Executive summary:

Human Biomonitoring (HBM) is an effective tool to access human exposure to environmental pollutants and potential health effects of such pollutants. The European Environment and Health Strategy as well as the Environment and Health Action Plan 2004 - 2010 of the European Commission recognised the value of HBM and the relevance and importance of coordination of HBM programmes in Europe. Various activities showed that in the EU significant efforts are made to collect biomarker data in environmental health. However, the activities were fragmented and results could not be sufficiently compared.

The main goal of the project was to develop a coherent approach to HBM in Europe as requested by Action 3 of the EU Environment and Health Action Plan through coordination of ongoing and planned HBM activities. Within this scope a pilot study (DEMOCOPHES) has started in September 2010 to demonstrate the feasibility and usefulness of an EU harmonised approach to HBM. 16 EU Member states and one other European country, being also part of COPHES used the harmonised guideline protocol prepared by COPHES to perform the pilot study. The work was additionally guided by the further COPHES teams by means of quality assurance and control systems for chemical analysis and data management, of training on fieldwork, data management and communication, via the delivery of guidance and publication material as well as discussion documents for communication to policy makers.

The pilot study focused on feasibility of a harmonised approach and was restricted to mercury, cadmium, cotinine and phthalates. In order to allow a dynamic process and to support the evaluation of current and future policy making (including e.g. REACH) Bisphenol A was analysed in six MS. A dynamic communication strategy has been developed to raise awareness with respect to environmental health.

While not yet representative for the European population, COPHES and DEMOCOPHES proved to be successful in collecting information on the distribution of chemicals in 17 European countries which can be compared between the countries and allow comparison with international data from NHANES (Links), Health Canada and European studies performed on national or regional level.

Based on the collected data, COPHES showed that in general, exposure of the European population to the chemicals tested is well below the available health based guidance values, but that biomarker values show a large variation in the population and between countries. In addition it became apparent that biomarker levels in children were highly correlated with

the levels in their mother, which may indicate a common environmental factor, and that social class has a significant influence on each of the biomarker levels.

The experiences of COPHES and DEMOCOPHES clearly showed that synergies are generated by a common approach and that there is a clear need and benefit of a European framework for future sustainable HBM. For the further development of a common European HBM approach that would allow the generation of EU reference values, the current effort needs to be expanded to:

(i) measuring exposure to a larger amount of substances; and

(ii) using data obtained for a suitable reference population, representative for the European population.

Project Context and Objectives:

The main objective of this coordination action was to develop a functional framework that contributes to the definition, organisation and management of a coherent approach towards HBM in Europe. The framework aggregated experiences from existing and planned HBM activities in European countries and investigated what is needed to improve and support better comparability of HBM data across them.

The project consisted of eight thematic work packages. The work packages 2, 3, 4 and 5 addressed the individual steps of a Human Biomonitoring environmental health survey with respect to a harmonized approach. WP 5 was in addition responsible for overall communication, WP 6 for training and capacity building and WP 7 for considering newly upcoming scientific knowledge. WP 8 focused on the link to policy making. WP 1 was a horizontal activity that aims at bringing together the work done within WP 2, 3, 4 and 5 to provide a consistent study protocol for a European Human Biomonitoring survey, which was tested out in 17 countries through DEMOCOPHES, funded by LIFE+.

WP2 concentrated on concepts and strategies to harmonise recruitment and sampling procedures, WP3 covered sample processing including biobanking, WP4 was responsible for data analysis and interpretation, WP5 did communication and dissemination, and WP6 managed training and capacity building. Implementation into one sustainable framework, ethical and legal matters was performed under WP1. WP7 focused on links with current research projects dealing with development, validation and use of novel biomarkers including non-invasive markers and effect markers namely in the field of genotoxicology and -omics. WP8 addressed the longer-term vision and sustainability. WP8 investigated requirements, needs, and major challenges for HBM and its potential to be used as a tool in European policy, highlighted and discussed options for links to the existing regulatory frameworks and provided a proposal for a future sustainable framework and structure for HBM at European scale. WP9 dealt with managerial matters.

The project tasks were performed in three periods consisting of the preparatory phase (collection and analysis of information on national practices, and preparation of the study protocol) - test phase (support to the pilot study) - and conclusions and recommendations (evaluation of DEMOCOPHES with particular attention to specific questions, extraction of lessons to learn and recommendations, identification of key levers for harmonization).

