is showcased below. This study goes beyond the approach of classic epidemiology where outdoor PM concentration is the main proxy for assessing exposure. Here, exposure timeseries are based on outdoor (*red line*) as well as indoor (*green line*) concentrations that were estimated based on personal trajectories. Then exposure to PM_{10} (*black line*) as well as inhalation adjusted exposure (*blue line*) were also calculated. Furthermore, exposure assessment was extended to the calculation of intake dose, taking into account a representative body weight and breathing rate, based on the agent's age and gender.

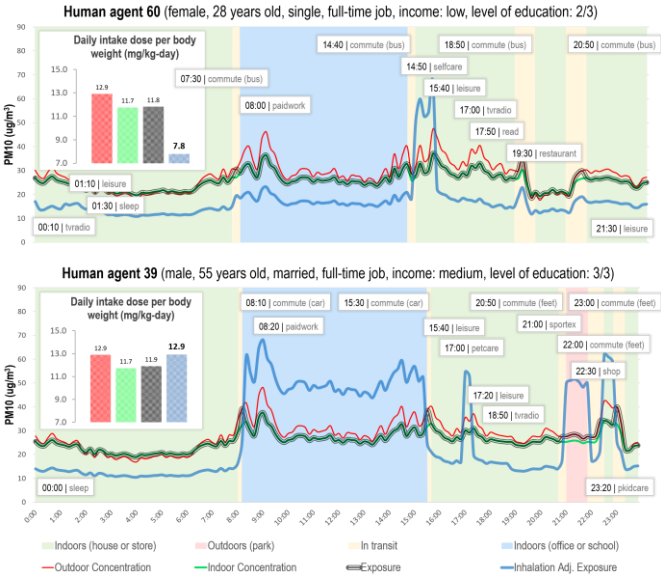

Figure 11. Exposure to PM10 and daily intake dose of two human agents. Personal exposure *in black*; inhalation adjusted exposure *in blue.*

Figure 18 illustrates an example where the effect of sociodemographic characteristics in exposure refinement can be clearly observed, since for two human agents that are phenomenally exposed to similar outdoor PM10 levels (12.9 μg/m^3), the actual exposure in terms of daily intake is differentiated by 65% (7.8 and 12.9 μg/m^3 respectively), due to the prevalence of different behaviours.

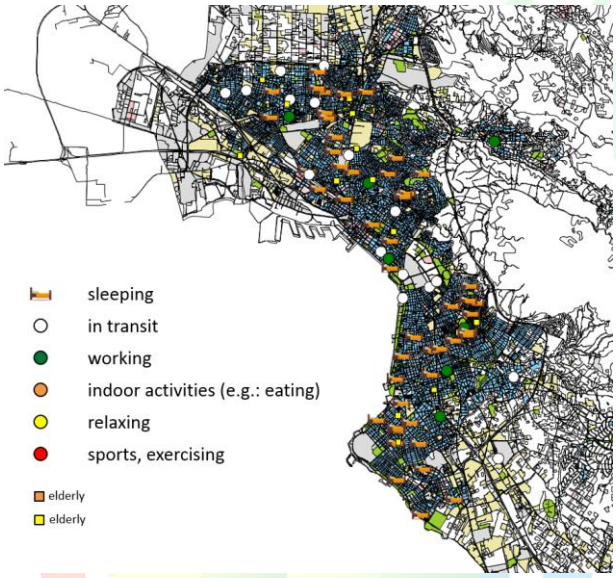

Figure 12. Moving human agents on a representative day in the city of Thessaloniki - running example of the ABM platform.

On average, personal exposure results were between 10 and 20% more accurate than the equivalent estimate using outdoor PM concentration as exposure proxy. The identification of exposure peaks and troughs throughout the day leads to useful conclusions regarding capping exposure to high pollution levels.

Overall:

- The ABM approach brings a new way to study the complex systems, allowing to take into account the heterogeneity of the entities composing a system.
- This approach permits the **cost-effective construction of refined time-activity diaries and diurnal exposure profiles.** The refined exposure assessment model can address effectively vulnerable population sub-groups, integrating socio-economic status indicators.
- Utility functions are provided that can shape human agents' preferences based on individual characteristics. **Different SES groups will follow different behaviours and this will be reflected in different decisions regarding mode of transport, consumer products or even diet patterns**. Eventually this will result to a more accurate exposure assessment.
- Changes in exposure levels can be calculated for individuals and specific subgroups of population based on different spatio - temporal behaviours.
- This approach can also be established for different cities, without changing the basic programming architecture.
- ABM-generated distributions of human agents' behavioural patterns can also work as an input into a probabilistic exposure assessment model.
- This study represents the first step towards improving the calculation process of population exposure to environmental substances so that we would be able to draw better conclusions on the association between environment and health.
- Such a model could be further used in order to study the effect of different measures/policies to reduce pollution levels in cities/countries. It can be used as a means for estimating and comparing the probable effects of different public health strategies prior to implementation. These simulations can lead to better initial choices and reduce the time and expense required to identify effective strategies.

The dietary exposome

Food as consumed contains many different chemicals which are either desirable (e.g. micronutrients) or undesirable (e.g. pesticide residues or mycotoxins). For all these chemicals, levels in the diet that are either too high (e.g. pesticides residues) or too low (e.g. essential vitamins) maybe detrimental to human health.

Food is the most important exposure pathway for trace metals (e.g. As, Cd, Pb, Hg) and POPs for the general population. Indeed, food is typically responsible for more than 90% of total adult exposure to PCDDs/Fs and co-planar PCBs (WHO 2002; Centre for Food Safety 2012) and to Hg and Cd (for non-smokers). In this light, when considering human exposure through the whole life it is imperative to properly take into account exposure to chemicals through diet. In the course of the risk assessment process, exposure estimates are required based on the consumption of the foods containing these substances and the level of the substances present in those foods. In both cases dietary intakes were calculated using the following formula:

$$I_j = \sum_{k=1}^{n} C_k \cdot L_{k,j}$$

where I_j is the dietary intake of chemical j; C_k is the consumption of food k and $L_{k,j}$ is the concentration level of chemical j in food k.

Dietary exposure to each contaminant of interest was calculated individually using the following formula:

$$E_j = \frac{\sum_{k=1}^{n} C_k \cdot L_{k,j}}{BW}$$

Where E_j is dietary exposure to the chemical j and BW is the human body weight

The above methodology was applied to a population study as well as to an individual level.

For the first application we have used data collected in the frame of the French Total Diet Study undertaken between 2006 and 2009 by the French National Institute for Agricultural Research (INRA), in collaboration with the French Food Safety Agency (AFSSA). Food consumption patterns disaggregated for age, gender, educational level and geographical region were derived from the INCA 2 study which was carried out by AFSSA between 2006 and 2007 and included 4,079 individual subjects (2,624 adults aged from 18 to 79 years and 1,455 children aged from 3 to 17 years). By way of example, population daily exposure to arsenic for different gender and age classes and educational level are reported below.

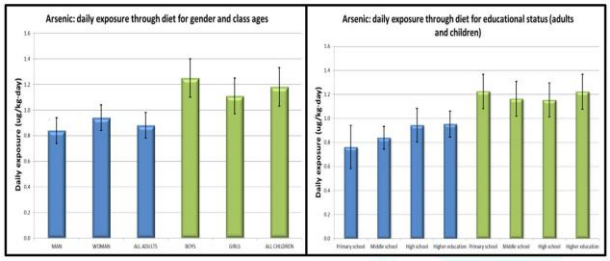

Figure 13. Arsenic daily exposure for some population groups

For the second application we used the individual food consumption data collected in the pilot study carried out in Athens in the frame of the FP7 project HEALS. Thirty mothers and their children were followed for one week and their individual food consumption habits were collected through the Fatsecret app.

Individual daily intake to trace metals (As, Cd, Cr, Hg and Pb) and persistent organic pollutants (PCDDs, PCDFs, PCBs, PFOS and PFOA) are reported below.

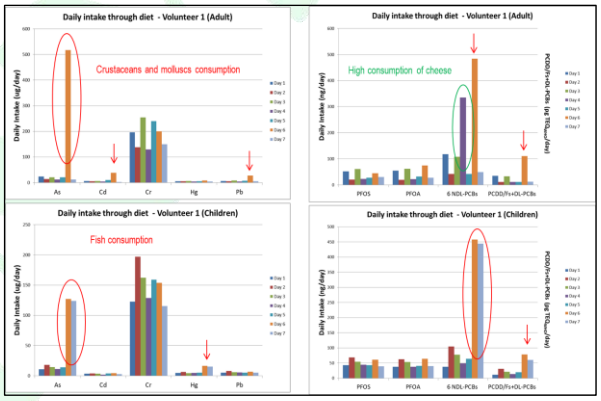

Figure 14. Individual daily exposure of adult (above) and children (below) to trace metals (left) and POPs (right)

Results of the two applications showed that both in adults and in children fish and seafood (e.g. crustaceans and molluscs) are the main contributors to POP and to most of trace metal (As, Cd, Hg and Pb) exposure.

The main contributors to chromium intake are bread and dried bread products and alcoholic beverages. In children, the main contributors to chromium intake are milk and pasta. Generally, cheese and dairy products are significant contributors to dioxin and PCB exposure. For children, the most consumed foodstuff is milk; the latter has a vector rate equal to that of ultra-fresh dairy products and cheese, which have more fat content and thus higher concentrations of POPs.

People with higher educational level show higher exposure to POPs and to most of the trace metals (As, Cd, Hg and Pb) due to the higher average consumption of fish and seafood. Children show higher exposure level to all the contaminants investigated due to their lower body weight with respect to the adult one.

The effect of prenatal exposure to phthalates and metals on child psychomotor development

Phthalate and heavy metals prenatal exposure was determined by targeted metabolomics in urinary and plasma samples from (n=165) mothers during the third trimester of pregnancy (prenatal exposure) and from their children at the 24th month of age (postnatal exposure), using LC–MS/MS. Psychomotor development was assessed in children at the age of 2 years by the Bayley Scales of Infant and Toddler Development.

Child motor development was inversely associated with natural log concentrations (μg/g creatinine) of 3OH-MnBP (β = − 2.3; 95% CI − 4.0 to − 0.6), 5OH-MEHP (β = − 1.2; 95% CI − 2.2 to − 0.3), 5oxo-MEHP (β = − 1.8; 95% CI − 3.3 to − 0.2) and sum of DEHP metabolites (β = − 2.2; 95% CI − 3.6 to − 0.8), DnBP metabolites (β = − 1.9; 95% CI − 3.4 to − 0.4), and high molecular weight phthalates (β = − 2.5; 95% CI − 4.1 to − 0.9) in the urine collected from mothers during pregnancy after adjustment for a variety of potential confounders. Postnatal child exposure to phthalates was not associated with any of the measured scores of child psychomotor development. To further elucidate the potential mechanism that relates phthalates exposure with child motor development, untargeted metabolomics analysis using a combination of LC-MS/MS and NMR of the mother urine samples was carried out. Typical metabolites profile from both NMR and LC-MS/MS analysis are illustrated in Figure 15 and Figure 16 respectively.

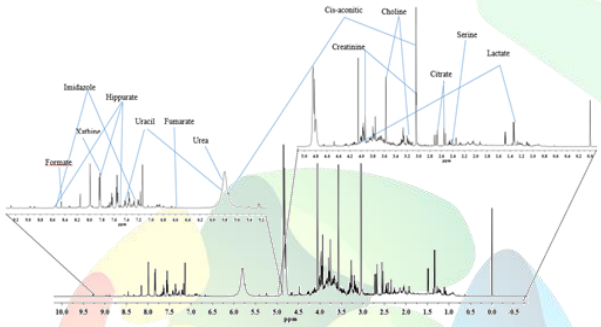

Figure 15. Typical metabolites profile from NMR analysis.

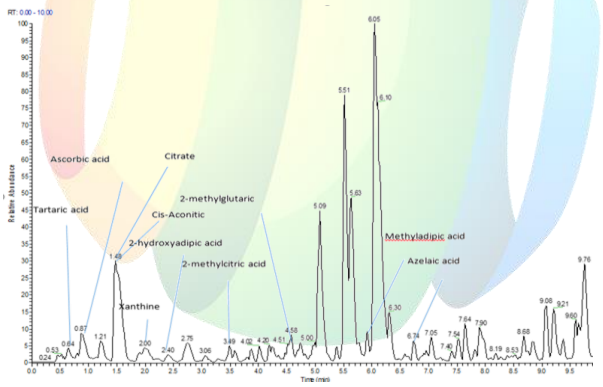

Figure 16. Typical metabolites profile from LC-MS/MS analysis.

Metabolic pathway analysis using Agilent GeneSpring revealed that alterations in urine metabolites are related to the TCA cycle, suggesting impaired mitochondrial respiration; the latter is central to energy metabolism and cellular signaling and plays fundamental roles in synthesis of nucleotides and active transport processes. Inhibition of mitochondrial oxidative phosphorylation could also cause defective mitochondrial energy production during the process of fetus formation and development that are reflected in early life motor development.

EWAS analysis figured out the negative or beneficial contribution between various neurodevelopment and environmental indices. The overall analysis came up a wide range of associations that are illustrated with a globe diagram in Figure 17. Results reported, also, in volcano plots, which combine the results of the statistical significance test with the magnitude of the fold change, enabling visual identification of parameters that are statistically significant and characterized by large-magnitude fold changes.

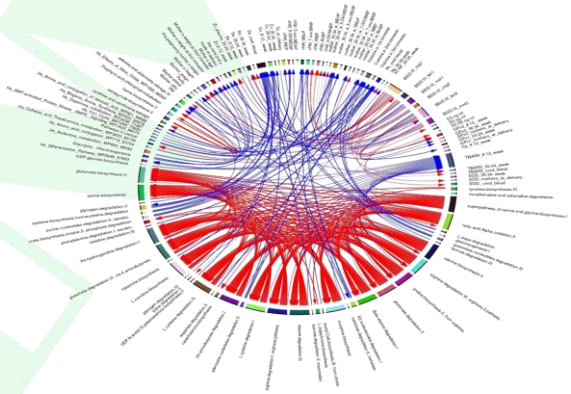

Figure 17. Correlation globe plot of the REPRO_PL study.

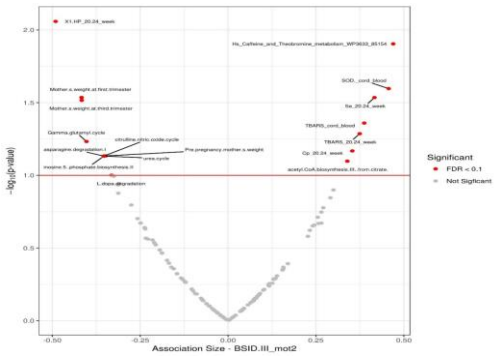

Figure 18. Association of the motor development volcano plot with exposure and modifiers at two years of age.

The aforementioned -omics analysis was also followed for the analysis of 172 mother and child samples, which were derived from the existing molecular epidemiology study PHIME. Key adverse outcome pathways related to TCA cycle, glycolysis, and carnitine metabolism, indicating the possibility of disruption of mitochondrial respiration, in accordance to the key findings of the REPRO_PL cohort study.

Cross-Mediterranean Environment and Health Network (CROME)

The concept

The Cross-Mediterranean Environment and Health Network project - CROME (www.crome-life.eu) is a 42 months demonstration project coordinated by EnvE Lab that started in July 2013 and got funded under the EU LIFE+ Programme 2007-2013.

The main objective of CROME-LIFE is to demonstrate a technically feasible integrated methodology for interpreting human biomonitoring (HBM) data to quantitatively assess the impact on human health due to acute/chronic exposure to chemicals acting as neurodevelopmental and neurological toxicants and/or human carcinogens such as toxic and organic substances.

The CROME-LIFE method and tools are being applied in four demonstration sites (Greece, Slovenia, Italy and Spain) tackling different levels of environmental exposure, age windows, and socio-economic and genetic variability.

First results include the definition of the methodological framework which starts by estimating exposure using human biological monitoring data and work both forward to disease linking internal doses in target tissues with health impacts through advanced statistical methods and backwards (using reverse dosimetry) to environmental exposures.

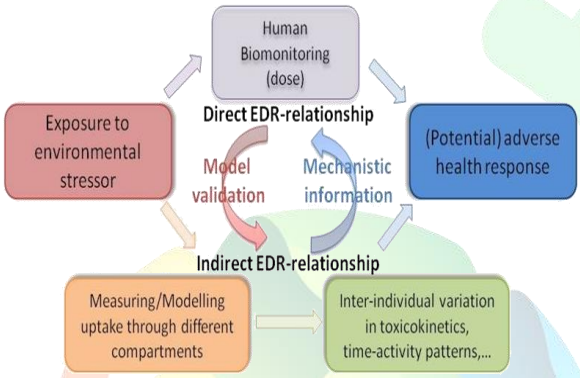

Figure 19. CROME methodological framework "middle out approach"

Re-evaluation of existing cohort data

Already existing data from past population studies (PHIME, PROBE, INMA) were collected and stored into the CROME geo-database after Quality Assessment / Quality Control. Statistical analysis of Latium (Italy) population data (450 human blood samples collected among adolescents) has been carried out through the application of GLM models in order to identify the associations between metals concentration levels in blood and several exposure determinants including the residence and land use at the participant residence and workplace, the frequency of fish and milk consumption and the exposure to PM10 data. Results showed that Cr has a statistically significant association with diet (i.e. fish and milk consumption) and with land use both alone and in combination. Hg has a more complex interaction between diet and human activities (i.e. proximity to industrial activities). No pathway alone is dominant but the combined effect results in statistically significant associations with blood concentration levels. Pt and W show an interaction effect between diet and land use. Internal exposure to Ni is mainly driven by diet (co-exposure to milk and fish).

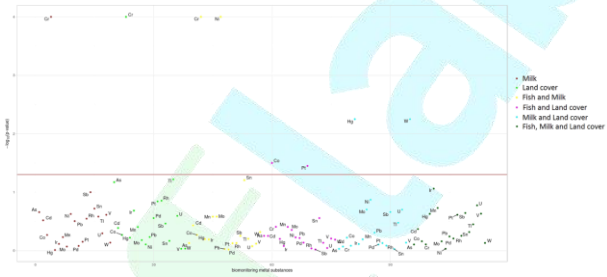

Figure 20. Manhattan plot of associations of the environmental factors with HBM levels of metals ($p < 0.05$). The red line represents a $p < 0.02$, which means a more robust association.

Next step is the execution of the fields campaigns both environmental and human biomonitoring which will start in the first months of 2015. These include four country-specific case studies (one for each participating Country) and one common case study in all participating countries focusing on exposure to Hg and neurodevelopmental disorders. Applications for Ethical Review have been prepared and submitted to the National Ethical Committees. Applications consist of detailed explanation of the studies from background to design. They include also the questionnaires and inform consent to be distributed to the study participants. Environmental campaigns already started in the demonstration sites through the sampling of several food items, with a special emphasis on fish species, and drinking water.

Dissemination activities have been continued throughout this year with the aim of disseminating the project outcomes to the scientific community, informing citizens and involving stakeholders about the associations between exposure to chemical and the impact on human health. They involved a wide range of dissemination channels including the participation to major International and National conferences, publication of scientific papers in peer-reviewed journals, written and electronic press releases and TV interviews, technical newsletters and project leaflets to be distributed during the main project events.

Assessment of PAHs exposure and genotoxic effects

Genotoxic effects of inhaled particulate matter (PM) are mainly attributed to absorbed polycyclic aromatic hydrocarbons (PAHs). Human respiratory tract (HRT) deposition of a specific particle depends on its aerodynamic diameter. Thus, xenobiotics contained in finer particles can easily be transferred in human body via systemic circulation. Benzo[a]pyrene (B[a]P) is the only PAH classified as known carcinogen to humans by IARC.

An extensive campaign was carried out from January to April 2013 at two locations in the urban area of Thessaloniki to determine the chemical composition of urban aerosols and to correlate their toxicity with biomass combustion as a way of residential heating. PM1, PM2.5 and PM10 particles were collected in Teflon filters using low flow air samplers in two air pollution monitoring stations, representative of urban/residential and traffic influenced pollution respectively.

Nineteen individual PAHs were analyzed by GC/MS and concentrations in air were calculated for both monitoring stations. Potential cancer risk due to exposure to the mixture of urban ambient air PAHs was calculated using the toxicity equivalent factor (TEF) approach based on Benzo(a)pyrene (B[a]P) (Figure 21).

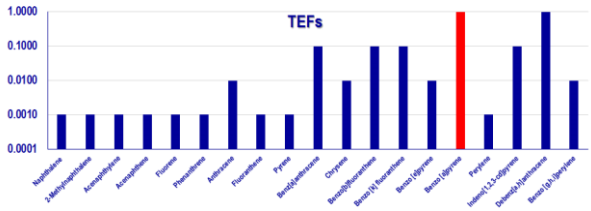

Figure 21. Toxic Equivalent Factors (TEFs) for the different PAHs, on the assumption that the TEF for B[a]P is equal to 1

The TEQ (Toxicity Equivalent Quotient) (carcinogenicity equivalent, in ng/m^3) was calculated by multiplying the concentrations of each compound in the PAH mix with the respective TEF for cancer potency relative to BaP. Daily inhalation rate (*IR*) and deposition fractions of particulate matter to the main regions of the respiratory system were calculated for eight age groups of human population. The ultimate cancer risk was estimated for each age group using the CEPA Inhalation Unit Risk (*IUR*) for B[a]P.

The results showed that PM (PM1, PM2.5, PM10) and PAHs concentrations, during the cold period, were higher in the urban background monitoring station than in the traffic station. This pattern was attributed to biomass combustion, which can be considered as the primary source of PAHs in the populated areas of Thessaloniki during the last two years winters. PAH and levoglucosan levels were highly correlated, indicating that particles emitted from biomass combustion are more toxic than PM emitted from other sources. The median ΣPAHs levels at the urban background site are 8.31, 9.82 and 9.91 ng/m^3 for the PM1.0, PM2.5 and PM10 fraction respectively. At the traffic station, the corresponding levels are 2.82, 3.52 and 3.92 ng/m^3 (Figure 22). Therefore, practically, most of the PAHs are adsorbed in fine particles (PM2.5 and finer).

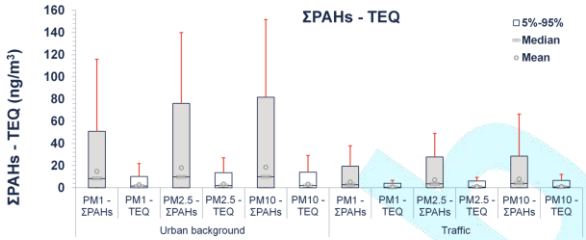

Figure 22. Total PAHs concentrations for the two monitoring stations

At the urban background site median TEQs are 1.61, 1.93 and 1.96 ng/m^3 for PM1.0, PM2.5 and PM10; the corresponding values at the traffic site are 0.43, 0.63 and 0.69 respectively (Figure 22). The TEQ at the urban background monitoring station is 3 times greater than the equivalent value found at the traffic station. TEQ/PM ratios at the urban background site are 0.091, 0.083 and 0.066 ng/μg PM for PM1, PM2.5 and PM10 respectively. At the traffic site, the respective ratios are 0.045, 0.44 and 0.032 ng/μg PM.

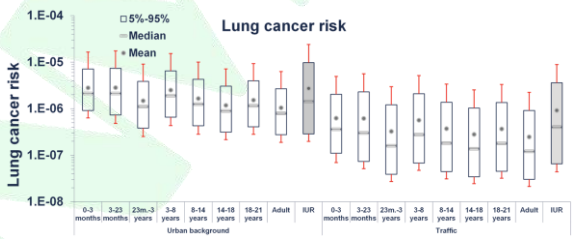

Figure 23. ICR calculated for each age group

The estimated lung cancer risk was non-negligible for residents close to the urban background monitoring site. Higher risk was estimated for infants and children, due to the higher bodyweight normalized dose and the human respiratory tract (HRT) physiology. HRT structure and physiology in youngsters favor deposition of particles that are smaller and more toxic per unit mass. In all cases, the estimated risk (5.7E-07 and 1.4E-06 for the urban background site and 1.4E-07 to 5.0E-07 for the traffic site) was lower to the one estimated by the conventional methodology (2.8E-06 and 9.7E-07 for the urban background and the traffic site respectively) that is based on Inhalation Unit Risk; the latter assumes that all PAHs adsorbed on particles are taken up by humans. With the methodology proposed herein, the estimated risk presents a 5 to 7 times difference between the two sampling sites (depending on the age group). These differences could not have been identified had we relied only on conventional risk assessment method. Consequently, the actual cancer risk attributable to PAHs on PM emitted from biomass burning would have been significantly underestimated.

Waste and health

Athens, the capital of Greece, is populated with around 5 million inhabitants. The average amount of municipal solid waste is equal to 6 ktn/d (Hellenic Statistical Authority 2008). The average composition of the waste in Attica Figure 24 includes organics (42%), paper (29%), plastic (14%), metal (3%), and other material (6%).

Figure 24. The main waste management site in the area of Athens (landfill in Fili) and the respective waste composition

The average transportation distance of the MSW is 19 km. Two of the main MSW facilities in Athens are the landfill in Fili. The HERACLES (Waste Management) Greek cohort, is a study aiming at assessing the contribution of environmental contamination due to waste management practices in the urban and periurban environment associated to children neurodevelopment. The study has been established in 2012. Around 350 children aged 3 to 8 living in the proximity between 0.5 to 12 km were enrolled. For the association, several exposure factors have been investigated, including exposure to heavy metals, such as Cd, Hg and As in urine, Pb in blood, Mn and Hg in hair (Figure 25), exposure proxies, such as distance from the contaminated sites, concentration of heavy metals in the soil of the child address, additional factors considered as exposure and effects modifiers such as sociodemographic parameters (socioeconomic status, mother education, father education, stress events) as well as child anthropometric parameters and post-delivery factors (child body mass index, child gender, breastfeeding, presence of micronutrients, minerals and vitamins, Se in the mother plasma during pregnancy, delivery and in cord blood).

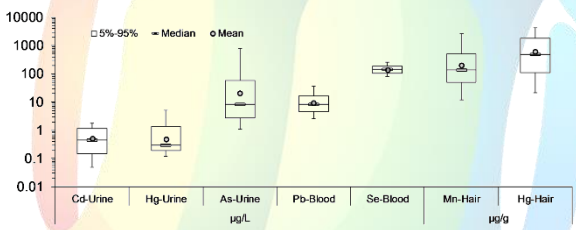

Figure 25. Levels of heavy metals in the various human biospeciments

Finally, detailed dietary habits, such as consumption of meat products (pork meat, beef, lamb, sausages), fish, sea food, poultry (eggs, chicken), dairy products (milk, yogurt), nuts, fruits, vegetables and snacks (biscuits, chocolates) were also recorded. Neurodevelopmental progress in children was estimated with (a) the Child Behavior Checklist, also called the Achenbach System of Empirically Based Assessment, is a report form to screen for emotional, behavioral, and social problems and (b) Wechsler Intelligence Scale for children – Fourth Edition (Wechsler, 2003), which is an individually administered measure of intelligence intended for children. WISC-IV yields measure of general intelligence as reflected in both verbal and nonverbal (performance) abilities and specific indices including verbal comprehension, perceptual reasoning, working memory and processing speed. Auto-correlations of the various parameters, are illustrated in the correlation globe (*Figure 26*).

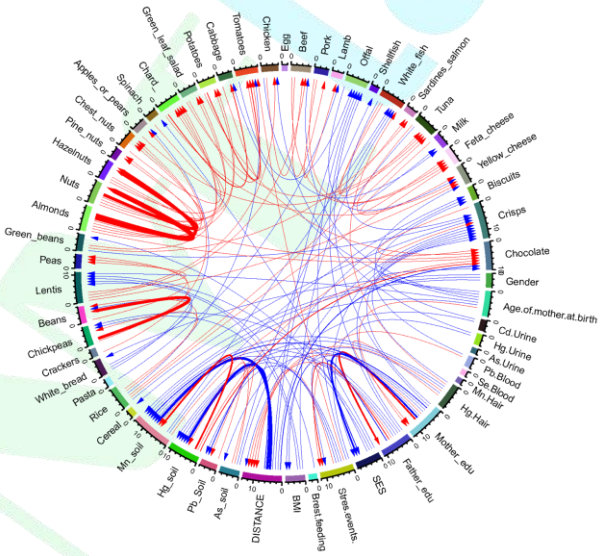

Figure 26. Correlation globe of environmental, dietary and exposure factors in the HERACLES study

EWAS analysis results relevant to the Child Behavioral CheckList (CBCL) test battery results show that socio-cultural factors are strongly associated with children behavior. More specifically the mother school title and the age of the mothers at birth show both a robust statistical association (p-value<0.05 and in some cases p-value <0.01) with most of the CBCL indices considered. Looking at the volcano plots both parameters show a negative association with the CBCL scores indicating that lower educational level of the mothers as well as a lower age of the mother at the children birth may have negative impact on the children behavior.

The stress index was derived by merging the total number of stressful events detected by the mother and their average intensity is also playing an important role on the children behavior (p-value<0.05 and in some cases p-value<0.01) showing a negative effect on both internalizing and externalizing problems indices such as anxiety and depression, withdrawal and depression and somatic complaints, aggressive and rule-breaking behavior. The concentration of lead in blood shows a strong statistical significance (p-value <0.05) with most of the CBCL indices analyzed. In this case the association shows a positive direction revealing a negative impact of higher blood

concentration of lead on the on cognitive functions in children. This result is confirmed by a number of research studies which indicate exposure to lead as one of the most environmental determinants of neurodevelopmental disorders in children. Of opposite sign but still with robust statistical significance is the association of the concentration of selenium in blood which appears to beneficially, especially with regard to Internalizing Problems and ADHD as measured by CBCL battery indices. These results confirm the antioxidant properties of selenium which is a well-known regulator of brain function.

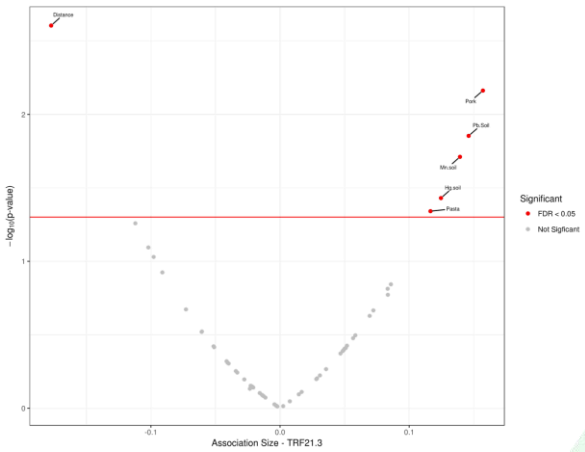

Figure 27. Associations of attention deficit / hyperactivity problems (from the CBCL test battery) with the environmental, dietary and exposure factors

Distance of the residence address from the waste management site was found also to be a key factor associated with almost all the indices of the WISC IV test. More specifically, this variable showed a robust statistical association (p-value <0.001) with the Intelligence Quotient (IQ), Verbal Comprehension index, Perceptual Reasoning index, Working Memory index. Analysis of the results shows a positive association with the WISC IV scores indicating that living far from the waste management site has a positive impact on the children cognitive functions. Interesting conclusions can be drawn from the analysis of food consumption patterns. Tomato consumption appears to be statistically (p-value <0.05) associated with intelligence quotient (Figure 28), Verbal Comprehension index and Working Memory index while cereal consumption reveals a strong association (p-value < 0.01) with the Perceptual Reasoning index. Both food items are positively associated with cognition indices meaning that their consumption has potential positive effects on the cognitive functions of the children. Epidemiological evidence suggests that consumption of lycopene, a natural antioxidant present in tomatoes, is able to reduce the risk of chronic diseases such as cancer, cardiovascular diseases as well as psychiatric syndromes. In another study reported that low serum levels of lycopene have been associated with increased risk of psychiatric disorders.

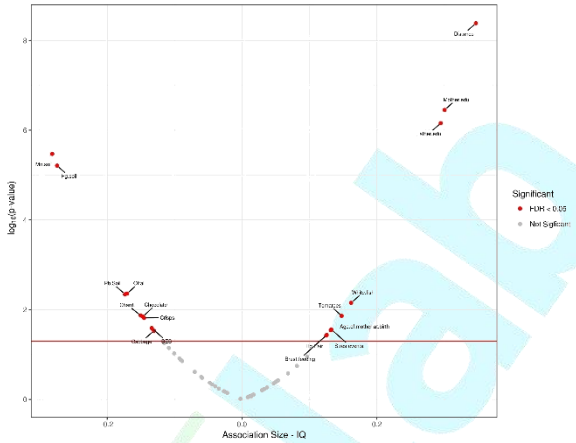

Figure 28. Association of intelligence quotient (from the WISC-IV test battery) with environmental, dietary and exposure factors

Consumption of fish showed a hybrid behavior depending on the type of fish and the neurodevelopmental indicator considered: higher consumption of white fish appears to have positive effects on the IQ and Verbal Comprehension index (p-value <0.001) while higher consumption of white fish reveals a negative effect (p-value <0.01) on Perceptual Reasoning index and Working Memory index.

A key finding of the study is that concurrent evaluation of environmental, societal and nutrition factors, allowed the identification of the most critical parameters. Distance of the family residence from the landfill was identified as the most important parameter, highlighting the contribution of the area contamination to child neurodevelopment. However, the beneficial effect of parental education and of children/family socio-economic status need to be underlined. Additional beneficial effects arise from specific dietary patterns such as consumption of white fish and tomatoes, while the same occurs for breast feeding. White fish is rich in omega 3 fatty acids. Direct actions of omega-3 polyunsaturated fatty acids on neuronal composition, neurochemical signalling and cognitive function constitute a multidisciplinary rationale for classification of dietary lipids as "brain foods." The validity of this conclusion rests upon accumulated mechanistic evidence that omega-3 fatty acids actually regulate neurotransmission in the normal nervous system, principally by modulating membrane biophysical properties and presynaptic vesicular release of classical amino acid and amine neurotransmitters. On the other hand, tomatoes are considered as strong antioxidants, providing protection against the reactive oxygen species (generated by heavy metals) that affect neuronal mitochondria and eventually children neurodevelopment.

Quantitative Structure-Activity Relationships (QSARs)

A major area of work within the INTEGRA project is the development of QSAR models. QSARs are regression or classification models, included in "in silico" approaches that form a relationship between the biological effects and the chemical structure of a chemical compound, Y = f (X).

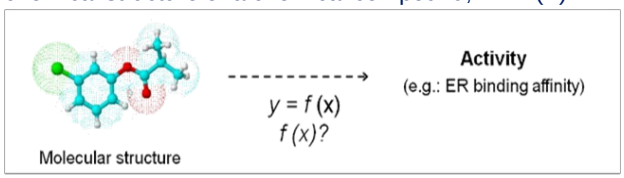

Figure 29. Basic methodological scheme for QSAR development.

QSARs are widely used to estimate the required inputs of Physiologically Based Bio-Kinetic (PBBK) models. PBBK models provide quantitative descriptors of Absorption, Distribution, Metabolism and Excretion (ADME) of an environmental or pharmaceutical chemical and their application is of major importance in toxicity testing and health risk assessment. The input parameters for PBBK modeling are either species-specific or chemical-specific. The species-specific parameters relate to alveolar ventilation rate (Qp), cardiac output (Qc), tissue blood flow rates (Qt) and tissue volumes (Vt) and should be within the documented range for the particular species and life stage. The chemical-specific inputs include partition coefficients (blood/air (Pba), tissue/air (Pta) or tissue/blood (Ptb)) as well as metabolic parameters such as the maximal velocity of metabolism (Vmax), the Michaelis – Menten constant (Km) or the intrinsic clearance (Vmax/Km). These physicochemical parameters should be obtained on the basis of independent measurements (in vitro, in vivo) or using algorithms in the valid domain of applicability, like QSARs.

EnvE-Lab research focuses on the development of a simple and unified QSAR model, which could be used to predict both major physicochemical and biochemical properties of a large group of environmental chemical compounds. The activity data to be modeled (Y) includes the tissue/ blood partition coefficients for different human tissues (kidney, heart, muscle, adipose, brain, lung, liver), the elimination half-life, $t_{1/2,elim}$, as well as the metabolic parameters, V_{max} and K_m.

Up until now, several approaches incorporating QSARs have been proposed for the prediction of partition coefficients for PBBK modeling, including (a) the Peyret, Poulin and Krishnan algorithm, which is based on the fractional content of cells, interstitial fluid in tissue, plasma in blood, erythrocyte in blood, tissue lipids and the lipophilicity of the compound of interest and (b) the molecular fractions algorithm proposed by Béliveau et al. that takes into account the frequency of occurrence of the several molecular fragments of the compounds.

In this study, particular emphasis was given to the development of QSAR models using two different descriptor sets (X):

1. Linear Free – Energy Relationship (LFER) Descriptors

$$logSP = c + e \cdot E + s \cdot S + a \cdot A + b \cdot B + v \cdot V$$

Where SP: biological property of the examined chemical,

E: excess molar refractivity, S: chemical's dipolarity/polarizability, A: hydrogen-bond acidity, B: hydrogen-bond basicity, V: McGowan characteristic volume of the chemical.

2. PaDEL Descriptors

1D and 2D molecular descriptors: constitutional, topological, electronic and geometrical.

The first step for the development of QSAR models was the preparation of the collected data. This process included the a) reduction of the initial descriptors in order to avoid the semi-constant (>80%) and intercorrelated (>95%) ones, b) distribution and categorization of chemicals using Principal Component Analysis (PCA) and c) data splitting into training, validation and test set.

The data was, then, analyzed using two statistical methods:

a. Genetic Algorithm based Multiple Linear Regression (GA-MLR)
- Ordinary Least Squares (OLS) model
- Genetic Algorithm (GA) for descriptors' selection.

b. Artificial Neural Networks (ANN)
- Levenberg-Marquardt (LM)
- Scaled Conjugate Gradient (SCG)
- BFGS Quasi-Newton (BFG)

The developed models were evaluated according to the coefficient of determination and Mean Squared Error (MSE). The Applicability Domain (AD) of the developed best models was determined using geometric, range-based, distance-based and Probability Density Function (PDF)-based methods. Then, the models were applied to several chemical compounds with unknown values of physicochemical and biokinetic parameters.

The results obtained from the analysis for adipose/blood partition coefficient are presented below.

Table 1. Statistical values for the developed models.

Descriptors	Method	R^2	R_{tr}^2	Q_{cv}^2	R_{ext}^2	MSE_{tr}	MSE_{val}	MSE_{ext}
LFER	MLR	0.82	0.84	0.72	0.85	0.12	0.21	0.16
	LM-ANN	**0.94**	**0.93**	**0.96**	**0.98**	**0.05**	**0.04**	**0.03**
	SCG-ANN	0.92	0.87	0.97	0.95	0.07	0.06	0.05
	BFG-ANN	0.91	0.92	0.84	0.92	0.09	0.06	0.05
PaDEL	MLR	0.86	0.88	0.84	0.85	0.09	0.12	0.19
	LM-ANN	**0.96**	**0.96**	**0.95**	**0.94**	**0.04**	**0.05**	**0.03**
	SCG-ANN	0.92	0.91	0.93	0.93	0.07	0.05	0.06
	BFG-ANN	0.94	0.95	0.89	0.90	0.04	0.06	0.06

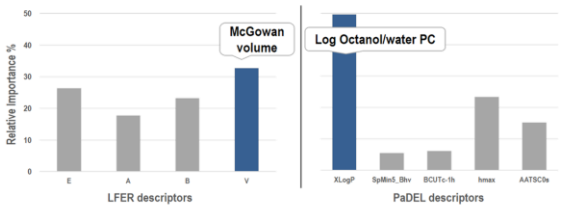

Figure 30. Relative importance of input descriptors for the developed best models.

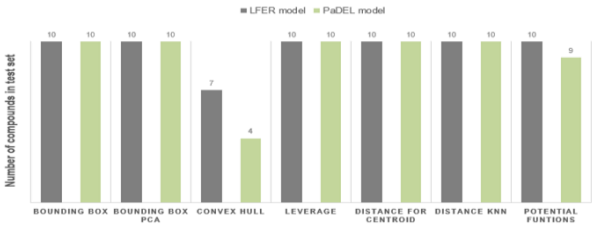

Figure 31. Applicability domain of the developed best models.

The results obtained for the parameters of $t_{1/2,elim}$ as well as V_{max} and K_m are the following:

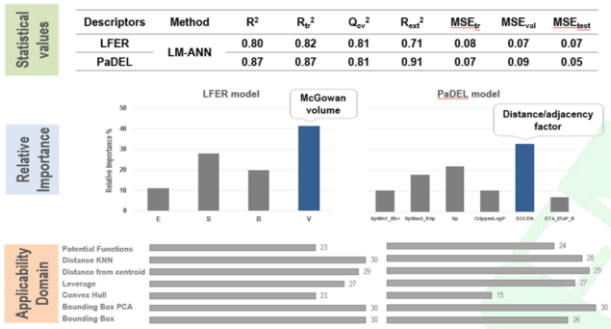

Figure 32. Results for the elimination half-life, $t_{1/2,elim}$.

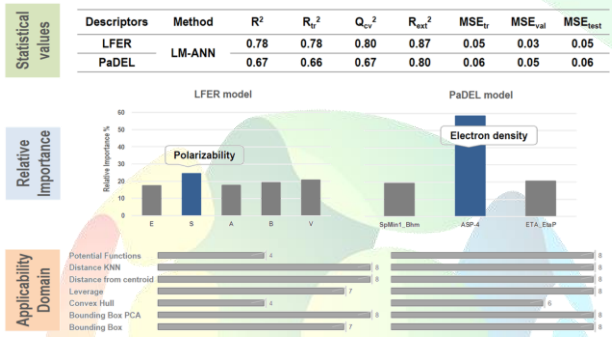

Figure 33. Results for the maximal velocity of metabolism, V_{max}.

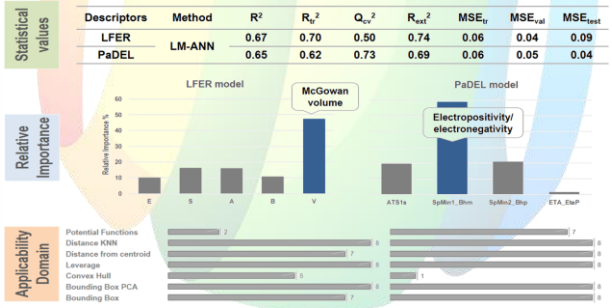

Figure 34.Results for Michaelis-Menten constant, K_m.

The results showed that LM-based ANN outperformed GA-MLR and SCG/BFG-based ANN methods. The use of ANN provides the essential flexible mathematical framework for describing the non-linear biological interactions. Furthermore, the analysis concluded to one PaDEL and one LFER model for each of the responses of interest. Specifically, the estimated values of coefficients of determination for both training, validation and test set for the developed best models exceeded the desirable criteria for QSAR acceptance, which are 0.6, 0.5 and 0.6, respectively. In addition, the calculated MSE values for all sets were significantly low, verifying that the models could be both reliable and predictive. In the majority of the predicted responses, the models that were developed using PaDEL descriptors offered a larger chemical space than the one obtained from the models using LFER descriptors.

The proposed models were examined for their fitting capacity, validity and applicability. They were stable, reliable and capable to predict physicochemical and biochemical parameters of "data poor" chemical compounds that fall within the applicability domain. In this way, the broader use of Physiologically Based Bio-Kinetic (PBBK) models in chemical risk assessment could be reinforced, especially when considering the current shift of toxicological research to non-animal testing as aptly shown by the large international efforts on high throughput screening. Finally, the Prevention through Design (PtD) concept for environmental chemicals is supported, by allowing the successful prediction of toxicokinetic behaviour based on molecular parameters.

Exposure reconstruction from HBM data

The establishment of relationships among events along an exposure chain, health evaluation as well as risk assessment is the key issue to understand how the exposure of environmental chemicals effect on public health. Although daily, Biomonitoring Data (BD) are reported in order to evaluate the internal exposure, the gap between the correlation of external exposure and BD stills remain. That procedure to estimate the relationship between internal and external exposure is termed as "Exposure Reconstruction" (ER) or "reverse dosimetry". Exposure reconstruction is an ongoing scientific research field and various computational techniques have been formulated such Deterministic Inversion, Stochastic Inversion/Bayesian Approach, Exposure Conversion Factor Approach, Discretized Bayesian Approach and Bayesian Markov Chain Monte Carlo in order to give a solution to the problem.

Considering that these techniques are the foundations for developing new and improved approaches ER, a conceptual/computational framework was been developed based on Bayesian Markov Chain Monte Carlo combined with a generic Physiological Based Pharmacokinetic (PBPK) model (Figure 35).

The analysis of the developed ER framework consists of 3 basic steps. At first the prior parameter distribution, the joint probability distribution, the population model and the

determination of the measurement model have to be specified.

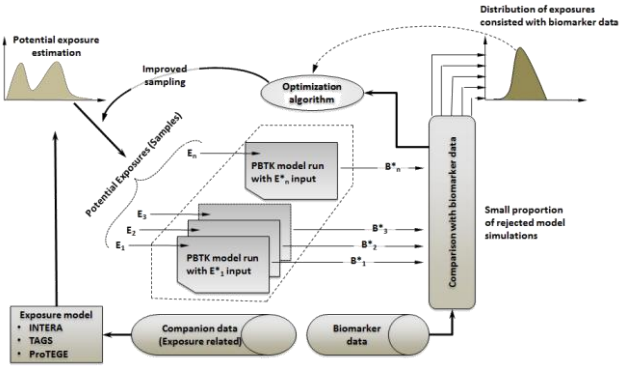

Figure 35. Optimization-aided exposure reconstruction based on HBM data using time-evolving PBPK models

At the next step exposure is calculated using MCMC simulation considering the observed biomonitoring data. Finally, the evaluation of the results is realized using MC simulation, with emphasis to the comparison of prior and posterior distribution as well as parameter independence.

MCMC simulation (Figure 36) refers to a class of iterative simulations in which the random variables of interest are drawn from a sequence, or chain, of distributions that eventually converge to a stable posterior distribution.

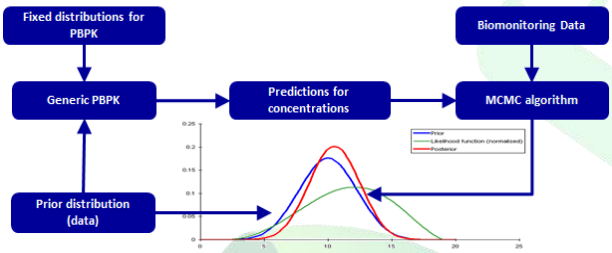

Figure 36. Conceptual/computational framework for the exposure reconstruction

Moreover, Differential Evolution (DE) and MCMC algorithms have been combined to solve this problem for the first time. Differential Evolution Markov Chain is a population MCMC algorithm, in which multiple chains run in parallel. In fact DE is a simple genetic algorithm for numerical optimization in real parameter spaces. As a result, this combined computational framework speeds up the calculation and convergence, even for nearly collinear parameters and multimodal densities.

The results of the simulation corresponded very well to a dataset of synthetic data, as well as to real biomonitoring data (Figure 37).

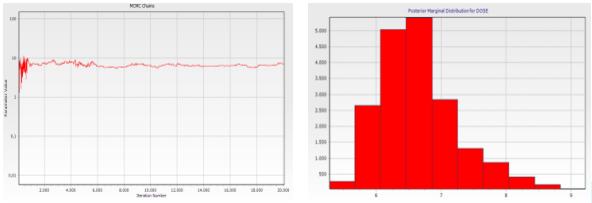

Figure 37. MCMC simulation convergence and Posterior Distribution for dose

Validation of the computational tool using real life HBM data

Exposure reconstruction of trichloromethane (TCM)

Aiming at investigating the effect of domestic cleaning activities on children passive exposures to trichloromethane from their mere physical presence at home, we evaluated urinary TCM data from children and matched-mothers. In practice, using the children urinary chloroform levels, indoor air background chloroform concentrations were reconstructed. These concentrations were used for estimating mother exposure. Re-running forward the model using these concentrations levels as exposure for the mothers, their urinary chloroform was predicted, as well as the respective chloroform blood levels (internal exposure). Regarding our study on the effect of domestic cleaning activities, our analysis showed the valid use of urinary chloroform levels as a proxy to internal exposure to chloroform, but only if background exposure concentrations were considered. Given that chloroform are metabolized and excreted rather rapidly, their levels in morning urine reflect primarily indoor air concentration and, to a smaller extent, drinking water levels. Activities that lead to significant increase in chloroform release into the indoor air such as dishwashing, bleaching, showering, bathing etc. affect the observed biomarker levels, by raising the uptake rate of chloroform from the indoor air. Based on the urinary levels and by reconstructing exposure so as to fit the measured biomonitoring data, blood and exhaled breath chloroform levels were also calculated for the matched-mothers' and children.

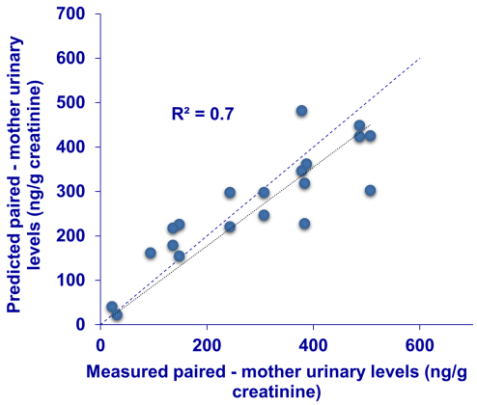

Figure 38. Measured vs. predicted urinary chloroform levels for the paired mothers, based on indoor concentrations derived from exposure reconstruction of paired-children data

In the current study highly dynamic exposure phenomena had to be investigated. Thus differences in: (a) intensity of activity (which is affecting inhalation rate, thus actual uptake, as well as elimination through exhalation) and (b) urinary excretion rate were incorporated as physiologic parameters in the model. This allowed us to better account for the effect of human physiology differences on the observed differences in TCM urinary levels. Thus we managed to attribute the exposure levels resulting in the observed urinary TCM levels more accurately. The effect of gender, age and activity intensity on inhalation rates was also taken into account. Excretion rates were estimated based on the measured urine volumes collected. When this data was not available, age and gender specific urinary excretion rates were used; this is because blood flow to the kidneys and the subsequent excretion rate are not altered by intensity of activity. By reconstructing exposure, it was found that the related cleaning activities contribute to different levels of chloroform exposure. Among these activities, mopping was found to result in exposure up to 15 μg/m^3, followed by showering. However, different cleaning activities affected differently the exposure of study participants; this reflects differences in the use of domestic products such as varying chloroform concentrations in the product used, the amount of products used, housing and ventilation conditions as well as physiological differences among the exposed subjects.

Translating urinary concentration into exposure levels, allowed us to estimate internal exposure as well. Cleaning activities resulted in chloroform blood concentrations close to 100 ng/L, while mopping seems to be associated to higher internal exposure levels; this is the result of the higher intensity of activity during mopping, when intake rate is increased due to increased inhalation rate.

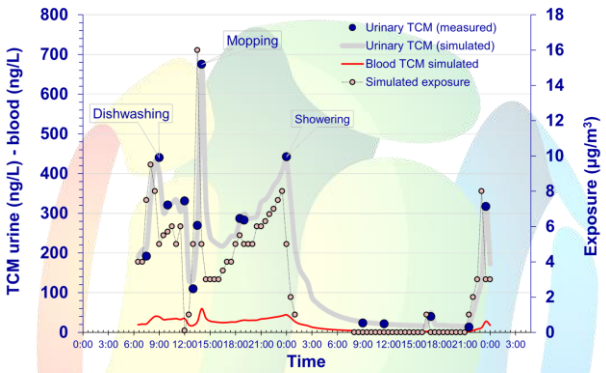

Figure 39. Measured urinary TCM (blue dots) and modelled chloroform levels in urine (grey line), blood (red line) and ambient air (dashed line)

However, potential differences in consumer product-related exposure (amount of product use, chlorine concentration of the product) and housing conditions (air exchange rate) act as confounders prohibiting the derivation of robust conclusions about the relative significance of the respective activities. In any case, we need to highlight that the use of a validated PBBK model allows us to use a biomarker acquired by a non-invasive technique (urinary chloroform), which is also one magnitude of order higher than the respective blood biomarker. This allows us to better differentiate exposure conditions and thus identify the contribution of cleaning activities in the overall exposure to chloroform.

Exposure reconstruction of triclosan

Another application of validating the computational platform of INTEGRA was the estimation of triclosan exposure levels during teeth brushing. Seven volunteers were writting in a time-activity diary the time of teeth brushing and the amount of toothpast used, while all day urinary voids were collected and analyzed. Based on the urinary triclosan concentrations, and knowing the timing that exposure events occurred, the amount of triclosan intaken per brushing was successfully estimated. The results of the simulation for a typical individual are illustrated in Figure 40. Starting from the measured urinary triclosan (black dots) and knowing the moment that the individual was exposed to triclosan, the dose received in each brushing was estimated (green dots). The accurate prediction of the dose is shown by the very good fit of the measured urinary concentrations against the ones predicted by the model. This further allows us to estimate the actual internal dose, meaning the concentration of triclosan in blood (red line) and eventually to potential target tissues.

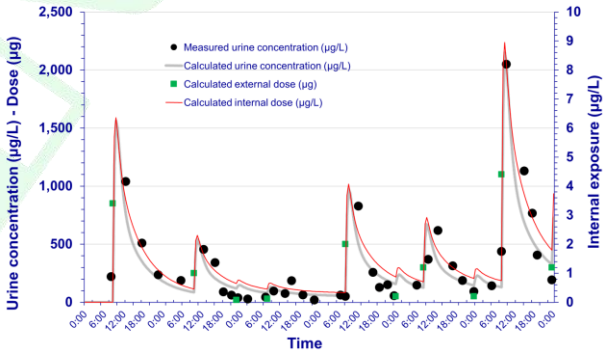

Figure 40. Measured (black dots) and modelled (grey line) urinary triclosan levels, modelled levels in blood (red line) and predicted dose (green dots)

Exposure reconstruction of bisphenol A

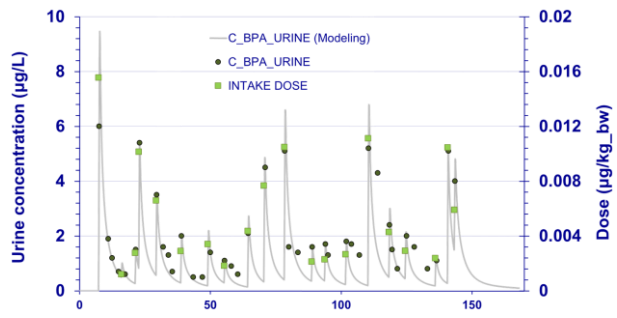

Figure 41. Measured (black dots) and modelled (grey line) urinary bisphenol A levels, and predicted dose (green dots)

Similarly, diurnal exposure to bisphenol A through food and drink items was estimated starting from urinary biomonitoring data. The results indicated that overall daily exposure to bisphenol A remains below 0.1 μg/kg_bw/d, while internal dose of free plasma bisphenol A was in the range of few pg/L

External and internal exposure assessment to PAHs from multiple sources

Exposure to PAHs has became of particular scientific and regulatory interest the last year, especially in view of the potential for petroleum substances to be included in the different REACH processes (notably Evaluation and Authorisation). In order to meet the requirements of REACH, it is of particular importance the capability of models to predict direct (arising from the use of substances) and indirect (e.g. fuel combustion) PAH exposures. The capabilities of the INTEGRA platform for addressing integrated multi-source, multi-route (MSMR) exposure to PAHs was demonstrated in a workshop organized by CONCAWE. A typical scenario that was demonstrated, dealt with the prediction of the environmental fate and exposure of annual emissions of 400 tones B[a]P in air within EU, and for regional emissions of 15 tons. Distribution across different environmental media and the contribution of different pathways and routes to the overall exposure were estimated (Figure 42) both for adults and children.

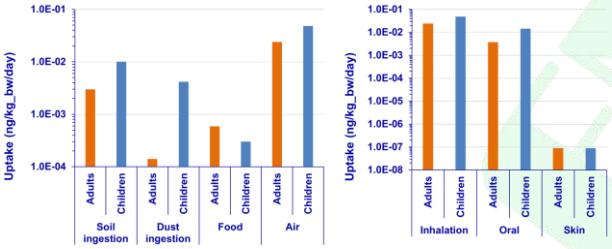

Figure 42. Contribution of pathways and routes in aggregate PAHs exposure

Moreover, internal exposure to B[a]P and urinary concentration of 3-OH-B[a]P (the most specific B[a]P metabolite) was also estimated.

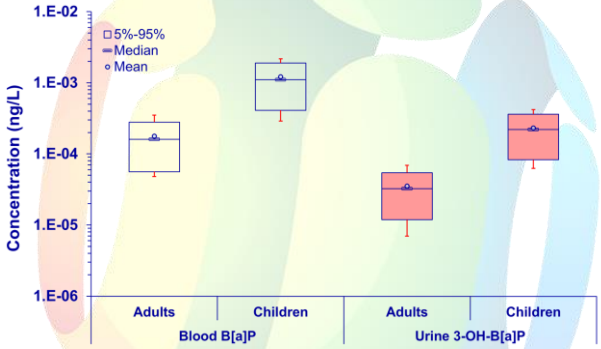

Figure 43. Internal exposure and urinary concentrations of major B[a]P metabolite

The time-dynamic nature of the INTEGRA computational platform, allows also to capture environmental, exposure and internal dose dynamics in high temporal resolution, quantifying the effect of real-life different exposure conditions (such as driving, eating smoked fish or operating an open fireplace) in actual uptake, internal dose and expected biomarker urinary levels (Figure 44).

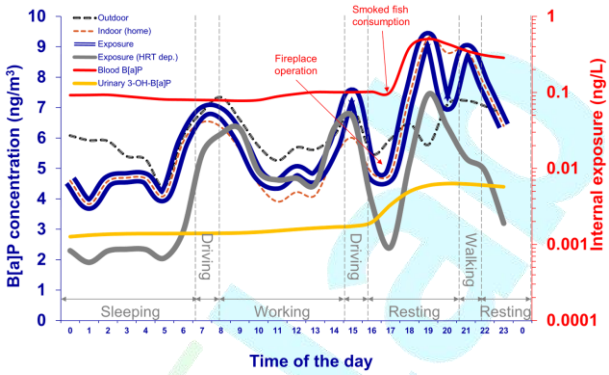

Figure 44. Diurnal variability of environmental, exposure and internal dose dynamics

Climate change, air pollution and human health

Integrated Climate forcing and Air pollution Reduction in Urban Systems (ICARUS)

The ICARUS main objective is to develop integrated tools and strategies for urban impact assessment in support of air quality and climate change governance in EU Member States leading to the design and implementation of appropriate abatement strategies to improve the air quality and reduce the carbon footprint in European cities.

Under the perspective of urban transportation, the co-benefits to urban air quality, noise and public health were investigated from the introduction of greenhouse gas (GHG) emission reduction policies to the city of Thessaloniki and the Great Thessaloniki Area (GTA). The traffic related policies implemented, included the introduction of underground rail in the city centre and changes in vehicle composition, i.e. allowing a larger share for the diesel engine passenger cars, the hybrids and the electric cars.

Air and noise pollution were assessed for a baseline scenario in year 2010 and two future scenarios in year 2020, a business-as-usual (BAU) and a GHG emission reduction scenario (CO2 scenario). This assessment was carried under an integrated methodological framework, composed of a series of interconnected models and repeated for the years 2010 and 2020. The models used, included the (a) SIBYL, to project vehicle stock numbers; the (b) VISUM, to simulate traffic flow as a result of changes in travel demand; the (c) COPERT IV, to compute the pollutant emission (PM10, PM2.5, NO_2, NO_X, O_3, CO and benzene) per vehicle engine and type; the (d) OSPM to compute pollutant concentrations in traffic corridors; the (e) CALPUFF, to compute pollutant concentrations on motorways and urban/peri-urban roads; and the (f) NMRB-2008, noise model to evaluate traffic noise generation and its propagation from traffic corridors and motorways under the ISO 9613-1 and the 9613-2 constraints.

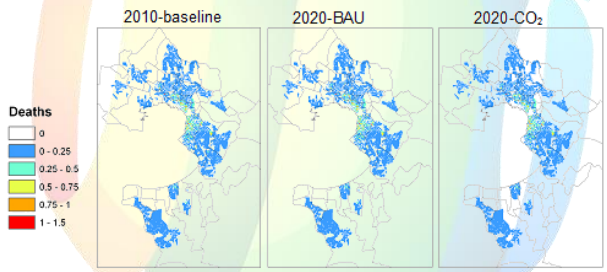

Figure 45. Spatial distribution of annual number of deaths attributed to PM_{10} in 2010, 2020-BAU and 2020-CO_2

Exposure to air population was assessed via the inhalation pathway and its health impact was estimated by concentration response functions on high resolution population data (per building block, differentiated by age and gender). The health end points computed include annual mortality attributable to PM10 and NO_2 exposure and the leukemia lifetime expected cases due to benzene exposure, which were aggregated at the municipality level.

Noise was computed from the shortest distance of Source (e.g. motorway) to the Receptor (e.g. building block of a particular height) and its exposure was weighted by the population and differentiated between each municipality in the Thessaloniki Area. The health end points computed include, sleep disturbance, sleep annoyance due to road transport and myocardial infractions.

The impact of the Greenhouse Gas (GHG) emission reduction scenarios to health was identified to be significant. Simulations show that traffic flow will decrease by 33% on roads in direct proximity to the metro line (e.g. Monastiriou, Egnatia, Nea Egnatia, Delfwn), by 44% on roads within the historic center and by 22% in all adjacent roads to the historic centre. These reductions in flow were further amplified by changes in the traffic mode, where diesel, hybrids and electric cars will constitute 22%, 7.7% and 2% respectively, to the total vehicle fleet.

It was estimated that for the municipality of Thessaloniki, the expected decrease (%) in the annual number of deaths for the GHG scenario were 8% and 11% attributed to the PM10 and NO_2 respectively and 27% to the leukemia lifetime expected cases due to Benzene. In comparison, for the municipality of Panorama, the expected % decrease in the annual number of deaths for the GHG scenario are 1% and 23% from PM10 and NO_2 respectively and 33% to the leukemia lifetime expected cases due to benzene.

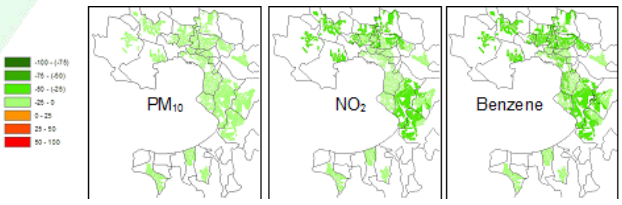

Figure 46. Decrease (%) in the annual number of deaths for the GHG scenario

Similarly the highest reductions in sleep annoyance due to road transport noise and the myocardial infractions were identified in the municipality of Thessaloniki, where the aforementioned policies have the highest impact.

Monitoring air quality in Charilaos Trikoupis bridge

The Charilaos Trikoupis bridge, known as bridge of Rio-Antirrio (Figure 47), is one of the world's longest cable-stayed bridge of multiple openings in the world, with a total length of 2,252 meters. It connects Western Greece with the rest of the country.

Figure 47. Charilaos Trikoupis bridge

Six monitoring campaigns were realized in the course of the last three years. The exact periods of the two annual campaigns were selected taking into account the high traffic seasons according to a careful examination of the bridge traffic patterns. In each of the campaigns $PM_{2.5}$, PM_{10} and TSP were sampled every 24 hours near the edges of the bridge located in the urban areas of Rio and Antirrio respectivelly, using low (for PM2.5 and PM10) and high (for TSP) volume automatic sequential samplers. Dynamic measurements of CO, NO_x, SO_2, $PM_{2.5}$ and PM_{10} were also performed continuously during the 10-day periods. TSP were collected on quartz filters (203 mm × 254 mm) in order to determine lead (Pb). Lead concentrations were measured using an inductively coupled plasma mass spectrometer (ICP-MS). Moreover, meteorological data (wind speed and direction, temperature, cloud cover and humidity) were recorded. The pollution data were analyzed statistically and the quality of the air was characterized according to the US Environmental Protection Agency indicators and the European Common Air Quality Index framework.

The results indicated that air pollution levels are in generally below the regulatory thresholds. Across the three summer sampling sessions (N = 10 days) the average PM_{10} daily concentrations at the Rio site were 19.7 μg/m^3, 20.1 μg/m^3, 19.2 μg/m^3 only slightly higher than that at the Antirrio site that were 17 μg/m^3, 17.5 μg/m^3 and 12.6 μg/m^3 (for the 1st, 3rd, 4th periods respectively). The $PM_{2.5}$ were 8.7 μg/m^3, 10.61 μg/m^3, 8.9 μg/m^3 at Rio site while at Antrirrio were 7.8 μg/m^3, 9.22 μg/m^3, 7 μg/m^3 (for the 1st, 3rd, 4th periods respectively). Moreover, the traffic emissions from the bridge are not the main source of air pollution in the area. During the winter period of sampling (2nd) $PM_{2.5}$ and PM_{10} levels were below 25 and 50 μg/m^3 on both sides of the bridge almost every day. These limits were exceeded only one day (5/12/2013) on the side of Antirrio (26.4 and 52.2 μg/m^3 for $PM_{2.5}$ and PM_{10} respectively). However, during the winter period, $PM_{2.5}$ and PM_{10} levels are higher due to the use of light oil and biomass burning for space heating. Pb levels were very low; the average daily value recorded (2.6 ng/m^3) is two orders of magnitude lower than the regulatory limit of 0.5 mg/m^3. Hourly average concentrations of CO, SO_2, NO and NO_2 for the both sides were below the regulatory thresholds. Overall the contribution of the Charilaos Trikoupis bridge to the surrounding air pollution levels is very low. This is the result of the relatively low daily volume of vehicles (~10000 vehicles per day), the respective traffic fleet composition (~80% of the traffic fleet are passenger vehicles) and the speed limit (80 km/h) which does not favor traffic emissions. In addition, the strong and frequent winds further contribute to the rapid dispersion of the emitted pollutants. The air pollution data was also characterized according to the United State (US) Environmental Protection Agency (EPA) indicators and the Common Air Quality Index framework.

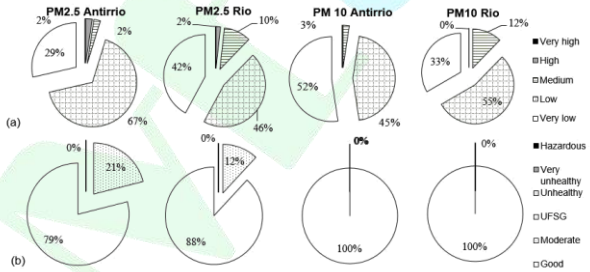

Figure 48. (a) European Common Air Quality Index framework, (b) US Environmental Protection Agency indicators

The US EPA AQI was calculated for NO_2, PM2.5 and PM10 and the results showed that the main driver of associated health risks in Rio-Antirio Bridge was PM2.5 at both locations. Figure 48 illustrates that during the 4 periods of measurements the daily air pollution was characterized as "moderate" with 21% and 12% for the Rio and Antirrio, respectively. But it has to be noted that the 87% of these measurements was observed the winter period. Simultaneously, CQAI showed that in Rio and Antirrio PM2.5 was also again the dominant pollutant. It was highlighted that the 2% of the measurement was at level of the high pollution and this percentage was observed during the winter. The highest concern is that ambient air PM levels in the urban environment are greatly affected by seasonal effects of emissions patterns and deposition processes occurring in the different regions of the human respiratory tract, which are related to the physiology/morphology of the respiratory system and the PM size distribution. Despite the lower level of traffic during the winter period, higher levels of PM were observed then. That could be related to the relative increase in all-size fraction of PM emissions in Greece, especially during the cold months of the year due to biomass combustion for space heating. Yet, the results of the AQI calculations indicate that care has to be taken to cater to the needs of susceptible individuals. US EPA remarks that "moderate" level of pollution can be alarming for a very small number of people.

Sources of Oxidative Stress Induced by Ambient Air PMx

The present study aimed at investigating the most important sources that drive the redox activity of ambient PMx (PM_1, $PM_{2.5}$, PM_{10}) at two sites in Thessaloniki, the 2nd largest city in Greece, capturing different degrees of non-traffic and traffic-related activities. For this reason, an extensive campaign was carried out at two types of locations in the area of Thessaloniki to determine the chemical composition of urban aerosols and to correlate their toxicity with PM sources. A rough estimation of ROS sources was obtained based on correlations between DTT
activity and chemical species found in the respective PM samples and on connecting those species with sources. Also, the chemical analysis results of the $PM_{1,2.5,10}$ filters were used to Positive Matrix Factorization for identifying the contribution of various sources to the ROS-generation potential of chemical species of PMx (Figure 49).

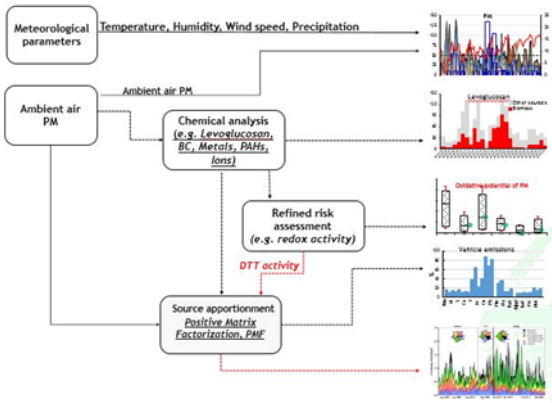

Figure 49. Methodology framework

At the traffic station median concentrations for $PM_{1,2.5,10}$ were higher than at the urban background site (Figure 50). From the chemical analysis of the PMx it was found that oxidative potential of PM was not correlated to its mass concentration.

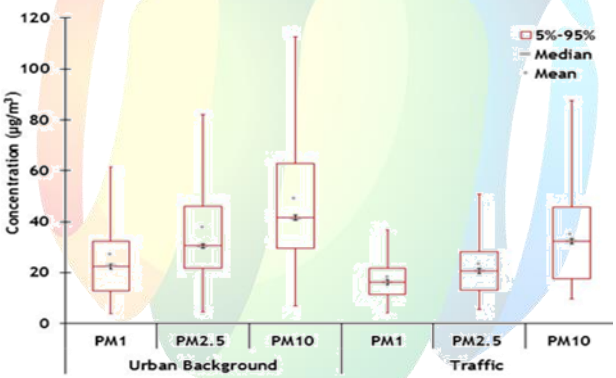

Figure 50. PM concentrations per size and site

On the contrary, a strong correlation between chemical composition and oxidation capacity of PM was observed. A rough estimation of ROS sources was obtained based on correlations between DTT activity and chemical species found in the respective PM samples and on connecting those species with sources. Particulate matter of urban background station not only had higher concentration values than particulate matter of traffic station, but also represented higher oxidative potential values (Figure 51). In addition, oxidative potential increases with decreasing particle size (Figure 51).

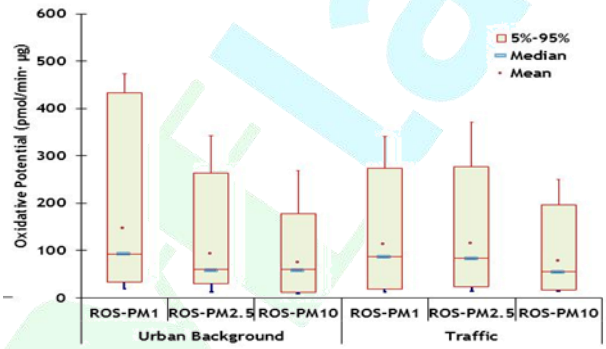

Figure 51. Mass normalized oxidative potential of PMx per site

Pearson and Spearman's correlations coefficients between DTT activity and the measured chemical components (i.e., metals, ions, PAHs and black carbon) were performed for each site and PM sample. The regression was conducted on chemical components (μg m^{-3}) and the volume normalized levels of DTT activity (nmol min^{-1} m^{-3}) as the primary metric of interest as this is the most relevant metric for human exposure and epidemiological studies.

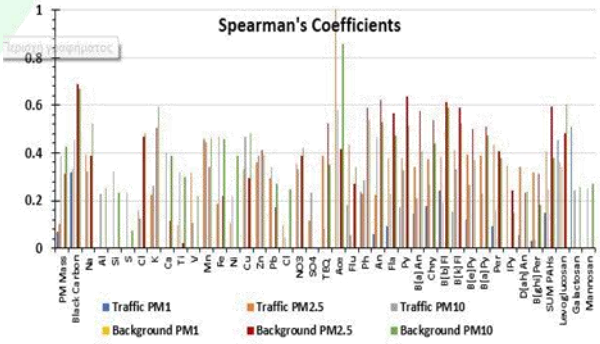

Figure 52. Spearman's rank correlation coefficients

Figure 52 presents the Spearman's rank correlation coefficients. At the urban background site, the species which best correlated with DTT activity of PM_{10} and $PM_{2.5}$ were BC, K and Phenanthrene which are the tracers of biomass burning. These findings suggest that other components other than transition metals, such as quinones and other organic compounds, contribute significantly to the oxidative activity of PM.

Figure 53 presents the Pearson's correlation coefficients Based on these results, PAHs have strong correlation with the oxidative potential of the urban background site PM1

concentrations. Moreover, the redox-active metals Cu and Zn, which generated from biomass combustion also contribute to the oxidative potential of the background site PM1. Nevertheless, at the traffic site redox-active metals Cu, Zn were also somewhat correlated with the DTT activity of the traffic site $PM_{2.5}$.

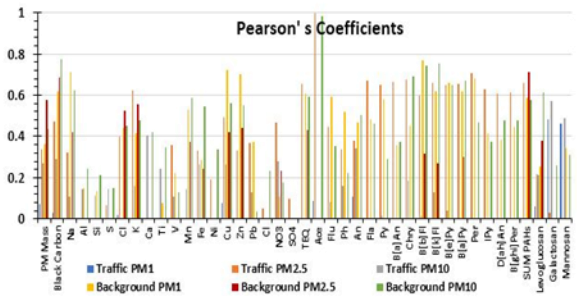

Figure 53. Pearson correlation coefficients.

To identify the contribution of various sources to the oxidative properties of $PM_{1,2.5,10}$, a PMF (positive matrix factorization) analysis was conducted using the DTT activity and measured chemical composition data at each sampling site. At background site 4 factors (Figure 54) were determined by PMF and 5 at traffic site (Figure 55).

- Soil dust had high loading of Al, Si, Ca, Ti, Mn, Fe.
- Vehicular traffic had high loading of BC, V, Ni, Cu, Zn and Pb.
- Secondary aerosol was characterized with high loadings of SO_4^{2-}, BC NO_3^-, BaA and Chy.
- Biomass burning had very high concentrations of BC, K, levo and PAHs (BbF, BkF, BeP, BaP, IcdP, BghiP).

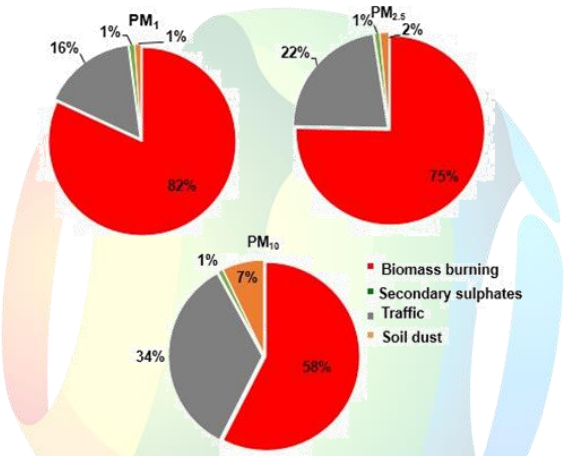

Figure 54. Source contributions to DDT activity at background site

At the urban background site biomass burning dominated the ROS-generation potential contributing by 82% to the DTT activity of PM_1, while relatively low contributions were observed from vehicle emissions (16%). The major drivers of the DTT activity of $PM_{2.5}$ at the urban background site were biomass burning and vehicle emissions, with 75% and 22% of contributions, respectively.

At the traffic site five factors were identified as important by PMF. Vehicle emissions were the dominant contributor to DTT activity of PMx contributing 62% to PM_1, 66 % to $PM_{2.5}$ and 51% to PM_{10}. Biomass burning contributed 15% to the DTT activity of PM_1, 12% to $PM_{2.5}$ and 13% to PM_{10}.

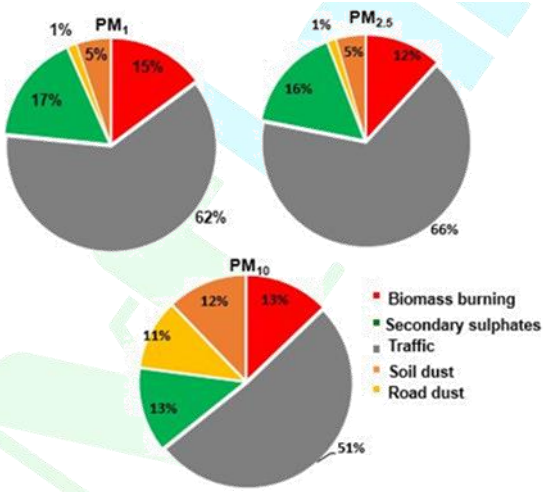

Figure 55. Source contributions to DDT activity at traffic site

Vehicle emissions and biomass burning were the two most important sources that drive DTT redox activity of ambient PMx in Thessaloniki, Greece. Biomass burning was the largest contributor at the urban background site while vehicle emissions at the traffic site.

Linking Up Environment, Health and Climate for Inter-sector Health Promotion and Disease Prevention in a Rapidly Changing Environment (BlueHealth)

The BlueHealth Consortium will, for the first time, bring together leading research, public health and policy institutes at the forefront of understanding the relationships between the environment and human health across Europe to address opportunities for BlueHealth interventions with interactive cross-sector stakeholder engagement. Key questions to be addressed include: a) How are the unexplored benefits of urban blue infrastructure (e.g. promotion of physical activity and stress reduction) distributed across the EU and will address the public health challenges of the 21st Century?; b) Which social groups derive the most benefit, and are there pockets of good practice that promote more equitable distribution?; c) Can these benefits of blue infrastructure programmes be assessed in ways that inform good design (e.g. through the use of prospective longitudinal evaluation of ongoing and planned environmental interventions)?; d) Can some of these benefits to health and well-being be used in settings without direct exposure to urban blue spaces (such as hospitals and care-homes) through the use of virtual reality technology?; e) How might different climate and environmental futures influence the ability of urban blue infrastructures to deliver these benefits to public health and well-being?; f) How can existing health and planning policies be built upon to best ensure that these benefits to health and wellbeing are factored into the policies for maintenance and retrofitting of existing, and the development of future, urban blue infrastructures; and g) What innovation and commercial, as well as public health prevention, opportunities exist to best utilise the increased knowledge the BlueHealth project will provide?'

The Aim of the 4.5 year BlueHealth project is to quantify the impacts on population health and wellbeing of existing and novel interventions and policy initiatives connected to urban blue infrastructure, and to identify opportunities and obstacles for cross-sectoral collaboration in this area. Assessments of the health and wellbeing (and environmental) benefits, risks, trade-offs, and costs will improve our understanding of the role of urban blue infrastructures, both positive and negative, on cross-sector health promotion and disease prevention. Many of these infrastructures were originally designed for other policy goals (e.g. transport, flood prevention). However, innovative design and planning can promote health by ensuring that the co-benefits are captured. For example, walking and cycle paths can become integrated features of existing and future blue infrastructures; promoting better access to water bodies for recreation can foster better mental health and increases in physical activity; and blue infrastructure can also aid sustainability and connectivity with other transport networks. Given peoples' preferences for blue spaces and their willingness to visit them, the evidence suggests that the population uptake of blue infrastructure initiatives that encourage, for instance, greater levels of active recreation, will be particularly high, and thus important for disease prevention and health promotion at the individual, community and populations levels. On the other hand, the predicted increased use of water in urban areas introduces new challenges for improving human health and wellbeing (e.g. as exposures to known and unknown environmental stressors such as flooding, pathogens and chemical pollutants increase), as well as making the attainment of the long term sustainability of urban blue ecosystems more difficult.

To fully understand the unique role of blue infrastructures for health and wellbeing, wherever possible we will compare relevant 'blue' interventions to similar interventions located in 'grey' infrastructures (i.e. highly built environments with little to no natural environment) and 'green' infrastructures (e.g. parks, woodland, street trees), as well as 'mixed' infrastructures. This will enable us to identify both the direct and opportunity costs of the blue infrastructure interventions, as well as examine urban blue infrastructure design and planning as a means for adaptation to climate change. For example, by comparing the uptake of a new cycle path along a river (blue infrastructure) instituted as part of a larger flood control plan with similar projects on an urban road (grey infrastructure) or through a park (green infrastructure), we can directly examine the potential synergistic benefits of blue infrastructure investment in a cross-sectoral setting (e.g. health, transport, planning, tourism, engineering, environment, fisheries and aquaculture, recreation, and climate).

Throughout the project, we will utilise innovative indicators and other measures which demonstrate the health, economic, environmental, and social impacts of Case Study interventions, policies and best practices. In addition to building on existing methodologies, we will use mobile phone technologies (e.g., GPS tracking with point-to-point location-based questionnaires, environmental monitoring) to assess indices of health and environment both 'on-line' and in situ. Highly innovative work will be dedicated to different but complementary forms of state-of-the-art virtual reality technology to provide therapeutic intervention, planning and communication opportunities to increase physical and/or virtual accessibility to blue environments among key populations (e.g. hospital patients, care home residents, disabled persons, deprived persons) normally without access; and to explore the underlying mechanisms of how blue infrastructures can act positively on health and wellbeing.

Thessaloniki - Waterfront case-study

In Work Package 3 (WP3) intervention case-studies will be performed in different cities with Blue Environment in order

to assess the impact of different blue environments on mental health and in emergent infectious diseases.

The intervention case-study of Thessaloniki will be based on the renovation of the 3 km city Waterfront. In 2013, the renovation of the Thessaloniki Waterfront was complete and delivered to the citizens. In 2000, the Municipality of Thessaloniki launched an International Architectural Competition for the redevelopment of the New Waterfront and in 2006 the construction of the 1st prize (Nikiforidis - Cuomo) begun. The first part (around 75.800 m^2) was completed in 2008 and the second part (around 163.000 m^2) started in 2011 and was completed in 2014. The total length of the New Waterfront is 3 km. There are 2.353 new trees, 118.432 new plants, 58,75 acres of green spaces and 11.557 m^2 of playgrounds.

The New Waterfront of Thessaloniki is a linear place with relatively limited depth and big length, a fact that gives it the characteristics of a "front", of a thin layer, inserted on the difficult and challenging limit between land and sea, between natural and constructed landscape. The sea background of the gulf of Thessaloniki, constitutes an amazing scenery, where the ephemeral and mutable elements, create a different atmosphere each time.

Figure 56. Overview of the Thessaloniki Waterfront

Two major characteristic areas were developed for the New Waterfront, which set the principles for the basic choices of the proposal.

The Breakwater: an ideal place for walking, without interruptions, without distractions. The "walker" is exposed to the light, to the open perspective, and has a continuous walk on the charming limit between two opposites: the stability of the massive breakwater – the instability and lucidity of the liquid element.

The Green Spaces: at the inner side of the coast, 13 green spaces were formed, as a succession of "green rooms – gardens", each with a special thematic characteristic. The choice of this term, rooms – gardens, describes the intentions: it is about a sequence of spaces that attempt to maintain the familiar atmosphere of the private, while forming the public space. It is not about big "parks", but "rooms" of small size that remind of the domestic gardens that existed in the area and used to reach the natural seashore, before the landfill of the coast.

The objectives of the Thessaloniki Waterfront case-study are:

1. To investigate the health impact of the renovation of the Thessaloniki Waterfront to the daily life of the residents of Thessaloniki and evaluate the life style changes.
2. To evaluate the transcriptomic and the metabolic profile of the people who spend time at the Waterfront at their daily life and between the people who do not spend time at the Waterfront.
3. To evaluate the long-term alterations in the lifestyle and the wellbeing of Thessaloniki residents.
4. To connect the outcome of the differential transcriptomic and metabolic profile of the different groups of people with major diseases like diabetes, cancer and coronary diseases.

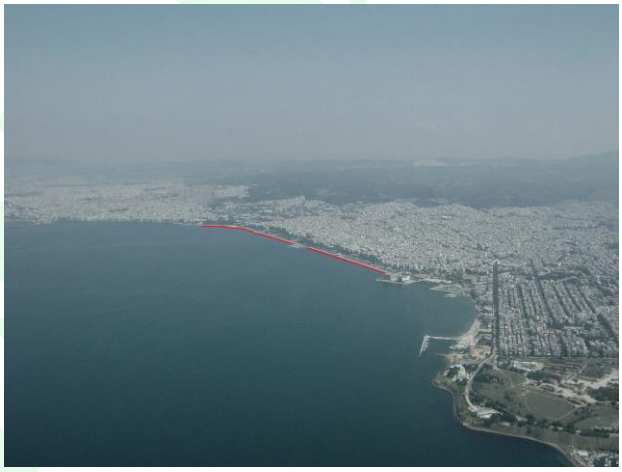

Figure 57. Area of intervention (Red line – 3.2 km)

The study will be conducted with two groups of people. One group will be recruited at randomized points at the Waterfront and the other group will be office workers who do not spend daily time at the Waterfront. It is meant to include a representative random group of volunteer adults in terms of age groups and sex, all of them residents of the Metropolitan area of Thessaloniki. Study participants will have an age range between 18 to 75 years and will be recruited 25 individuals per group and 50 in total.

Participants will answer the same questionnaire, before the recruitment and 6 months after the intervention.

In order to examine the differences of the transcriptomic and the metabolic profile of the participants, blood, urine and saliva sampling will take place. Ethical approval for the study has been obtained in November 2017 and the recruitment of volunteers has already been started with the participation of EnvE Lab in several environmental actions organized by NGOs and municipalities of the wider Metropolitan Area of Thessaloniki.

Detection of Indoor Airborne Chemical & Biological Agents Thematic Group

The European Reference Network for Critical Infrastructure Protection (ERNCIP) will provide a framework within which experimental facilities and laboratories will share knowledge and expertise in order to harmonize test protocols throughout Europe leading to better protection of critical infrastructure against all types of threats and hazards and to the creation of a Single Market for security solutions. The ERNCIP Detection of Indoor Airborne Chemical & Biological Agents Thematic Group which is led by EnvE Lab, will define scenarios for indoor, airborne contamination (threat, contamination area, topology, conditions of use for the equipment, etc.), which are realistic/are considered important in the EU or have been used in other projects. This activity will be supported by the use of the state-of-the-art on flow and dispersion 3D modelling/simulation and source term evaluation from detector network measurements.

Figure 58. ERNCIP Detection of Indoor Airborne Chemical & Biological Agents Thematic Group logo

The overall aim of this thematic group is to investigate issues that can be addressed on the EU level regarding Detection, Identification and Monitoring (DIM) of airborne, chemical and biological threats in enclosed spaces. Towards this aim, three main activities have been foreseen during the next months for accomplishing the TG objectives. In order to evaluate the applicability of the current sensor technologies and what has to be done, it is critical to evaluate what are the actual needs that have to be addressed i.e. what we expect from the sensors against CB threats in enclosed spaces. Thus, a critical starting point of the overall approach will be the definition of relevant scenarios of indoor airborne threats (chemical and biological) in critical infrastructures. The needs that have to be addressed will define the criteria for performing a critical review on the existing sensors available in the EU and used either for chemical or for biological agents. Computational simulations will provide the spatial and temporal gradients of contamination within indoor critical infrastructures. Finally, evaluation of capabilities of existing sensors based on their capability to give early warning will allow us to identify gaps and define requirements for next generation detectors in the EU.

More in detail, specific questions have to be answered, such as:

- Define the criteria and usage scenarios, suitable for chemical and biological DIM of contamination by airborne substances in enclosed spaces.
- Gather information from the relevant stakeholders and from the literature on the potential chemical and biological threats.
- Define typical threat scenarios, as most relevant
- Perform a critical review on the existing sensors available in the EU, based on the criteria and usage scenarios identified in Task 1. This will allow us to evaluate the suitability of the existing technologies for early and accurate identification of indoor airborne chemical and biological threats. Parameters to be examined, include whether to add a commercial off-the-shelf product or not, products under development/close to release or prototype - Technology Readiness Levels (TRL) level should be taken into account.
- To challenge the existing technologies against quantitative results, to identify gaps, future areas and emerging technologies. Specific considerations include:

The main scope of sensor use, is the (as possible as early) detection, identification and monitoring of the contamination with a toxic agent within an enclosed indoor location. The capability of a sensor to (a) early detect and (b) to identify a threat is of major importance. The importance of these capabilities are graphically illustrated in Figure 1, where the difference in the capability of detection (detector 1 and detector 2, with different detection limits) and eventually the identification of a hypothetical threat agent X, results in significant differences in actual exposure and internal dose, defined as the Area Under the Curve (AUC), that represents the integral of internal dose in time. These differences in actual dose will result in completely different casualty patterns. This comprehensive exposure and toxicokinetics and toxicity framework provides a robust analysis to be used for the assessment of the suitability of sensors and sensoring systems.

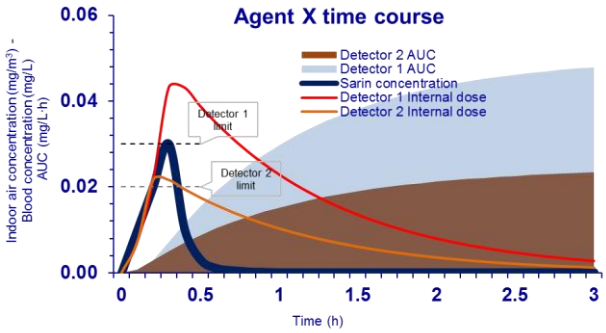

Figure 59. Agent X environmental and toxicokinetic time dynamics following a hypothetical attack under two different detection capabilities scenarios

Industrial contamination, waste and human health

Post-Emergency, Multi-Hazard Health Risk Assessment in Chemical Disasters (PEC)

A consolidated methodology for risk assessment of chemical mixtures and combined natural and technological (NaTech) hazards is currently not available. In this project an integrated multi-hazard risk assessment toolkit has been developed and the validity of this model will be evaluated on a case study by considering the effects on the structures, the environment and human health of hypothetic natural and manmade disasters, such as earthquake, flood or terroristic attack leading to accidental release of large amounts of toxic chemicals into the environment. Immediate acute and long-term population health impacts of the toxic chemicals absorbed have been determined and quantified according to (i) characteristics (type and intensity) of the initial disaster, (ii) degree of vulnerability of buildings and infrastructures, (iii) quantity of chemicals stored/handled in the plants, magnitude of their dispersion into the environment and levels of chemical contamination in the disaster area. The key receptors considered in simulations include employees present in the affected plants during the incident, emergency responders, and the local population.

A thorough meteorological characterization of the study area has been performed to identify the most common meteorological conditions for both the cold and the warm season. Simulations of accidental continuous, transient, instantaneous or catastrophic release of toxic and/or flammable material were modelled through a modelling approach consisting of a two-step procedure: first the evaporation into the atmosphere (in the case of releases of contaminants released in liquid phase) was assessed through the application of an evaporation model, then the atmospheric dispersion was estimated through both a Gaussian atmospheric dispersion model implemented in MATLAB® as well as through the US-EPA ALOHA® hazard modeling software to derive air concentration levels of chemicals in the area surrounding the incident and identified the realistic risk zone maps corresponding to defined thresholds.

Results of the simulations were exported as KML format to be imported in Google Earth. Later on the concentration field obtained has been superimposed to the population data layer of the study area to derive vulnerable population falling in different categories (sever, mild and low level of health risk).

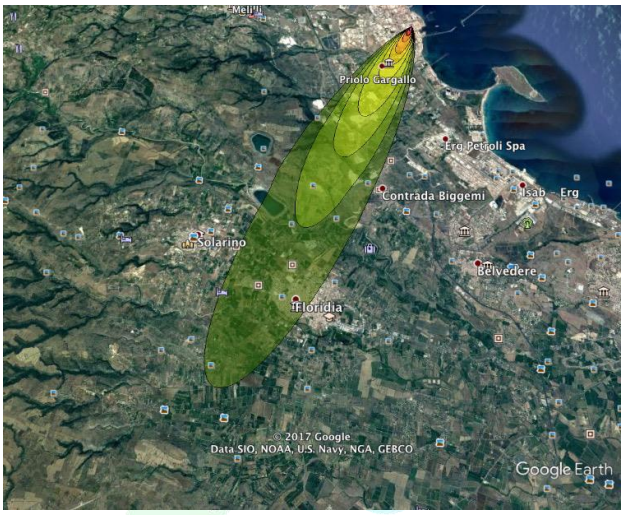

Figure 60 Concentration field of Benzene following a catastrophic accident of Primary Fractionator during the Winter season

Human exposure to toxic chemicals released into the environment following critical damages in chemical plants has been assessed dynamically by the INTEGRA platform which includes multi-route exposure models needed to derive through PBBK modelling internal doses of parent chemicals and metabolites in human target tissues both in the short term and long-term period.

Internal doses of toxic chemicals in human target tissues has been modelled using innovative in silico methods (PBTK modeling, exposome-oriented approaches) taking into account the long-term potential contamination of different environmental media after the incident and how this contamination continue to affect the population via the described pathways and routes of exposure

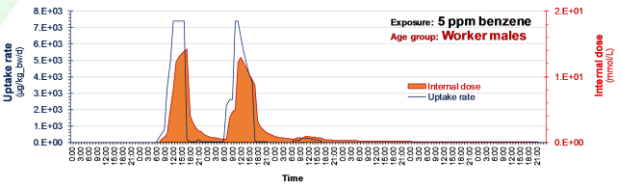

Figure 61. Uptake rate of benzene and internal dose of benzene toxic metabolites time variability following the accidental event (5 ppm scenario, male worker)

Results showed lifetime internal exposure is strongly differentiated among rapidly and non-rapidly eliminated compounds; even short term exposure events, result in long term internal exposure in the case of slowly eliminated compounds such as cadmium. Children are exposed to higher internal exposure, as a result of the higher bodyweight normalized intake.

Industrially Contaminated Sites and Health Network (ICSHNet)

The concept

The Industrially Contaminated Sites and Health Network (ICSHNet) is a four-year-long COST Action due to start in the beginning of 2015. The Network is coordinated by the Istituto Superiore di Sanità (Italy) and aims at establishing and consolidating a European Network of experts and institutions involved in assessing the health impacts and/or managing remediation and response in industrially contaminated sites.

Figure 62. The cost logo

This will be achieved by developing a common framework for human health exposure and risk assessment through conferences, workshops, training and dissemination activities.

To implement the scientific programme ICSHNet involves 65 members from 15 different COST countries and it is structured in four working groups: WG1 – Environment and health data; WG2 –Methods and tools for exposure assessment; WG3 – Methods and tools for health risk and health impact assessment and WG4 – Risk management and communication.

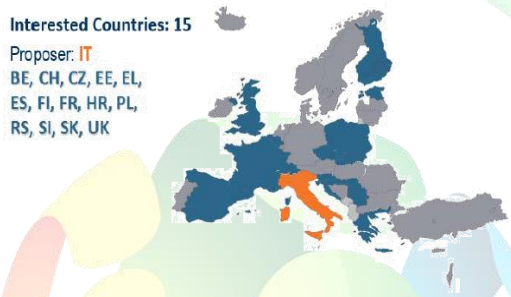

Figure 63. Participant countries of the ICSHNet

Through expert networking, conferences, workshops, training and dissemination activities, ICSHNet aims at clarifying knowledge gaps and research priorities; supporting collection of relevant data and information; stimulating development of harmonised methodology; promoting collaborative research initiatives, developing guidance and resources on risk assessment, management and communication and creating the conditions for the undertaking of comparable health impact assessments of contaminated sites in Europe and beyond.

Contaminated sites in Greece

Asopos basin – Cr(VI)

A major local environmental issue in Greece is related to the presence of hexavalent chromium Cr(VI) in drinking water of the Oinofyta municipality (50 km North of Athens, Greece), within the wider area of Asopos basin and the related cancer mortality. In 1969, a ministerial decision gave permission for depositing processed industrial waste in the Asopos river, which runs through Oinofyta. This decision, furthered by a presidential decree in 1979, permitted free disposal of processed liquid industrial waste into the river. Initial concerns were raised after Oinofyta area citizens complained about the discoloration and turbidity of their drinking water. Regular protests ensued from the 1990s onward. In 2007, the Ministry of Environment, Regional Planning and Public Works of Greece imposed fines on 20 industries for disposing industrial waste with high levels of hexavalent chromium into the Asopos river. Since 2007, three independent sets of hexavalent chromium measurements are available for the Oinofyta area, indicating that public drinking water Cr(VI) conentrations were above 8 μg/l. According to official Oinofyta municipality authorities, in early 2009 the main drinking water supply of Oinofyta was diverted to receive water from Mornos lake (reservoir) which is part of the drinking water supply network of the city of Athens. Therefore, more recent measurements made by the Oinofyta municipality (June 2009- July 2010) record relatively lower levels of Cr(VI) (<0.01-1.53 μg/l). A measurement made by the Oinofyta municipality in 1996, showed Cr(VI) levels of 54 μg/l in the public drinking water supply. Association to health effects was based upon existing epidemiological data already published by Linos et al1. [1]. The SMR for all cancer deaths over all the years was slightly increased but not statistically significantly (SMR = 114, 95% CI 94-136). For primary liver cancer, the observed deaths were eleven fold higher than the expected number of deaths (SMR 1104, 95% CI 405-2403, $p < 0.001$); statistically significant SMRs for primary liver cancer were observed among both males and females. Observed deaths associated with kidney and other genitourinary organ cancers (five deaths with ICD-9 code 189, and one death with ICD-9 code 184) were more than threefold higher than expected in women (SMR 368, 95% CI 119-858, $p = 0.025$). The SMR for lung cancer was also statistically significantly elevated (SMR 145, 95% CI 101-203, $p = 0.047$).

Accidental Aspropyrgos recycling plant fire - dioxins release

Calculating the health burden due to increased exposure to dioxins and furans of the Aspropyrgos area (Close to Athens) residents by an accidental fire in a plastics

[1] Linos, A., A. Petralias, C.A. Christophi, E. Christoforidou, P. Kouroutou, M. Stoltidis, A. Veloudaki, E. Tzala, K.C. Makris, and M.R. Karagas, Oral ingestion of hexavalent chromium through drinking water and cancer mortality in an industrial area of Greece - An ecological study. Environmental Health: A Global Access Science Source, 2011. 10(1).

recycling plant in June 6, 2015 was the challenge of this case study.

Figure 64. Snapshot of the recycling plant fire in Aspropyrgos

For this purpose, several type of data were combined mechanistically, including: a) dioxins and furans biomonitoring data of previous years to determine the background exposure of the population (equal to 7,3 pg/g_lipids) and b) exposure to environmental media as shaped the days of the fire. The equivalent potential toxic dioxins in the air was found to be 1.8 pg/m^3 TEQ WHO (in accordance with measurements of NCSRD Demokritos), a value that is significantly greater than the 0.1 pg/m^3 TEQ WHO atmospheric background concentration of an industrial area.

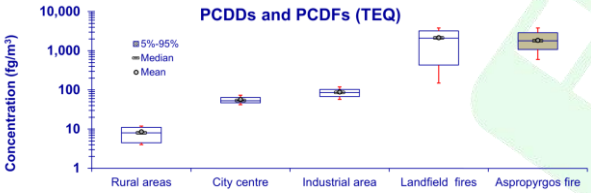

Figure 65. Levels of dioxines and furans at various Athens sub-areas, as well as during the fire in the recycling plant

In various parts of the food chain calculated values were less than 1 pg TEQ / g_fat. The change of the internal exposure of the population as to the background is then calculated using a validated Physiology Based BioKinetic (PBBK) model for dioxins and furans.

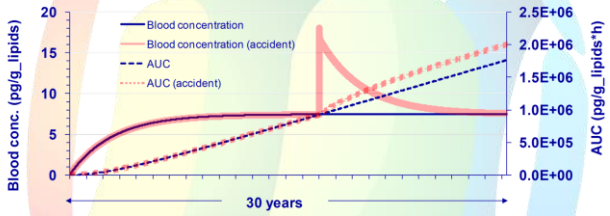

Figure 66. Internal exposure to dioxines under (a) usual conditions (continous line) and (b) under accidental release (doted line)

Considering bioaccumulation, for 6 days exposure to dioxins / furans smog, additional burden of internal exposure for the exposed population is about 13%. Cancer risk increases similarly, and is estimated equal to $3 \cdot 10^{-7}$.

Goldmining in Skouries Halkidikis – heavy metals contamination

In Skouries of Halkidiki (Northern Greece), a mining company want to establish an open-pit mine in the middle of the Skouries forest on the Kakavos mountain, which happens to be the main freshwater source for the entire region. By the company's own estimates, the open pit will generate 3,000 tons of toxic dust per hour. Galleries will be dug at 700 meters deep, taking the mine below sea level, so that even water that is not contaminated with heavy metals and other toxic materials from the mine will surely be contaminated by seawater. A 9 kilometer long tunnel aimed at connecting two mining sites will cut through a geological fault line that caused a devastating earthquake in the area in 1932. Finally, an ore processing factory will be built in the mountain where gold will be separated from other substances. The company claims this will be done without using cyanide, but this method has not been shown to be effective on Skouries ore. This raises additional concerns about the possible disposal of cyanide inside the forest. Major environmental compartments are expected to be contaminated, including:

- Water resources: The Kakkavos mountain supplies water to the entire N.E. Halkidiki. The proposed mining activity will directly and irreversibly affect the region's water resources. The EIA does not meet any of the goals of the Framework Directive 60/2000/EK - "Establishing a framework for Community action in water policy" which has been incorporated into Greek law.
- Air pollution. Only in "Skouries" the particulate emissions are estimated to 430 t/y PM10, with high concentrations of heavy metals, particularly arsenic. The ore dust production sums up to 4.324 t/h with high concentrations of sulfur compounds such as heavy metals antimony, arsenic, barium, cadmium, chromium, lead, mercury, etc. The emission of carbon monoxide, nitrogen oxides, volatile organic compounds, sulfur dioxide and particulate matter PM10 and PM2,5, is in total 715 t/y in the first two years of operation and over 950 t/y over the next years.
- The decrease in soil pH due to acidic runoff and the high heavy metal concentration makes the soil unsuitable for organisms and plant growth. The mining activity will cause drying topsoil within kilometers of the open pit and severe soil erosion with subsequent catastrophic flood events.

Life cycle analysis of municipal waste management - Industrial symbiosis options for reduced ecological footprint

Municipal solid waste (MSW) management is nowadays one of the biggest problems in both developed and developing countries. Prevention, recycling, treatment and final disposal of MSW are regulated through a number of general policy principles and international directives. It is imperative therefore to create awareness among local authorities, manufacturers, companies and generally society of the available varied technological solutions.

Integrated waste management solutions using the concept of industrial symbiosis (IS) have been developed and evaluated taking into account the European and national waste management legislation. IS, as part of the emerging field of industrial ecology focuses on the flow of materials and energy through local and regional economies. IS engages traditionally separate industries in a collective approach to drawing competitive advantage involving physical exchange of materials, energy, water, and/or by-products. The keys to IS are collaboration and potential synergies offered by geographical proximity and industrial function. Life Cycle Assessment (LCA) provides the methodological framework. LCA is conducted according to ISO 14040 Moreover, LCA used to describe the environmental impacts of products and processes while assessing the material and energy flows throughout their lifetime.

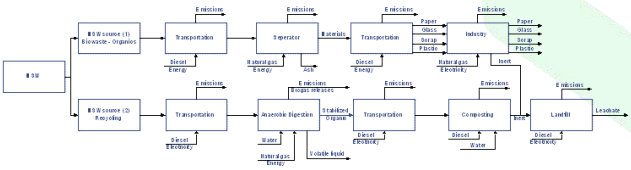

Figure 67. Waste management scenario: Waste is pre-treated and pre-sorted into biodegradable and non-biodegradable material for further anaerobic digestion and composting. Residues end in landfill. Plastic, paper and ferrous material are recycled.

Indicators of efficiency, effectiveness, and environmental and public health impacts are used to facilitate the comparative evaluation of the different MSW management scenario. Hence, material flow accounting, gross energy requirement, exergy and emergy intensity, local, regional and global emission and release intensity and morbidity or mortality indicators are used to support the comparative assessment.

This integrated framework was applied in the case of MSW management in the two larger cities in Greece, Athens and Thessaloniki, with a special focus on energy and material balance, including potential global and local scale airborne emissions as well as groundwater and soil releases. Public health impacts were assessed based on adverse effects on respiratory health, congenital malformations, low birth weight and cancer incidence.

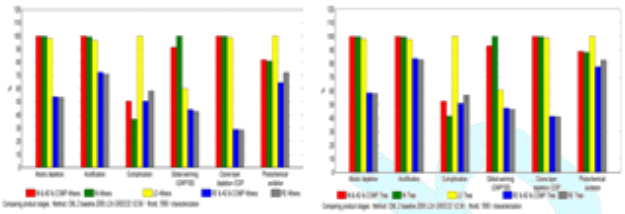

Figure 68. Impact categories of life cycle assessment for Athens and for Thessaloniki

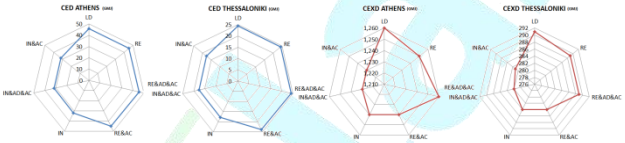

Figure 69. Cumulative Energy and Exergy Demand for Athens and for Thessaloniki

A significant and non-intuitive result is the fact that integrated framework analysis produces different conclusions than a simple environmental impact assessment based only on estimated or measured emissions. Taking into account the overall life cycle of both the waste streams and the technological systems and facilities envisaged under the plausible scenarios analyzed herein, modifies the relative attractiveness of the solutions considered. The results of the assessment based on selected impact indicators lead to the following conclusions: biological methods have the smallest abiotic matter, acidification potential, greenhouse gas effect, ozone depletion and photochemical oxidation among the waste management systems considered.

However, not all options are benign on the local environment and on the local population health, since both can be influenced by non-negligible local emissions.

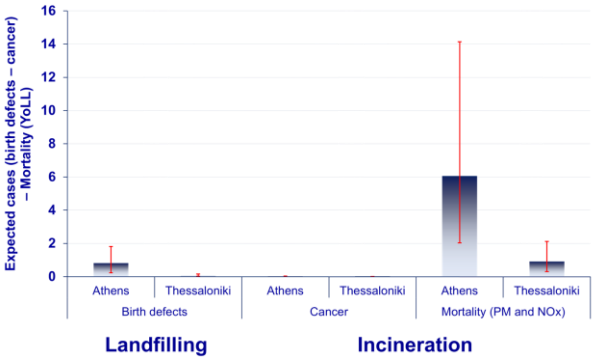

Figure 70. Health impact assessment among the various waste management options

As far as public health is concerned, adverse effects on respiratory health, congenital malformations, low birth weight and cancer incidences are still observed especially from incineration and landfilling.

Innovative waste management and energy recovery systems

Anaerobic digestion

Anaerobic digestion (AD) of organic material occurs in the absence of oxygen and the presence of anaerobic microorganisms. It occurs in three stages, Hydrolysis/ Liquefaction, Acidogenesis and Methanogenesis.

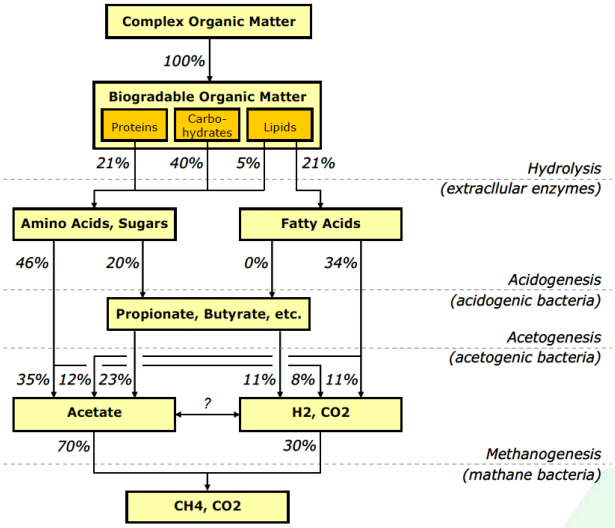

Figure 71. Anaerobic digestion process

The EnvE Lab apparatus contains a system of coupled four anaerobic bioreactors, of 6.5 l in volume each, equipped with stirrers for waste agitation. The digesters are single-stage units, which can operate both as CSTR and batch reactors.

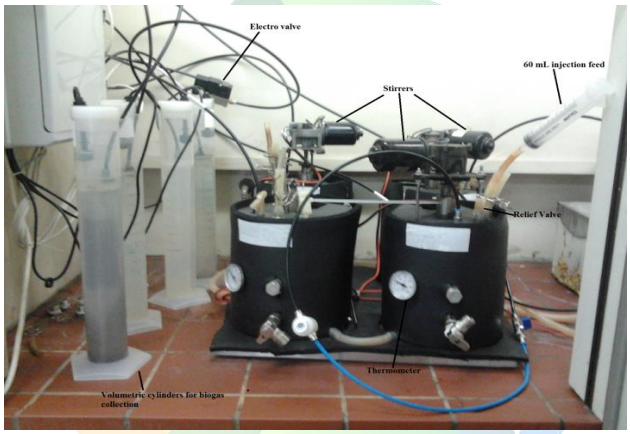

Figure 72. Anaerobic bioreactors

EnvE Lab research deals with anaerobic digestion from biodegradable matter in order to produce biogas (waste to energy). In particular, the organic fraction of Municipal Solid Waste (OfMSW) was used as feedstock trying to optimize the reactor operation considering the percentage of wastes and inoculums.

The four anaerobic digesters give to EnvE Lab the independence to compare different feedstock and conditions at the same time aiming at optimizing the design of integrated AD systems for different operational conditions, feedstock composition and treatment goals.

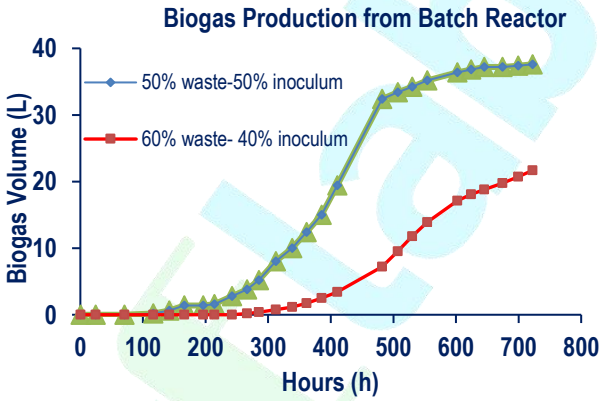

Figure 73. Biogas production from a batch work bioreactor using as feedstock the OfMSW 50% and inoculums 50%

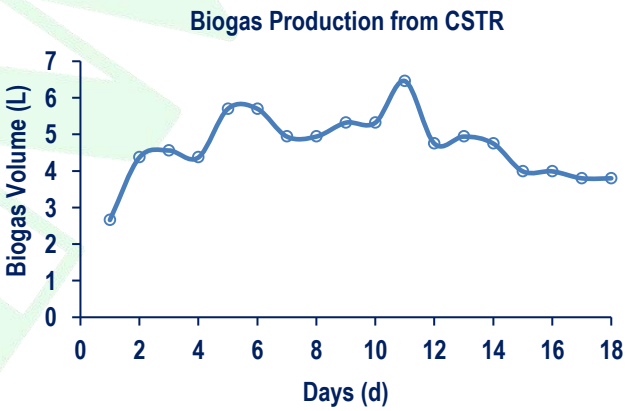

Figure 74. Biogas production from a CSTR bioreactor using as feedstock 0.2L/d of optimal waste

Waste-to-energy systems and algae photo-bioreactors

Valorization of zero or negative value raw materials has become the hot spot of the 21st century with the biological methods leading the way. From composting to the fourth generation bio-refinery, microorganisms are utilized thanks to their abilities to bio-convert different organic macromolecules into valuable materials and renewable energy resources. Throughout this quest for identification of renewable resources, great attention has been paid into the evolution of the anaerobic digestion into a robust process able to treat a plethora of mixed substrates. While microorganisms are able to valorize different waste streams, they have a number of inherent limitations which through appropriate management can be bypassed or ever used in advantage of another biological process in a win-win process scheme. One of these limitations is the inefficiency of anaerobic microorganisms to convert a

number of natural macromolecules into biogas mainly due to slow hydrolysis.

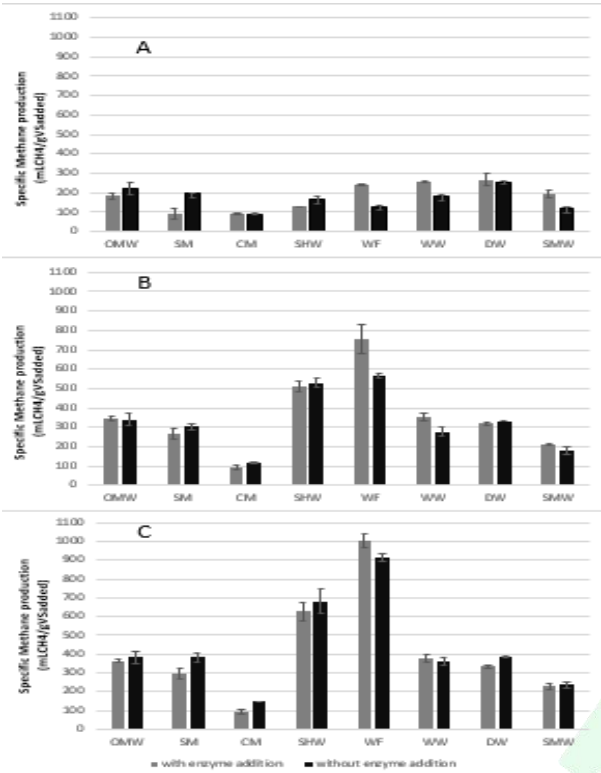

Figure 75. Specific methane production (mL/gVS_{added}) on days 5, 12 and 30 for the enzymatically pretreated and not pretreated substrates (Olive Mill Waste, Sterilized Mass, Cattle Manure, Slaughterhouse Wastes, White Fat, Winery Wastes, Distillery Wastes, Slaughterhouse, Solid Mill Wastes)

In order to improve the efficiency of the process toward these macromolecules, in the last couple of years a number of small scale digestion experiments took place in our laboratory where we assessed the effectiveness of initial enzymatic pretreatment enhanced by the addition of commercially available enzymes. Based on the generated data, the effect that the examined enzymes have on the anaerobic digestion of the mixed substrates can be divided into three categories:

A) No or negligible effect, as is the case of olive mill and distillery waste.

B) Positive effect on the process with the methane production taking place faster and the organic matter exhausts more rapidly. This category includes white fat and olive mill solid waste.

C) Negative effect with the methane production taking place slower and the cumulative methane production being lower when compared to the methane generated by the batches that no external enzymes added. This category includes cattle manure and sterilized mass.

Photo bioreactors

Another inherent limitation of anaerobic digestion is the generation of carbon dioxide during anaerobic respiration. This in some cases can be volumetrically equal to the generated methane. The presence of carbon dioxide in the biogas is undesirable as it is reducing the heating value of the gas while increasing storage and management costs. In order to reduce the concentrations of carbon dioxide from the biogas, we designed and constructed a bench-scale anaerobic digestion system coupled to photo-bioreactors where algae are employed for the valorization of the carbon dioxide, hydrogen sulfide and ammonia available in the biogas.

Figure 76. The photo-bioreactors within the temperature controlled cabinet

After harvesting algal biomass will be used for the recovery of high value added products, raw material for fuel manufacturing and industrial product development. Algae are a group of photosynthetic microorganisms that can fix carbon dioxide from different sources into biomass. During the last years this ability of algae has been explored in order to identify pathways through which the application of these species can reduce the environmental burden of human activities. Algae are an important carbon sink and their cells can contain more than 50% of fats and oils, sometimes rich in ω-3, from where pharmaceuticals or raw material for biodiesel production can be extracted. It noteworthy that for every kg of algal biomass, 1.65-1.83 kg of CO_2 must be consumed. The spent algae cells can be further valorised as activated carbon building blocks or substrate to anaerobic digesters.

Fur farming by-product bio-methanation

European fur production is a dynamic and well established industry with long tradition in the production of quality products. The European Union is the main exporter of pelts worldwide accounting for the 64% of the total production with the States of Denmark, Netherlands, Finland and Greece being the main producers.

The waste generated from mink breading facilities includes manure and waste feed. Both are collected under the animal cages in small piles of up to 50cm in height. The waste management options for this waste stream are constrained by high solids, organics and nitrogen content that hamper significantly the ability of aerobic biological processes to treat or valorize them.

A waste management option which can be employed for the valorization of fur farming waste is anaerobic digestion (AD). AD is a biomass bio-conversion process disengaged from weather conditions which offers the advantages of self-sustainability, income generation and waste valorization with limited material requirements.

The substrates evaluated in this work were fresh and weathered mink manure (FMM, WMM respectively), waste mink feed (WF) and bone and meat meal (BMM) that is being generated by the mink carcasses after pelting.

The substrates were assessed in batch vials under mesophilic conditions mainly due to the known problems related to the inhibition of the process by elevated concentrations of unionized ammonia. This inhibitory process is driven by the bio-conversion of protein into ammonia and it is assisted by the high temperature and pH experienced in thermophilic systems.

The ranching derived substrates were found in the solid state with TS higher than 33%. The solids are composed mainly of organic matter with VS levels higher than 83%. They have significant nitrogen content with TKN concentrations ranging between 14 and 93 g/kg, while the pH of manure is alkaline. This is in contrast to that of the WF, which is acidic and that of BMM, which is neutral. Finally the theoretical methane production of the substrates ranges between 545 and 705 $mLCH_4/gVS_{added}$.

The highest production from the substrates assessed (Figure 77) observed by BMM with 591 ± 38 mL/gVS_{added}, a value corresponding to the 83.7% of the theoretical methane production for this substrate. The second highest yield offered by the waste mink feed with 548±33 $mLCH_4gVS_{added}$ corresponding to 91% of the theoretical bio methane potential with a significant daily productivity of 65.0 $mLCH_4gVS$-d. The production level offered by mink manure is significantly lower compared to the mink derived by-products with 365 and 428$mLCH_4/gVS_{added}$ for the fresh and weathered mink manure respectively.

Based on our system analysis the total annual manure streams generated by the Greek mink ranches are calculated at 8100 tons of solids. While this value seems low, this waste stream corresponds to around 160.000 tons of pig slurry (5% TS) or 100.000 tons of cattle manure (8% TS).

In all four assessed substrates, pH had shown a small reduction up to 0.4 units during the first days of the experiments in response to the increasing concentrations and primary accumulation of the volatile fatty acids. This process however got reversed as the acids were consumed and converted into biogas by methanogens.

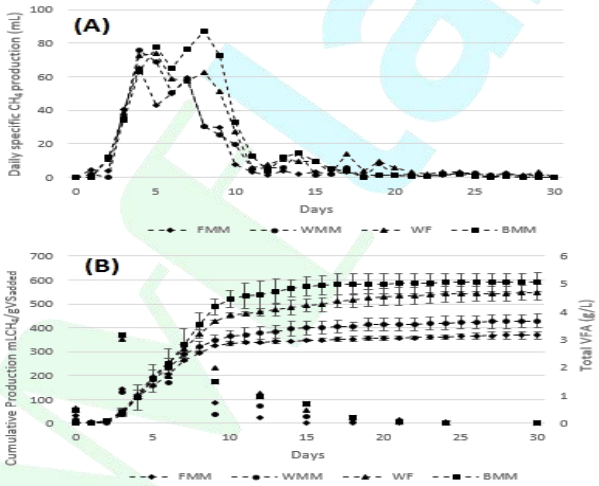

Figure 77. Daily (A) and cumulative (B) specific methane production for the four substrates assessed

According to mink farmers the generated mass of waste feed is approximately the 6% of the feed provided. Thus, the generated mass was calculated at 268 tons of solids per year. According to rendering facility managers out of 1000kg of raw minks slaughtered, 290kg of BMM and 60kg of mink fat are recovered. The total mink bodies produce 160 tons of BMM product per year.

Based on the above calculated total mass of substrates, the volume of CH_4 that can be generated through management of the mink-derived byproducts in Greece, reaches 2.85 million m^3, which equals to approximately 2600 m^3 of fuel oil in terms of lower heating value equivalents.

Experimental results indicated that in contrast to pig and cattle manure, minks generate waste which may offer very high specific and volumetric methane productions. Thus, we deem that with proper management the economic viability of bio-methanation plants can be ensured. The anaerobic digestion process lends itself toward mink-derived waste and byproducts offering a robust process from where significant volumes of biomethane can be recovered while at the same time environmental sustainability is safeguarded.

The applicability of farm scale biomethanation plants for the valorization of the municipal organic wastes

Redirection of organic municipal waste away from landfills is one of the challenges that waste managers face every year. Only in Greece more than 2.7 million tons of municipal organic waste are generated annually. Currently most of these are landfilled, resulting in wastage of a resourceful substrate, over exploitation and pollution of surface and ground waters, as well as in releases of greenhouse gases into the environment.

Anaerobic digestion provides a waste management option for OFMSW, while offering the opportunity to recover marketable products both in the forms of biogas and slow release bio-fertilizers. As a result, less waste is dumped into landfills, while at the same time the process can be used by local authorities to meet the waste redirection targets set by the European Community Landfill Directive (1999/31/EC). As a way to improve the bio-methane production of AD systems, different types of waste-wastewater can be mixed and treated together in co-digestion schemes. Mixing of different substrates is not only desirable for improving methane recovery rates and reducing life cycle costs; it also provides better organic load removal efficiencies as an effect of C/N ratio correction, pH balancing and improvement on the buffering capacity of the treatment systems.

The experiments were performed under thermophilic conditions in batch and large volume laboratory digesters, with the feed rate of food waste to manure reaching levels as high as 70% based on VS loading, the total solids levels at 15.7% and the OLR at 6.85kgVS/m3/d. At the higher feed rate the digestion process was slightly inhibited, probably due to sugar accumulation. In contrast waste mixtures containing up to 65.3% food waste with the OLRs as high as 6.2 kgVS/m3/d with the influent TS levels up to 14.3% can be accepted by CSTR systems with no signs of inhibition.

Our results show that the addition of food waste to anaerobic digesters operating under manure monodigestion conditions can improve specific methane production by 86% and the volatile solids reduction by 19%. In a farm scale digester (3000m^3, HRT 21-d) the addition of food waste can result in a fourfold increase of cash flow by only slightly increasing operational costs due to pasteurisation requirements. Additionally, gate fees and carbon credits can further improve the financial performance of treatment facilities.

Valorization of semi solid pickling wastes, through bio-methanation pathways

Vegetable and fruit pickling and the subsequent canning is a multibillion Euros industry presenting great export potential with the gross European pickle production reaching the 1.6 million tons per annum. Pickling is a traditional method of preservation employed for the long term storage of vegetables and fruits under either an acidic brine solution or an acidic oily solution.

The waste assessed in the present work were:

a) pickled green peppers in brine,

b) pickled red peppers marinated with olive oil and

c) mixed green olives stuffed with red pepper and cheese based cream in brine.

These substrates have high total solids, significant fat and NaCl concentrations and acidic pH as an effect of the addition of acetic acid during pickling. The theoretical specific production of the substrates fluctuates between 435 and 561 $mlCH_4/gVS_{added}$. The experiments performed in batches and under thermophilic conditions with a retention time of 30 days.

The highest specific production offered by the green stuffed olives with 519 $mlCH_4/gVS_{added}$, followed closely by red peppers in oil with a yield of 488 $mlCH_4/gVS_{added}$. These values correspond to 92.4 and 99% of the theoretical production for these substrates. In contrast to the high yields exhibited by red peppers and stuffed olives, the bio-methane yield offered by the green pepper in brine was only 149 $mlCH_4$/gVSadded, i.e. the 34% of the theoretical production for this substrate. In order to overcome the inhibition of the monodigestion of the green peppers, these were assessed under co-digestion conditions together with cattle manure. Under these conditions the efficiency of the process improved by 32% with the yield reaching the 270$mlCH_4/gVS_{added}$.

Anaerobic digestion and co-digestion of pickling solid waste and cattle manure was performed successfully with significant volumes of biogas recovered. The red peppers and the stuffed olives, thanks to their high content in fats and organic acids, offer very high specific and volumetric methane productions. Unfortunately, green peppers assessed contain significant concentrations of NaCl that is a known inhibitor of methanogenesis. The successful application of co-digestion reveals the merits of the combined treatment of substrates for minimizing inhibitor stress and improving the chances of success.

Biomethanation of cellulose rich agro-waste

Cereal farming is the main agricultural activity worldwide generating 1-3 tons of cellulose rich waste per ton of grain product. The main wastes of this process are the two straw types as well as the husk in the case of rice. While a small proportion of the agrowastes are used as feed for ruminants, a significant volume is burned on the fields prior to the new agronomic year. Recently, the exploitation of cellulose-rich waste has started to gain momentum as a possible substrate in biorefineries. Toward this target, the wheat and rice straws as well as the rice husk were selected and assessed as substrates to anaerobic digestion process. The substrates underwent milling in a hammermill and three fractions were generated, these were the 2 cm, 1 cm in length as well as in a powder form. In addition, the enzymes cellulase and xylanase were added into the substrates in order to evaluate the effect of the biological pretreatment methods. The enzymatic cocktails evaluated were these composted by 10, 50 and 100 mg /gVS_{added} per enzyme. The mechanical and biological pretreatment of the substrates was investigated in batch as well as continuous CSTR type reactors.

Figure 78. Batch and CSTR bioreactors

According to the results, the highest methane production 370 $mLCH_4$/ gVS_{added} offered by the wheat straw when it was pretreated through milling into 1 cm fractions with the addition of 10mg/gVS_{added} of cellulase and xylanase.

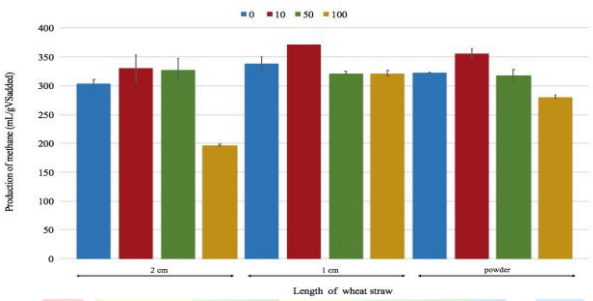

Figure 79. Methane production

It was found that the mechanical or biological pre-treatments in a number of cases inhibited the process. It seems that the type of pretreatment and required enzyme is a substrate specific method and significant pretreatment experimentation should be used before a pretreatment method becomes standardized within a biogas production facility.

Microalgae cultivation for biofuel production

Microalgae cultivation for biofuel production is a promising economic activity toward sustainable development. Biofuels derived from algae biomass offer several advantages compared to the biofuels generated at the first and second generation biorefineries. An advantage of microalgae is their ability to utilize carbon in closed systems. Although, algae cultivation it seems as an easy and first class solution to a number of environmental and economic issues, the availability of sustainable carbon dioxide sources is limited. Biogas is known for its high carbon dioxide concentration which can be considered as a substrate for microalgae cultivation. Thus, microalgae biomass is recovered and the concentration of carbon dioxide in the biogas is reduced, improving its heating value. Furthermore, through photosynthesis, microalgae generate organic compounds, such as lipids, proteins and carbohydrates, which can be valorized for biogas production generating in this way a closed carbon circle system. During the experimentation period batch photoreactors were used and different concentrations of biogas was added into the systems. The aim was to evaluate the effect of pH and to assess the growth potential of the microalgae *Chlorella vulgaris* with biogas as substrate. In order to evaluate acceptance and growth rate of the algae the batches were fed with 1.1, 2.3 και 3.4 g CO_2/L·d. Furthermore, the biomethanation of the generated biomass was also studied. For the biomethane potential tests a similar biogas test was used with organic loadings ranging between 6.25 and 18.75 gVS/L.

Figure 80. Different organic loadings

According to the results the highest biomass concentration of 2.3 g/L, in a 10-day cultivation circle, achieved for the feeding rate of 2.3 g CO_2/L·d while the highest bioconversion efficiency of CO_2 offered by the 1.1 g CO_2/L·d with approximately 26%. Moreover, the highest methane production was offered by the anaerobic digestion of microalgal lipids and measured at 669 mL CH_4/gVS. Growth of *Chlorella vulgaris* on biogas is a possible and sustainable method for biogas polishing. The results of anaerobic digestion suggest that microalgae biomass offers a high quality substrate that can be used for biomethane production.

New projects

European Human Biomonitoring Initiative (HBM4EU)

The European Human Biomonitoring Initiative (EHBMI) will establish and implement an ambitious European Joint Programme (EJP) and will provide policy makers with comparable and validated chemical exposure and health data at EU level. This will be done by integrating and building on previous and ongoing EU initiatives, national HBM programmes and studies (including cohorts, epidemiological studies and health surveys).

In contrast to former projects, the proposed programme will involve national programme owners and/or the national managers of those programmes, and include policy makers at national level. This inclusive approach, combined with the integration of HBM and environmental health research, will strengthen the EJP, enhance the sustainability of the initiative and amplify the impacts of the results.

In order to ensure that the knowledge we generate is targeted, timely and fit for purpose, we will establish a sustained dialogue with EU policy makers responsible for assessing and managing the risks to human health from chemical exposure via the environment, diet, consumer products and occupational exposure. Through effective communication and dissemination to policy makers, we will actively promote the exploitation of our results by policy makers in such a way as to impact positively on human health.

The overarching objectives will be achieved via the following specific goals, to be accomplished during the 5 year programme:

- Objective 1: Laying the foundations for a pan-European HBM platform that builds on national hubs and existing expertise;
- Objective 2: Developing a common methodology for the interpretation and use of HBM data in policy-making;
- Objective 3: Harmonising and optimising the practices of national HBM programmes, including sample collection, quality assurance and data management;
- Objective 4: Identifying gaps where further data are needed to inform current policy questions and design new, targeted studies to address these knowledge gaps;
- Objective 5: Including new HBM data and, where possible, existing HBM data in the European Commission´s Information Platform for Chemical Monitoring (IPCheM);
- Objective 6: Linking external to internal exposure in order to improve exposure models for risk assessment;
- Objective 7: Developing, validating, and applying exposure and effect biomarkers to improve our understanding of the health risks associated with aggregate exposures;
- Objective 8: Identifying chemicals of concern through novel methods for the holistic analysis of HBM samples and improving the use of HBM data in assessing exposure to and the risks of chemical mixtures;
- Objective 9: Enhancing our understanding of the causal association between chemical exposure and adverse health outcomes by combining mechanistic studies with existing cohort data;
- Objective 10: Promoting capacity building at national level through training and exchange programmes;
- Objective 11: Engaging with stakeholders, including the general public, throughout the programme to ensure the credibility, accountability and legitimacy of activities and results.

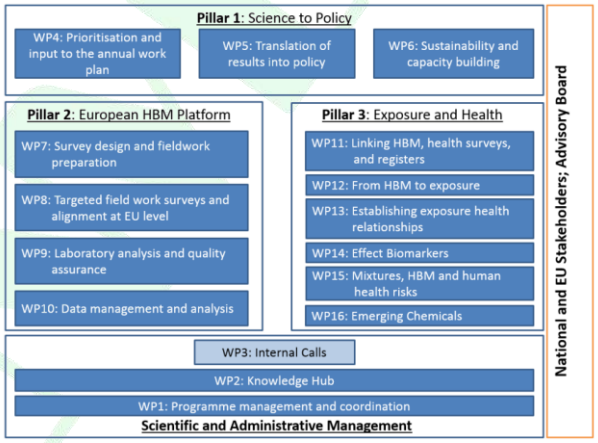

Figure 81. Overview of Work Packages and their organizational connections

Advancing beyond the state of the art and harmonising HBM in Europe. This project will establish a European HBM platform involving 26 countries. The EHBMI has two overarching goals: (a) to support public health, chemical, occupational and food safety policy in the EU; and (b) to advance understanding of human exposure to chemicals and of the causal associations between exposure and health effects. While human biomonitoring surveys exist in a number of EU countries, the design, time-scale and use of biomarkers measured are not aligned. In 2012, COPHES and DEMOCOPHES successfully piloted a common approach to HBM in 17 countries. Urine and hair samples were collected from 4,000 mother and child pairs and were analysed for cadmium, mercury, cotinine and phthalates68. The EHBMI will build on this work. Twenty six EU Member States and associated countries (Norway, Israel, and Iceland), as well as Switzerland, will together deliver a harmonized approach to EU-wide HBM and its exploitation in policy making. It is our ambition to lay the foundations for a sustainable HBM activity in the EU that will optimise resource use, share best practices, build capacity, carry out joint research and provide common guidelines for successful HBM programmes.

Green infrastructures for disaster risk reduction protection: evidence, policy instruments and marketability (GREEN)

The damage and losses caused by natural hazards in Europe over the period 1980-2013 amounted to 480 billion Euros in 2013 prices. More than 80% of the losses, 393 billion Euros, were caused by extreme weather events. Without concerted action and long-term adaptation planning, future risks are likely to be amplified by on-going human-induced climate change and socio-economic change. To improve the resilience of society, both structural and non-structural measures and grey and green infrastructure will be needed. In particular, a greater deployment of nature-based solutions such as Green Infrastructures (GIs) is being increasingly advocated by European institutions NGO's, governments and financing bodies as a part of flexible, effective and efficient, and no-regret measures for disaster risk reduction and adaptation to climate change.

The rationale behind the promotion of GI-based solutions is that they have the potential to contribute to both risk reduction (including, for example, flood and drought risk) as well as providing ancillary benefits such as positive effects on water quality, recreational amenities, economic resilience in agriculture and the provisioning of a wider range of other ecosystem services. Despite this recognized potential grey solutions have often prevailed over green solutions; primarily because grey infrastructure is often perceived to be more effective, efficient and easier to implement.

Although there is plenty of research indicating the potential benefits of GI, demonstration of its practical value for Disaster risk reduction (DRR) and role in both adaptation planning and sustainable development is lagging behind compared to other solutions and take up has been slow. This is primarily due to lack of actual applications, experience and coherence in the evidence base showing the direct and indirect benefits of GI solutions. In particular there is a lack of experience and coherence in implementation (including financing) and monitoring of GI solutions, including a lack of tools and methods supporting these processes.

GREEN is a two years project funded by DG ECHO in prevention and preparedness projects in Civil Protection and marine pollution with a budget 681,153 € to address these shortcomings and to provide the necessary innovation in methods, tools, and solutions to appropriately promote the role of GI for DRR, climate change adaptation (CCA) and sustainable. GREEN will improve existing and develop new assessment tools and services that are able to capture the multiple benefits of nature-based solutions; design and test business and policy models fostering innovative GI projects and services; and elaborate instruments for upscaling and monitoring the performance of GI strategies

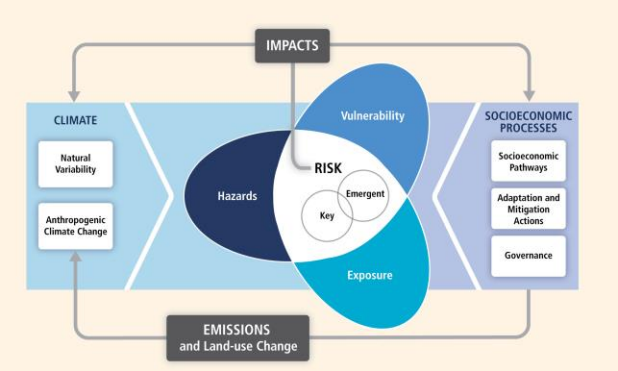

Figure 82.Definition of risk, IPCC (2014)

The specific objectives of GREEN are to:

1. Collect, critically review, and enhance the evidence that enables a sound and thorough assessment and monitoring of the functions and worthwhileness of green infrastructure-based solutions and ecosystem services for protecting economic, social and environmental assets and infrastructures in a representative number of regional, national and supra-national case/pilot studies;
2. Review the established and develop new business and policy strategies that foster realization of green infrastructure-based solutions; and to identify the regulatory 'enablers' and novel financial schemes that foster greater efficient deployment of GI-solutions;
3. Build a greater awareness about, and boost support for the practical application of GI-based solutions through ample engagement of stakeholders and businesses in designing innovative strategies, projects and services; and through systematic and tailor-made consultations and dissemination activities;
4. Develop criteria and instruments for mapping the potential of a large scale deployment of GIs throughout Europe, and by doing so promote their uptake; and to demonstrate the value and feasibility of green infrastructures-based solutions for the scope of regional, national and supranational DRR/CCA planning and nature conservation;
5. Foster market replication of the demonstration pilots through developing training, guidance documents and capacity building; making available large scale mapping outputs and well-documented generated datasets; and fostering business oriented knowledge products and services.
6. Develop methodologies able to extrapolate and/or up-scale the empirical evidence supporting the value of GI-based solution to regional and Pan-European level using also novel earth observation based services.
7. Provide guidance on and demonstration of the possibilities for large scale deployment of GI supported by structural and investment funds.

Exploring The Neurological Exposome (NEUROSOME)

NEUROSOME is a European integrated training network which investigates the causal associations among genetic predisposition, cumulative exposure to multiple environmental chemicals of children and neurodevelopmental disorders. The project brings together beyond- the-state-of-the-art advances in human biomonitoring and systems biology, exposure monitoring and toxicological testing technologies and advanced tools for computational analyses of the exposure-to-health effect continuum according to the exposome paradigm.

NEUROSOME

Figure 83. The NEUROSOME logo

The NEUROSOME methodology will be applied in population studies across different exposure settings to neurotoxicants (metals and selected organic compounds) in Europe. This will help us understand how environmental stressors lead to or exacerbate neurodevelopmental disorders. New standards for human biomonitoring data interpretation in conjunction with environmental and exposure information will be developed for ready use in chemical mixture risk assessment. The project would rely on the evaluation and reanalysis of existing cohort biosamples (e.g. PHIME, INMA, PROBE, Taranto, CROME, HEALS, PELAGIE, MECANA) and selected re-sampling and external exposome assessment of the populations involved in the above studies.
In the NEUROSOME study, we shall investigate:

a) the effect of genetics and the signalling pathways which could modulate the detrimental effects of toxic metals (Hg and MeHg among them) and selected organic compounds (phthalates, phenols, POPs) at low exposure in Mediterranean cohorts.
b) cumulative exposure of compounds relevant to neurological disorders such as toxic metals and specific organic chemicals (e.g. organophosphate pesticides), since there is a significant body of evidence showing a greater than additive effect of co-exposures to toxic metals and organic compounds.
c) the interplay between genetic variability and co-exposure to environmental chemicals for extended periods of time and how this contributes to the development or exacerbation of central nervous system disorders during child development (neurodevelopmental disorders) and later in life (neurodegenerative diseases).

NEUROSOME is funded in the frame of Marie Sklodowska-Curie Actions (MSCA-ETN- ITN) with an overall budget of 3.49 million Euros from the European Commission's Framework Programme Horizon 2020 over the course of four years, starting from 01 October 2017. The project is coordinated by Prof. Denis Sarigiannis. The project consortium is made up of 9 Beneficiaries Institutions and 5 Partners Organizations among the leading and well-experienced Organisations both in Europe and USA with a huge training experience in Environment and Health.

NEUROSOME places particular emphasis on the training of young researchers providing support for 14 Early Stage Researchers (ESRs) in all. NEUROSOME seeks to train the next generation of exposome scientists able to tackle the global challenges associated with the impact on human health due to environmental exposure. Great emphasis is placed on training ESRs through collaborative exchanges and practical courses. The ultimate goal is to produce a new generation of exposome researchers, trained in academia, applied research and industry, with transdisciplinary skills (environmental end exposure modelling, human biomonitoring, -omics technologies, high dimensional bioinformatics and environmental epidemiology) and understanding of fundamental science and its direct application to environmental health challenges.

NEUROSOME aims at protecting public health against neurodevelopmental disorders using the latest advances in environmental health science, namely the exposome paradigm. Although environmental health literature is rich with knowledge on the individual steps linking environmental contamination to disease, there is a lack of established causality for developing the respective Adverse Outcome Pathways (AOPs), especially considering cumulative exposure, where different mechanisms of toxicity are involved, interacting with each other on different levels of biological organization, dynamically in time. To better describe an AOP, we need to identify all the key processes from exposure to health outcome, corresponding to different molecular signatures revealed by multiple omics technologies. Overall, this requires synthesis among different scientific disciplines, including environmental and exposure modelling, recent advances in toxicology (including in vitro, in vivo and in silico aspects) with a special focus on omics technologies and bioinformatics, as well as environmental epidemiology, taking stock of gene- and exposome-wide associations..

DOse REsponse of MIxtures (DOREMI)

This project proposes the development of an integrative exposure biology framework combining human biomonitoring and in vitro data for the identification and characterization of AOPs relevant to neurodevelopmental disorders, applied in real-life chemical mixtures including potential neurotoxicants such as heavy metals and plasticizers, as well as the development of dose-response relationships related to the key events associated to the perturbed pathways. The overall aim of the project is to derive dose-response levels of neurodevelopmental effects associated with co-exposure to environmentally relevant mixtures and to identify effects greater than additively at environmentally relevant exposure levels, following a pathway of toxicity (PoT) approach.

Taking into account all the above, it is important to quantify the association between combined exposure to environmentally relevant levels of metals and selected endocrine disrupting compounds such as plasticizers and neurodevelopmental effects. The key research question in this context is how to derive a quantitative dose-response relationship linking co-exposure to mixtures of metals and plasticizers and neurodevelopmental toxicity covering the low-end of the dose range that is environmentally relevant. We shall answer this question going through the following steps:

- Elucidation of the synergistic mechanisms among the toxic metals and plasticizers studied
- Development of the respective AOPs for neurodevelopmental disorders and the combination of exposure and plasticizers for the prevalent combinations thereof.
- Finally, dose-time response modeling capturing the individual key events linked to co-exposure to the above chemical families to differentiate between key (sustained) and early events that will result in AOP activation

The complexity of biological responses following exposure to real-life chemical mixtures highlights the need to develop dedicated, comprehensive methodologies to quantify the dose-response relationships linking these complex exposures with the related neurodevelopmental effects. The DOse REsponse of MIxtures (DOREMI) project, aims at (a) the exploration of events that comprise AOPs leading to different neurodevelopmental effects (b) development of a dose-response function that relates the key events towards the deployment of the relevant AOP(s). In practice, the quantitative assessment of children neurodevelopmental progress will be associate with real-life chemical mixtures in a dose response manner. For this purpose, a combination of analysis in human biosamples and in vitro models is proposed.

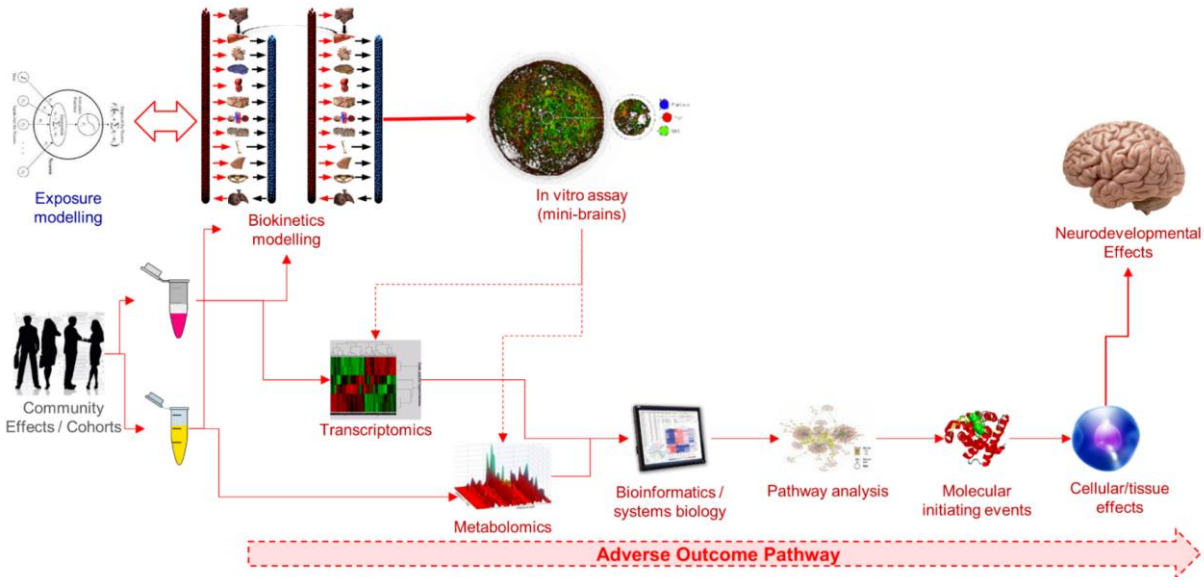

Figure 84. Conceptual representation of the proposed methodology information flow

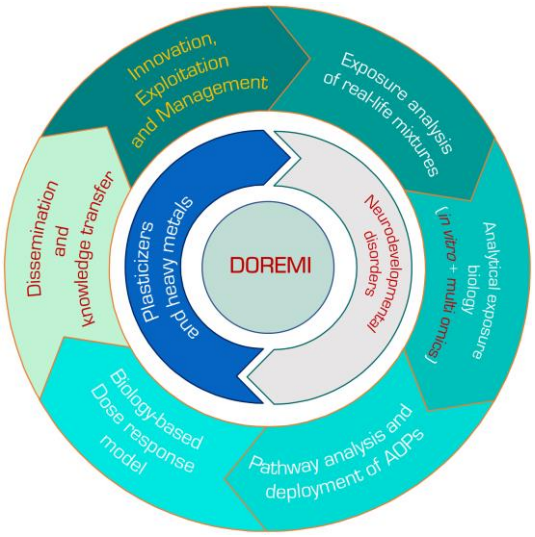

Figure 85. DOREMI workflow

EnvE Lab international profile

International collaborators network

EnvE Lab has a broad network of collaborators in each thematic area. In total, EnvE Lab collaborates with 85 research and academic institutions covering 26 different countries across the world in the frame of the six projects running in 2017.

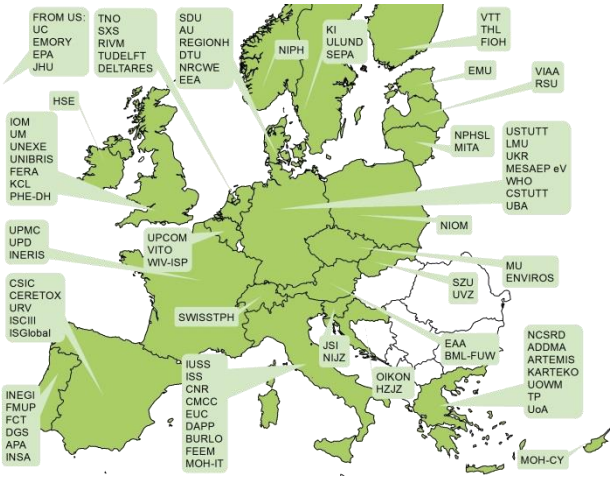

Figure 86. EnvE Lab collaborator network

In 2017 these collaborations gave rise to 71 presentations given in international fora. During the same period fifteen joint papers were published in international peer-reviewed journals and three book chapters were prepared.

World Health Organization (WHO)

Over the last five years EnvE Lab has established a close collaboration with the WHO European Centre for Environment and Health, which includes:

- The development of integrated methodologies for health impact assessment, taking into account multiple air pollutants and noise, related to GHGs emissions policies. EnvE Lab carries a long legacy in integrated health impact assessment from previous projects such as HEIMTSA, HEREPLUS, INTARESE, 2FUN. In the frame of URGENCHE, EnvE Lab has developed an integrated framework for assessing the health impact of GHG policies in Thessaloniki, bringing together different tools of environmental modelling and monitoring, composing novel methodologies. Knowledge exchange between EnvE Lab and WHO was strengthened by the close collaboration on expanding the methodologies to other cities/case studies in China involved in the project; to this aim an EnvE Lab team member visited the WHO Europe headquarters in Bonn for 3 months in early 2014.
- The assessment of combined or multiple exposure to health stressors in indoor built environments. The objective of this study was to undertake, summarize and present a systematic review of literature and project reports presenting evidence on multiple or combined risk exposure in indoor built environments. The review covered safety threats and injuries, indoor air pollution, use of household chemicals, noise, damp and mould, thermal conditions, crowding, inadequate hygiene standards, and harmful building and equipment/furnishing materials. In terms of indoor settings the review covered residential buildings as well as day care centers and schools. The results of the study were presented and used as the main scientific background at a capacity building workshop geared to public authorities of the WHO Europe member states in October 2013. WHO entrusted EnvE Lab with this task, because of our extensive experience and pioneering work on multiple stressors and more specifically chemical mixtures[2].
- Analysis of Environmental Health Economics to quantify the socioeconomic dimension of environmental pollution. Greece is an excellent case study considering the recent financial crisis, which has significantly altered the pattern of emissions and air pollution and introduced significant issues of environmental injustice.
- Assessment of current state of play in human biomonitoring focusing on optimal design of biomonitoring campaigns, as well as on the exploitation of biomonitoring data through internal dose modelling.
- Overview of human exposure to endocrine disruptors in Europe through a combination of environmental and consumer product monitoring and biological monitoring of the human population.
- Waste and human health; this forth collaboration axis entails the development of refined exposure assessment tools for the exploitation of exposome capabilities on public health assessment of risks related to industrially contaminated sites,

Organisation of the 19th Mediterranean Scientific Association of Environmental Protection (MESAEP) symposium in Rome

The 19th International Symposium on Environmental Pollution and its Impact on Life in the Mediterranean Region took place from October 4 to 6, 2017 at the CNR Headquarters in Rome, Italy. The conference attracted more than 330 abstracts from 23 different countries from all over the Mediterranean basin, on-Mediterranean countries in the EU and South Eastern Europe. Its focus was on quality of the environment and its impact on quality of life in the Mediterranean region with a particular emphasis on “Environmental and health inequity; science in the service of society”. After three days of presentations and scientific discussion there was a general agreement that the conference proved to be particularly interesting at these

[2] Sarigiannis DA, Hansen U. Considering the cumulative risk of mixtures of chemicals - A challenge for policy makers. Environmental Health: A Global Access Science Source 2012; 11.

challenging times of crisis in the Mediterranean region, providing a great opportunity for participants not only to dive in high quality science.

Figure 87. Presentations during the 19th MESAEP Symposium

Moreover, in collaboration with the flagship European projects/networks ICARUS (Integrated Climate forcing and Air pollution Reduction in Urban Systems) and PEC (Post-Emergency, Multi-Hazard Health Risk Assessment in Chemical Disasters) special workshops were held on climate change mitigation and air pollution abatement – towards win-win solutions and on natural and man-made environmental disasters. These events provided a great opportunity to debate and enhance the common understanding of the climate change and air quality issues in the light of environmental and health inequity in the respective scientific and stakeholder communities. Avenues of further research in the years to come were identified, such as the need to take into account low-level chronic exposure to environmental contaminants, or the quest for win-win solutions tackling jointly air pollution and climate change mitigation.

First International Training School on Environmental Health in industrially contaminated sites - COST Action IS1408 (ICSHNet)

The COST Action Industrially Contaminated Sites and Health Network (ICSHNet), was launched in 2015, and currently involves researchers and experts from 32 Countries. The Network is coordinated by the Istituto Superiore di Sanità (Italy) and aims at establishing and consolidating a European Network of experts and institutions involved in assessing the health impacts and/or managing remediation and response in industrially contaminated sites. A training school for early career investigators is one of the milestones of the Network, created in order to strengthen in-country capacity to face the environmental health challenges posed by Industrially Contaminated sites (ICSs). Early-stage researchers are key to the success of this Action by spreading knowledge methods through different scientific communities.

To this end the First International Training School on Environmental Health in industrially contaminated sites (ICSHNet) took place from 7 to 10 February 2017 at the Research Dissemination Center (KEDEA) of the Aristotle University of Thessaloniki, Greece with the participation of over 20 trainers and 50 trainees from across Europe. The Training course aimed to give them a good understanding of risk and uncertainty matched to a set of practical skills in facing the environmental health issues related to how to evaluate the health impact of industrially contaminated sites. The course had as the main objective to introduce students to the practice of exposure assessment, epidemiology and health impact assessment as applied to ICSs. Experts from these different disciplines provided the teaching and hands on training on a range of computational tools (software) and methodologies to assess population exposure and public health impacts from industrially infected areas. There was a general agreement that both the training school was a successful step toward a common understanding of the multiple and interlinked facets of the environmental health assessment in industrially contaminated sites. The final discussion reflected this collective understanding as witnessed by the very active participation of all trainers and trainees. A number of issues were discussed and clarified reinforcing the energy and competencies needed to face the great challenges which should be addressed in this scientific area. In the framework of the ISCHNet training school, a special session has been devoted to the issue of health risk assessment and management of gold mining in Skouries, Halkidiki (Greece). This session saw the participation of both specialists from Greece and abroad, as well as by local bodies and scientists representatives of Hellenic Gold who discussed and exchanged scientific opinions on the issue of the environmental and public health impact of mining from different perspectives.

Figure 88. ICSHNet first international training school

EnvE Lab response to societal needs

The extensive activities of EnvE Lab on the hot environmental issues of biomass combustion and the related PM pollution resulted in increased public awareness and positive regulatory change.

Health impact and monetary cost of exposure to particulate matter emitted from biomass burning in Thessaloniki

A major issue related to the extensive use of biomass as a space heating means during wintertime in Greece is the high levels of particulate matter. The study deals with the assessment of health impact and the respective economic cost attributed to particulate matter (PM) emitted into the atmosphere from biomass burning for space heating, focusing on the differences between the warm and cold season in 2011-2012 and 2012-2013 in Thessaloniki (Greece). Health impact was assessed based on estimated exposure levels and the use of established WHO concentration-response functions (CRFs) for all-cause mortality, infant mortality, new chronic bronchitis cases, respiratory and cardiac hospital admissions. Monetary cost was based on the valuation of the willingness-to-pay/accept (WTP/WTA), to avoid or compensate for the loss of welfare associated with illness.

The results of the 2012-2013 measurements were compared to the ones made in 2011-2012 to understand better the effect that different policy measures regulating the market price of heating fuel in tandem with the incumbent economic crisis in Greece and other countries in the European South may have on non-occupational exposure of the urban population to particulate matter and the associated health and monetary impact. Own-price elasticity of light heating oil was taken as el_{oil} = -0.39. A field survey encompassing ca. 300 households across the greater area of Thessaloniki implemented using the on-line SurveyMonkey tool provided consumer behavior information that was used to generate the cross-fuel elasticity table below.

The scenarios are based on reasonable assumptions and existing trends related to the energy market; however the interplay of multiple factors such as financial pressures or incentives might result in unexpected figures (as occurred with the increased biomass use), favoring one technological solution for space heating over another. Through analysis of specific scenarios we highlighted the attributable differences in public health burden, should specific space heating practices be adopted.

Table 2. Cross-price elasticities of alternative space heating energy carriers

	Light heating oil	***Natural gas***	***Biomass***	***Electricity***
Light heating oil	----	n/a	-0.97	-0.24
Natural gas	n/a	----	n/a	n/a
Biomass	-1.03	n/a	----	0.25
Electricity	-4.1	n/a	3.98	----

n/a: sufficient data non available to support the estimation of elasticity

The different policy scenarios examined, resulted in lower average urban background concentrations (Table 2).

Table 3. Fuel/technology use distribution and corresponding urban background concentrations

	Oil	**Natural gas**	**Biomass burning**	**Electricity**	**PM2.5 (μg/m³)**
2011-2012	44.0%	40.0%	5.6%	10.4%	**41.2**
2012-2013	22.3%	40.0%	26.7%	15.7%	**62.6**
Scenario 1	38.5%	41.5%	10.0%	10.0%	**36.3**
Scenario 2	43.5%	41.5%	5.0%	10.0%	**28.4**
Scenario 3	23.5%	62.5%	4.0%	10.0%	**26.5**
Scenario 4	20.0%	70.0%	0.0%	10.0%	**20.0**

Results showed that long term mortality during the 2012-2013 winter increased by 200 excess deaths in a city of almost 900,000 inhabitants or 3540 years of life lost, corresponding to an economic cost of almost 200-250m€. New chronic bronchitis cases dominate morbidity estimates (490 additional new cases corresponding to a monetary cost of 30m€.

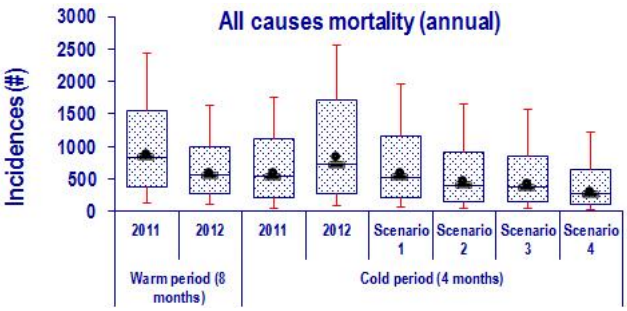

Figure 89. Estimated annual mortality due to PM exposure under current situation and "what if" scenarios

Estimated health and monetary impacts are more severe during the cold season, despite its smaller duration (4 months).

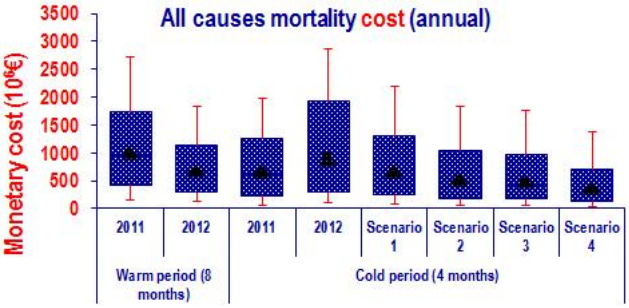

Figure 90. Estimated socioeconomic cost of PM attributed mortality based on total welfare change

Policy scenario analysis revealed that significant public health and monetary benefits (up to 2b€ in avoided mortality and 130m€ in avoided illness) might be obtained by limiting the biomass share in the domestic heat energy mix. Fiscal policy affecting fuels/technologies used for domestic heating needs to be reconsidered urgently, since the net tax loss from avoided oil taxation due to reduced consumption was further compounded by the public health cost of increased mid-term morbidity and mortality.

Recommendations on the technologies of pellet boilers

EnvE Lab expert opinion was requested by the General Secretarial of Industry for providing recommendations on the PM emission specifications of pellet and wood combustion boilers available in the Greek market. This reflected the concerns about the current emission levels of biomass combustion of modern devices present in the Greek market; the question posed was whether an intermediate level of emissions limit should be implemented before the Eco-Design directive becomes effective in 2018. In order to address this question, a thorough review related to technological aspects of boilers technology as well as a survey of the current situation in the Greek market were carried out.

From the review, it was found that the mass of particulate emissions is 180 times higher for old construction boilers compared to boilers based on newer specifications. Moreover, the number of particles emitted increases with an increase in emissions of non-oxidised gaseous components. Since the distributions of the number and mass depends on the particle size, it is concluded that the emission of particles, in particular ultrafine (size <100 microns) is amplified by non-ideal combustion conditions. Pellet burning results in coarser particle emissions compared to liquid fuels. The size distribution of aerosols is influenced by many factors such as the humidity of the fuel, the content of ash and the combustion process.

The European Committee for Standardization (CEN) has adopted standard EN 303-5 on 10-05-2012. This standard classifies the boilers into 3 categories, setting thresholds for their performance and emission limits for boilers that burn solid fuel. The boilers using as fuel solid biomass for non-industrial use in the Greek market intended for use in heating installations must comply the minimum performance and quality limits of exhaust gas set by the standard ELOT EN 303-5 according to Class 3. For this reason, the EN 303-5 is often used by local authorities as part of their regulations, to promote the purchase of high efficiency boilers and to create incentives for the use of efficient boilers with low emissions. This is the only European standard for boilers. Besides this standard apply another 4 standards for small residential applications of biomass:

- *EN 13240: For heaters - Solid Fuel*
- *EN13229 and EN 12815: For cooking Solid-Fuel fireplaces*

According to research conducted in Greece there are about 18 companies which manufacture pellet boilers and solid fuel some of which manufacture and fireplaces and stoves. It is important to stress that many of these companies have EN 303-5 with solid fuel boilers to category 3 but some of them have even certification of class 4-5, while the pellet boilers usually belong in category 4-5. Given the implementation of Directive 2009/125 / EC on Eco-Design requirements for (a) boilers and (b) local space heaters fired by solid fuels in 2018, the projected emission values Class 5 (40 mg/m^3) will be significantly reduced compared to the class 3 emission levels (150 mg/m^3). The technology and emissions of class 3 devices are closer to those of classes 1 (200 mg/m^3) and 2 (180 mg/m^3). Therefore, the reduction of emissions from existing boilers must be combined with changes in the technology, which will include the installation of electrostatic filters, the addition of secondary combustion, the increase of the gas paths inside the boiler and the construction of reverse steering technology boiler flame. Because the modification of existing boilers Class 3 are difficult to be transformed into class 4-5, a measure that would contribute significantly to reducing actual emissions is the use of better quality fuels.

The above analysis of available data shows that around 66% of Greeks biomass boiler manufacturers produce devices Class 4 and 5, i.e. with emissions below 100 mg/m^3. Emissions from the biomass boilers can be further reduced by using good quality biomass in accordance with the technical specifications of boilers. We may conclude that it is legitimate to establish an intermediate emission limit to 100 mg/m^3 for all Greek construction companies in order to push them towards more rapid harmonization with Community policy on eco-design (eco-design) by on the one hand and to protect public health from excessive aerosols emissions as occurred in the winter periods 2012-2013 and 2013-2014.

EnvE Lab in the news – TV interviews

Figure 91. A comprehensive interview at the "Eco News" show of SKAI TV Channel with Associate Professor Dimosthenis Sarigiannis, EnvE Lab director, talking about the main environmental health problems that Greece is facing nowadays. **Watch the video at: https://youtu.be/7Wr8ye0BeAk.**

Figure 92. A radio interview at ERT3 Thessaloniki radio 102.0 FM with Associate Professor Dimosthenis Sarigiannis, talking about waste management and health impacts caused by industrial and civil activities. Among else, the issues of traces of arsenic element in potable water and the use of wood burning as a domestic heating source were tackled. **Watch the video: https://youtu.be/VKRcYYrIENE.**

Figure 93. A TV interview at the "Eurodata" show of Alpha TV Channel with Associate Professor Dimosthenis Sarigiannis, talking about exposure to pesticides, their environmental effect, as well as ways of reducing pesticide impacts on human health. **Watch the video at: https://youtu.be/_cL4FycjmKc**

Figure 94. A TV interview at "Epikoinwnia" show of ERT3 TV with Associate Professor Dimosthenis Sarigiannis, talking about small quantities of radioactivity that were detected in the atmosphere in Athens. The isotope detected is ruthenium-106 (Ru-106). The abnormal radioactivity detection, although not of concern from radiation protection point of view, requires further investigation for the identification of the source of origin. **Watch the video at: https://youtu.be/RP_QO_ip5fs**

Figure 95. Assoc. Prof. Dimosthenis Sarigiannis addresses the possible hazards associated with chemicals found in everyday products, at an interview at the 'Kathimerina kai Apla" show of the ERT3 TV Channel. Among else, guidelines and safety tips are being given with regards to the safe handling of chemical and cleaning products found in home and school environments. **Watch the video at: https://youtu.be/nNnwQY1n9yc**

Figure 96. A TV interview with senior researcher Dr. Spyros Karakitsios, at the "Epikoinwnia" show of the ERT3 TV Channel. Dr. Karakitsios won the 2017 LRI Innovative Science Award that will support his research in the field of dose response of synergy in combined exposure to human or environmental species. The LRI awards is an initiative of the European Chemical Industry Council (Cefic), in conjunction with the Society of Environmental Toxicology and Chemistry Europe (SETAC Europe). **Watch the video at: https://youtu.be/H1x2LV_nXVI**

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Priftis A, Papikinos K, Koukoulanaki M, Kerasioti E, Stagos D, Konstantinopoulos K, Spandidos DA, Kermenidou M, Karakitsios S, Sarigiannis D, Tsatsakis AM, Kouretas D. **Development of an assay to assess genotoxicity by particulate matter extract**. Molecular Medicine Reports 2017; 15: 1738-1746.

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Sarigiannis D.A., A. Gotti, E. Handakas, S. Karakitsios. **Informatics and data analytics to support exposome-based discovery Part 2: Computational exposure biology**. Chapter in: Applying Big Data Analytics in Bioinformatics and Medicine. P. Papadopoulou and D. Lytras (eds.), IGI Global (in print).

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A. Arampatzis, C. Giannitsis, E. Ballhysa, T. Nikolopoulos, E. Sandaltzopoulou, K. Akritidis, N. Papaioannou, K. Samaras – Tsakiris, A. Theocharis, A Papadimitriou, D. Sarigiannis, G. Koliakos. **A Toolbox of Genetically Engineered E. coli for Precise Targeting and Programmable Elimination of Cancer Cells According to Their miRNA Profile**. 2017 2nd Bioengineering & Translational Medicine Conference, Minneapolis (MN), USA, 28-29/10/2017.

Dimosthenis Sarigiannis. **Exposome – Based Risk Assessment of Carbon Nanotube Functionalisation.** 2017 2nd Bioengineering & Translational Medicine Conference, Minneapolis (MN), USA, 28-29/10/2017.

D. Chapizanis, S. Karakitsios, D.A. Sarigiannis. **Integrated use of Agent Based Modelling with sensor webs for personal exposure assessment**. 2017 27th Annual Meeting of Exposure Science (ISES), North Carolina, USA, 15-19/10/2017.

N. Barouki, E. Handakas, S. Karakitsios, D. Sarigiannis. **A web based platform for air pollution data analysis and exposure assessment**. 2017 19th International Symposium on Environmental Pollution and its Impact on Life in the Mediterranean Region (MESAEP), Rome, Italy, 4-6/10/2017.

D.A. Sarigiannis, K. Tsioka, N. Papaioannou, E. Handakas, C. Gabriel, S. Karakitsios. **Exposomics analysis linking environmental exposures to neurodevelopmental disorders: A combination of metabolomics and bioinformatics analysis**. 2017 19th International Symposium on Environmental Pollution and its Impact on Life in the Mediterranean Region (MESAEP), Rome, Italy, 4-6/10/2017.

D. Sarigiannis, A. Gotti, E. Matiaki. **An integrated approach to combat atmospheric pollution in smart cities through policy interventions and behavioural change – The ICARUS paradigm.** 2017 19th International Symposium on Environmental Pollution and its Impact on Life in the Mediterranean Region (MESAEP), Rome, Italy, 4-6/10/2017.

D. Sarigiannis, K. Zarifidis, I. Zarkadas. **Anaerobic digestion of cellulose rich agro residues of rice and wheat farming: Focussing on the effects of biological and mechanical pretreatments.** 2017 19th International Symposium on Environmental Pollution and its Impact on Life in the Mediterranean Region (MESAEP), Rome, Italy, 4-6/10/2017.

D.A. Sarigiannis. **Assessing the impact of hazardous waste on children's health: the Exposome paradigm**. 2017 19th International Symposium on Environmental Pollution and its Impact on Life in the Mediterranean Region (MESAEP), Rome, Italy, 4-6/10/2017.

I. Furxhi, D. Sarigiannis, S. Karakitsios. **Assessment of public health risk from arsenic using biomarkers and biokinetics modeling**. 2017 19th International Symposium on Environmental Pollution and its Impact on Life in the Mediterranean Region (MESAEP), Rome, Italy, 4-6/10/2017.

D. Chapizanis, S. Karakitsios, D. Sarigiannis. **Emerging methodologies for personal exposure assessment: coupling portable sensors data and agent based modelling (ABM)**. 2017 19th International Symposium on Environmental Pollution and its Impact on Life in the Mediterranean Region (MESAEP), Rome, Italy, 4-6/10/2017.

D.A. Sarigiannis, Handakas, A. Gotti, S. Karakitsios. **Human exposure assessment to multiple chemicals using biomarkers**. 2017 19th International Symposium on Environmental Pollution and its Impact on Life in the

Mediterranean Region (MESAEP), Rome, Italy, 4-6/10/2017.

D. Sarigiannis, M. Vassou, I. Zarkadas. **Growth of microalgae chlorella vulgaris on biogas and anaerobic digestion of the recovered microalgal biomass for biofuels production: Toward a zero carbon society.** 2017 19th International Symposium on Environmental Pollution and its Impact on Life in the Mediterranean Region (MESAEP), Rome, Italy, 4-6/10/2017.

K. Papadaki, S. Karakitsios, D. Sarigiannis. **Modeling of elimination half – life for environmental chemicals**. 2017 19th International Symposium on Environmental Pollution and its Impact on Life in the Mediterranean Region (MESAEP), Rome, Italy, 4-6/10/2017.

D.A. Sarigiannis, K. Polanska, W. Hanke, A. Salifoglou, A. Gabriel, N. Papaioannou, E. Handakas, S. Karakitsios. **Pathway analysis of prenatal combined exposure to heavy metals and phthalates related child motor development.** 2017 19th International Symposium on Environmental Pollution and its Impact on Life in the Mediterranean Region (MESAEP), Rome, Italy, 4-6/10/2017.

D. Sarigiannis, S. Karakitsios, M. Kermenidou. **Generation of oxygen species is linked to ambient air PM_x sources**. 2017 19th International Symposium on Environmental Pollution and its Impact on Life in the Mediterranean Region (MESAEP), Rome, Italy, 4-6/10/2017.

D.A. Sarigiannis, K. Polanska, W. Hanke, A. Salifoglou, A. Gabriel, N. Papaioannou, E. Handakas, S. Karakitsios. **Pathway analysis of neurodevelopment toxicity due to prenatal combined exposure to heavy metals and phthalates.** 2017 53rd Congress of the European Societies of Toxicology, Bratislava, Slovakia, 10-13/09/2017.

D.A Sarigiannis, A. Gotti, S. Karakitsios, E. Matiaki. **A holistic approach in support of air quality for future green and resilient cities.** 2017 6th International Conference on Environmental Management, Engineering, Planning & Economics (CEMEPE) and SECOTOX, Thessaloniki, Greece, 25-30/06/2017.

D. Sarigiannis, K. Papadaki, S. Karakitsios. **Advanced modeling of adipose: blood partition coefficient for environmental chemicals**. 2017 6th International Conference on Environmental Management, Engineering, Planning & Economics (CEMEPE) and SECOTOX, Thessaloniki, Greece, 25-30/06/2017.

D. Sarigiannis. **Assessing the impact of hazardous waste on children's health: the exposome paradigm**. 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. **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. Chapizanis, S. Karakitsios, D. Sarigiannis. **Can Agent Based Modelling, coupled with sensors data, be used for personal exposure assessment?** 2017 6th International Conference on Environmental Management, Engineering, Planning & Economics (CEMEPE) and SECOTOX, Thessaloniki, Greece, 25-30/06/2017.

D. Sarigiannis, S. Karakitsios. **Cancer risk associated to combined chemical and radiological indoor exposure in Greece and Bulgaria**. 2017 6th International Conference on Environmental Management, Engineering, Planning & Economics (CEMEPE) and SECOTOX, Thessaloniki, Greece, 25-30/06/2017.

D. Sarigiannis, F. Kaldis, P. Katapodis, M. Lioti, R. Fried, I. Zarkadas. **Effect of lipolytic enzymatic pretreatment in the anaerobic digestion of fat, oil and grease (FOG)**. 2017 6th International Conference on Environmental Management, Engineering, Planning & Economics (CEMEPE) and SECOTOX, Thessaloniki, Greece, 25-30/06/2017.

D.A. Sarigiannis, Handakas, A. Gotti, S. Karakitsios. **Exposure assessment of multiple chemicals starting from biomonitoring data**. 2017 6th International Conference on Environmental Management, Engineering, Planning & Economics (CEMEPE) and SECOTOX, Thessaloniki, Greece, 25-30/06/2017.

D. Sarigiannis, A. Gotti, Handakas, S. Karakitsios. **Life cycle – based health risk assessment of plastic waste**. 2017 6th International Conference on Environmental Management, Engineering, Planning & Economics (CEMEPE) and SECOTOX, Thessaloniki, Greece, 25-30/06/2017.

D.A. Sarigiannis, K. Polanska, W. Hanke, A. Salifoglou, A. Gabriel, N. Papaioannou, E. Handakas, S. Karakitsios. **Pathway analysis of prenatal combined exposure to heavy metals and phthalates related child motor development.** 2017 6th International Conference on Environmental Management, Engineering, Planning & Economics (CEMEPE) and SECOTOX, Thessaloniki, Greece, 25-30/06/2017.

D. Sarigiannis, S. Karakitsios, M. Kermenidou. **Sources of oxidative induced by ambient air PM_x**. 2017 6th International Conference on Environmental Management, Engineering, Planning & Economics (CEMEPE) and SECOTOX, Thessaloniki, Greece, 25-30/06/2017.

D.A. Sarigiannis, S.P. Karakitsios, E. Handakas, A. Gotti. **Life cycle – based health risk assessment of plastic waste**. 2017 5th International Conference on Sustainable Solid Waste Management, Athens, Greece, 21-24/06/2017.

D.A. Sarigiannis, S.P. Karakitsios, A. Gotti. **Health Risk From Accidental Fire In A Plastics Recycling Facility**. 2017 5th International Conference on Sustainable Solid Waste Management, Athens, Greece, 21-24/06/2017.

D.A. Sarigiannis, E. Handakas, I. Zarkadas. **Food Waste Biomethanation In Farm – Scale Systems**. 2017 5th International Conference on Sustainable Solid Waste Management, Athens, Greece, 21-24/06/2017.

D.A. Sarigiannis. **Assessing the impact of hazardous waste on children's health: the Exposome paradigm**. 2017 11th Panhellenic Research Congress of Chemical Engineering, Thessaloniki, Greece, 25-27/05/2017.

D.A. Sarigiannis, S. Karakitsios. **Cancer risk associated to combined chemical and radiological indoor exposure in Greece and Bulgaria**. 2017 11th Panhellenic Research Congress of Chemical Engineering, Thessaloniki, Greece, 25-27/05/2017.

D. Sarigiannis, F. Kaldis, P. Katapodis, M. Lioti, R. Fried, I. Zarkadas. **Effect of lipolytic enzymatic pretreatment in the anaerobic digestion of fat, oil and grease (fog)**. 2017 11th Panhellenic Research Congress of Chemical Engineering, Thessaloniki, Greece, 25-27/05/2017.

D. Sarigiannis, D. Chapizanis, S. Karakitsios. **Emerging methodologies for personal exposure assessment: coupling portable sensors data and agent based modelling (ABM)**. 2017 11th Panhellenic Research Congress of Chemical Engineering, Thessaloniki, Greece, 25-27/05/2017.

D.A. Sarigiannis, Handakas, A. Gotti, S. Karakitsios. **Exposure assessment of multiple chemicals starting from biomonitoring data**. 2017 11th Panhellenic Research Congress of Chemical Engineering, Thessaloniki, Greece, 25-27/05/2017.

D.A. Sarigiannis, S. Karakitsios, A. Tsatsakis, K.S. Golokhvast, A.B. Engin. **High dimension biological analysis of carbon nanotube toxicity**. 2017 11th Panhellenic Research Congress of Chemical Engineering, Thessaloniki, Greece, 25-27/05/2017.

D.A. Sarigiannis, A. Gotti, Handakas, S. Karakitsios. **Life cycle – based health risk assessment of plastic waste**. 2017 11th Panhellenic Research Congress of Chemical Engineering, Thessaloniki, Greece, 25-27/05/2017.

D. Sarigiannis, K. Papadaki, S. Karakitsios. **Modelling the adipose: blood partition coefficient for environmental chemicals.** 2017 11th Panhellenic Research Congress of Chemical Engineering, Thessaloniki, Greece, 25-27/05/2017.

D.A. Sarigiannis, K. Polanska, W. Hanke, A. Salifoglou, A. Gabriel, N. Papaioannou, E. Handakas, S. Karakitsios. **Pathway analysis of prenatal combined exposure to heavy metals and phthalates related child motor development.** 2017 11th Panhellenic Research Congress of Chemical Engineering, Thessaloniki, Greece, 25-27/05/2017.

D. Sarigiannis, S. Karakitsios, M. Kermenidou. **Sources of oxidative induced by ambient air PM_x**. 2017 11th Panhellenic Research Congress of Chemical Engineering, Thessaloniki, Greece, 25-27/05/2017.

D. Sarigiannis, A. Gotti, E. Matiaki. **An integrated approach to combat atmospheric pollution in smart cities through policy interventions and behavioural change**. 2017 6th Environmental Conference of Macedonia, Thessaloniki, Greece, 5-7/05/2017.

D. Sarigiannis, A. Tsoha, M. Kermenidou. **In vitro genotoxicity and cytotoxicity of urban particulate matter: association with chemical composition**. 2017 6th Environmental Conference of Macedonia, Thessaloniki, Greece, 5-7/05/2017.

I. Furxhi, D. Sarigiannis, S. Karakitsios. **Assessment of risk from arsenic exposure in Serres**. 2017 6th Environmental Conference of Macedonia, Thessaloniki, Greece, 5-7/05/2017.

D. Sarigiannis, G. Dontis, I. Zarkadas. **Biomethanation and valorization of mink droppings and byproducts**. 2017 6th Environmental Conference of Macedonia, Thessaloniki, Greece, 5-7/05/2017.

D. Sarigiannis, S. Karakitsios. **Cancer risk associated to combined chemical and radiological indoor exposure in the Greece – Bulgaria cross – boundary region**. 2017 6th Environmental Conference of Macedonia, Thessaloniki, Greece, 5-7/05/2017.

D. Sarigiannis, D. Chapizanis, S. Karakitsios. **Emerging methodologies for environmental exposure assessment at a personal level**. 2017 6th Environmental Conference of Macedonia, Thessaloniki, Greece, 5-7/05/2017.

D. Sarigiannis, E. Handakas, D. Chapizanis, S. Karakitsios. **Exposure to PM in various micro – environments**. 2017 6th Environmental Conference of Macedonia, Thessaloniki, Greece, 5-7/05/2017.

D. Sarigiannis, S. Karakitsios, M. Kermenidou. **Impact of maritime transport on the local air quality of Thessaloniki**. 2017 6th Environmental Conference of Macedonia, Thessaloniki, Greece, 5-7/05/2017.

D. Sarigiannis, E. Handakas, S. Karakitsios, A. Gotti. **Life cycle assessment of municipal waste management in Thessaloniki**. 2017 6th Environmental Conference of Macedonia, Thessaloniki, Greece, 5-7/05/2017.

D. Sarigiannis, S. Karakitsios, M. Kermenidou. **Reactive oxygen species generation associated with sources of atmospheric particulate matter in ambient air of Thessaloniki**. 2017 6th Environmental Conference of Macedonia, Thessaloniki, Greece, 5-7/05/2017.

D. Sarigiannis, S. Zachariou, M. Lioti, I. Zarkadas. **Valorisation of the three phase olive mill wastewater with the addition of high protein co – substrates**. 2017 6th Environmental Conference of Macedonia, Thessaloniki, Greece, 5-7/05/2017.

D.A. Sarigiannis, K. Polanska, W. Hanke, A. Salifoglou, A. Gabriel, N. Papaioannou, E. Handakas, S. Karakitsios. **Combined exposure to EDCs resulting in**

neurodevelopmental disorders. 2017 SETAC, 27th Annual Meeting, Brussels, Belgium, 7-11/05/2017.

D.A. Sarigiannis, E. Matiaki, A. Gotti. **Conceptualizing stakeholder engagement in the realm of tackling air pollution and nurturing environment-conscious citizens, in the context of sustainable, urban resilient cities.** 2017 SETAC, 27th Annual Meeting, Brussels, Belgium, 7-11/05/2017.

D.A. Sarigiannis, A. Gotti, V. Handakas, S. Karakitsios. **Exposure to heavy metals, contaminated soil, diet and children neurodevelopment**. 2017 SETAC, 27th Annual Meeting, Brussels, Belgium, 7-11/05/2017.

D.A. Sarigiannis, I. Furxhi, S. Karakitsios, A. Tsatsakis, K.S. Golokhvast. **High dimension biological analysis of carbon nanotube toxicity**. 2017 SETAC, 27th Annual Meeting, Brussels, Belgium, 7-11/05/2017.

D.A. Sarigiannis, S.P. Karakitsios, K. Papadaki, E. Handakas, A. Gotti. **Integrated external and internal exposure to chemicals: the INTEGRA computational platform**. 2017 SETAC, 27th Annual Meeting, Brussels, Belgium, 7-11/05/2017.

D.A. Sarigiannis, S.P. Karakitsios, E. Handakas, A. Gotti. **Internal dosimetry metrics for risk assessment of endocrine disruptors – the case of bisphenol A**. 2017 SETAC, 27th Annual Meeting, Brussels, Belgium, 7-11/05/2017.

D.A. Sarigiannis. **Multiscale connectivity – a high dimension biology approach to unravel the exposome**. 2017 SETAC, 27th Annual Meeting, Brussels, Belgium, 7-11/05/2017.

D.A. Sarigiannis, A. Gotti, V. Handakas, S. Karakitsios. **The HERACLES Waste study: unraveling the associations between exposure to metals through diet and children cognitive functions**. 2017 SETAC, 27th Annual Meeting, Brussels, Belgium, 7-11/05/2017.

D.A. Sarigiannis, E. Handakas, A. Gotti, K. Papadaki, S. Karakitsios. **Exposure assessment of multiple chemicals starting from biomonitoring data**. 2017 The Society of Toxicology 56th Annual Meeting and Tox Expo™, Baltimore (Maryland), USA, 12-16/03/2017.

D.A. Sarigiannis, K. Polanska, W. Hanke, A. Salifoglou, A. Gabriel, N. Papaioannou, E. Handakas, S. Karakitsios. **Pathway analysis of prenatal combined exposure to heavy metals and phthalates related child motor development.** 2017 The Society of Toxicology 56th Annual Meeting and Tox Expo™, Baltimore (Maryland), USA, 12-16/03/2017.

D.A. Sarigiannis, S. Karakitsios, A. Tsatsakis, K.S. Golokhvast, A.B. Engin. **High dimension biological analysis of carbon nanotube toxicity**. 2017 The Society of Toxicology 56th Annual Meeting and Tox Expo™, Baltimore (Maryland), USA, 12-16/03/2017.

D.A. Sarigiannis, S.P. Karakitsios, A. Gotti, E. Handakas, A. Docea, A. Tsatsakis. **INTEGRA Life Cycle: A comprehensive in silico tool for the chemical exposome**. 2017 The Society of Toxicology 56th Annual Meeting and Tox Expo™, Baltimore (Maryland), USA, 12-16/03/2017.

Invited talks

Invited talk at the Toxicology Symposium organised by the Department of Biochemistry and Biotechnology of the University of Thessaly under the framework of the Master's Programme in Toxicology; it was held in Larissa, Greece,January 28-29. Lecture titled **"EU-wide human biomonitoring program and the exposome"**.

Invited talk at the workshop "Food Packaging' organised by the Association of Greek Chemists" that was held in Athens, Greece, February 17. Lecture titled **"Cumulative exposure to Chemicals and Public Health. A new challenge to the industry in the 21st century".**

Invited talk at the premises of the National School of Public Health in Athens, Greece, February 28. Lecture titled **"The exposome: a new tool for assessing the impact of cumulative exposure to environmental pollutants on public health"**.

Invited talk at the workshop "Health and safety in the research laboratories" co-organised by the Hellenic Institute of Hygiene and Safety in the Workplace (Elinyae), held in Thessaloniki, Greece, March 15. Lecture titled **"The importance of human biomonitoring for assessing occupational safety in research labs"**.

Invited talk at the Conference in Regenerative Medicine (CO.RE – 1)with title "Stem Cells in Surgery" held in Thessaloniki, Greece, April 7 – 8. Lecture titled **"The exposome: overcoming the nature vs. nurture dilemma in human health"**.

Invited talk at the Sixth Ministerial Conference on "Environment and Health" organised by the World Health Organisation (WHO) Regional Office for Europe in close partnership with the United Nations Economic Commission for Europe and the United Nations Environment Programme; it was held in Ostrava, Czech Republic, June 13 – 15. Lectures titled **"Exposome in urban settings The HEALS paradigm"** and **"Modern research for circular economy"**.

Invited talk at the Workshop "Fit-For-Purpose Exposure Assessments For Risk-Based Decision Making" co – organised by the International Council of Chemical Associations' Long – Range Research Initiative (ICCA-LRI) and Joint Research Centre (JRC); it was held in Como, Italy, June 21 – 22. Lecture titled **"Integrated Aggregate and Cumulative Exposure Assessment on Operationalizing the Exposome for Improving Chemical Risk Assessment Following the 21st Century Exposure Science Guidelines"**.

Invited talk at the seminar "INTEGRA" organised by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES); it was held in Paris, France, July 5. Lecture titled **"INTEGRA: Lifetime exposure assessment towards the development of the individual exposome"**.

Invited talk at the Triple Helix Aristotle Innovation Lab organised by the iGEM Greece 2017 team that held in Thessaloniki, Greece, July 13. Lecture titled **"Health and Exposome Research: Assessing Contributors to Lifetime Exposure and State of health (HERACLES)"**.

Invited talk at the Paris Descartes University in Paris, France, July 6. Lecture titled **"Investigating the exposome"**.

Invited talk at the HELIX Scientific Symposium organised by the Institute for Global Health of Barcelona (ISGlobal) and held in Barcelona, Spain, October 30 – 31. Lecture titled **"What have we learnt in HEALS and why does it matter?"**.

Invited talk at the Workshop "Setting research priorities in environment and health" organised by the World Health Organisation (WHO) Regional Office for Europe; it was held in Bonn, Germany, November 30 – December 1. Lecture titled **"Research for "Precision prevention""**.

Invited talk as Principal Investigator at the Workshop organised by the iGEM Greece 2017 team that was held in Thessaloniki, Greece, December 18. Lecture titled **"Synthetic biology and "Precision prevention""**.

Laboratory Personnel

Dimosthenis A. Sarigiannis, Director

M.Sc., PhD (University of California, Berkeley, USA) is Associate Professor specialising on environment and health engineering at the Department of Chemical Engineering of the Aristotle University of Thessaloniki and the institute for Advanced study of Pavia. He is visiting Professor at the Master's Program on Toxicology of the University of Thessaly and at the Master's Program on Toxicology and Environmental Risk at the Medical School of the University of Pavia. He is also senior scientist at the Chemical Assessment and Testing unit of the Institute for Health and Consumer Protection at the European Commission's Joint Research Centre (currently on leave). At the European Commission he has served as Scientific Coordinator of the IHCP, Action Leader for Consumer Product Safety and Quality and Community Reference Laboratory for Food Contact Materials, Action Leader for Human Exposure to Environmental Stressors and Health Effects and for Assessment of Chemicals at the European Chemicals Bureau, Scientific Assistant to the JRC Director General, Strategy Manager of the IHCP and as science advisor to the Greek Minister of the Environment. He was a principal contributor to the REACH Regulation and to the Environment and Health Action Plan and is currently member of the Health and Environment Working Party and of the Health Security Committee. He has been pioneering efforts to coupling biology-based modelling with toxicogenomics discovery systems for developing a mechanistically based understanding of the health risk of environmental chemical mixtures. He is member of the international forum for evidence-based toxicology, of the scientific committee for chronic risks of INERIS, and President of MESAEP. He leads the projects ICARUS, HEALS, PEC, CROME, NEUROSOME, ERNCIP and DOREMI. He has also contributed to the IPs HEIMTSA, 2-FUN, NO MIRACLE, HENVINET and, CAIR4HEALTH, HEREPLUS, TRANSPHORM, GENESIS, TAGS and INTERA.

Dr. Alberto Gotti is a Physicist of the University of Milan with over 21 years of experience in environment and health impact assessment, data assimilation and exposure modelling including physiology-based biokinetic modelling. In the last ten years he has worked for the European Commission"s Joint Research Centre, for the Intedisciplinary Institute of Environmental Research and for CERTH several projects.

Dr. Spyros Karakitsios is an environmental health scientist, with studies in physics (B.Sc.), environmental and computational chemistry (M.Sc.) and applied biology (PhD) of the University of Ioannina.

Dr. Ioannis Zarkadas is an Environmental Engineer from the University of Leeds (UK), his research activities focus on waste management, anaerobic digestion, Life Cycle Analysis.

Dr. Catherine Gabriel is a Chemical Engineer, with studies in Advanced Chemical Engineering (M.Sc.) and Inorganic Chemistry (PhD) in Aristotle University of Thessaloniki, with expertise in analytic chemistry.

Dr. Ilias Frydas is a Molecular Virologist and holds a PhD from the Veterinary Medicine School of the Ghent University in Belgium. Currently, involved as postdoctoral researcher at the HBM4EU and the BlueHealth projects.

Marianthi Kermenidou (PhD Student) is Environmental Engineer, from Democritos University of Thrace, Greece with a MSc degree. Her scientific field is indoor air pollution, chemical analysis, source apportionment and redox activity of PM.

Evangelos Handakas is a PhD Student Researcher, Chemical Engineer and civil infrastructure engineer with 2 M.Sc. degrees (MMAths and M.Eng). His research activities focus on the fields of biological systems modelling, and exposure reconstruction.

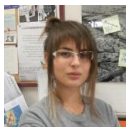
Krystalia Papadaki (PhD Student Researcher) is a Chemical Engineer, graduated from Aristotle University of Thessaloniki, Greece. Her research activities focus on QSARs modelling.

Dimitrios Chapizanis is a PhD Student Researcher. He holds a diploma in Chemical Engineering and his research activities focus on atmospheric pollution, exposure assessment and environmental risk.

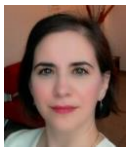
Evelin Matiaki MBA, MSc Civil Engineer is a European Projects Manager and a PhD Candidate at the Environmental Engineering Laboratory.

Maria Andrielou is a Communications Adviser. With more than 10 years of experience in the industry, policy and education field, Maria is responsible for building communication, dissemination and stakeholder engagement strategies.

Nafsika Papaioannou is a Chemical Engineer. Her expertise lies in analysing complex omics data. She has also experience with system biology approaches to integrating omics data into biological pathway/network.



Irini Furxhi holds and Msc in Toxicology. She has worked in "Etablissement Francais du Sang" (EFS) – France Compte in the diagnostic Molecular-Oncology laboratory.



Maria Diseri is an Agriculture and Food Technologist holding a MBA and a MSc in Toxicology. She has more than 10 years managerial experience in Greece and abroad, trained in multinational environment.