At the start of COPHES in December 2009 it was not yet clear if budget for a full pilot study would be available. On May 19th 2010 it was announced that the project DEMOCOPHES

would be proposed for financing through LIFE+ and would provide for the implementation of a pilot study in 17 European countries. The Grant agreement was signed in August 2010 and DEMOCOPHES started formally on September 1st 2010. In order to ensure a maximum success of this pilot, COPHES proved high flexibility and ensured intensive collaboration with DEMOCOPHES throughout the full project running time.

Work Package 1 'Operational EU HBM framework'

The main objective of COPHES was to build a coherent and sustainable framework for HBM surveys in Europe and to increase the comparability of data across countries. A key step in such a framework is the elaboration and testing of common and operating guidelines for setting up surveys. WP1 worked as an overarching ('umbrella') WP for WP 2, 3, 4, 5 and 6 and coordinated all relevant steps and parts of the work into a common and European study protocol, supported the implementation in the DEMOCOPHES countries and the evaluation of the feasibility of a European approach. A 3-step approach was followed. In the first step a common EU protocol was developed in close collaboration with 17 countries taking part in DEMOCOPHES. In the test phase the common protocol guided the development and implementation of the pilot study in the 17 DEMOCOPHES countries. The protocol team supported the implementation of the pilot survey study through a helpdesk, training activities, and direct contacts. The third phase focuses on results, evaluation and conclusions of the pilot study and recommendations for a coherent and sustainable framework. WP1 also provides and supports in ethical and protection of privacy aspects within the project.

Work Package 2 '<u>Sampling, recruitment and sample collection</u>'

Main task of WP2 was to provide agreed options for selection of participants, recruitment, fieldwork and sample collection and to develop recommendations for the Pilot Study DEMOCOPHES and a future EU-HBM survey.

Describing relevant existing study conduct practices for cross sectional HBM-studies in the EU, was the first objective and resulted in the detailed description of surveys conducted in BE, CZ, DE and FR. Based on this material and taking recommendations of ESBIO and the Implementation Group into consideration, advantages and disadvantages for selected decisions of each issue addressed in WP 2 were contrasted and recommendations for DEMOCOPHES given. These recommendations were translated into detailed standard operation procedures as bases for the national DEMOCOPHES conduct. Additionally, questionnaires and background material were provided for recruitment, interview on exposure pathways, urine and hair sampling and non-responders. With these measures the second objective, providing guidelines, and the third objective, give appropriate scientific support, were achieved. Providing material for the help-desk was the last objective which was achieved by answering questions raised in the countries and by a train-the-trainer

event. Lessons learnt from the DEMOCOPHES countries lead to a further elaborated guideline for future HBM measures on a European scale.

Additionally to the WP2 objectives, members of WP 2 assisted WP 3, 4, 5, 6 and 8.

Work Package 3 'Sample handling, analysis and biobanking'

Sampling handling and analysis are important issues to take into account in studies with biological samples and even more in HBM studies due to some of their characteristics. The biomarker concentrations measured in samples from non-exposed individuals are, in general, very low. This implies that a minimum contamination can have important consequences in the final results. On the other hand, these low levels required analytical techniques that can measure them in a reliable way and of course, the quality of the results must be guaranteed.

The pre-analytic phase is a potential source of errors and contamination where influencing and interfering factors can alter the quality of the samples. Therefore is essential to establish precise and common instructions in order to ensure the quality of the samples arriving at the lab. Next step, the chemical analysis requires specific precautions to achieve analytical data of high quality. It is important to take into account that all these precautions should be addressed in a framework of harmonization among different laboratories, in different countries that means different capacities, facilities, experience, etc.

The responsibilities of WP3 throughout COPHES have been focused on the control of these issues in order to establish the bases which ensure a high quality and reliability of the analytical results and therefore contribute to comparability of HBM results at EU level.

A detailed description of the measures for quality assurance in COPHES can be found in the protocol. In short:

-Overview on existing activities for biobanking in the EU.

-Preparation of general guidelines for processing and storing human specimens.

-A common Quality Assurance/Quality Control (QA/QC) pattern has been established as a base for harmonisation of EU laboratories. Common definitions and standards have been established for pre-analytical and analytical phase, including a glossary and Standard Operating Procedures (SOPs) for both phases.

-Comparability of the chemical analysis has been tested by inter laboratory comparisons and external quality assessment schemes.

Work Package 4 '<u>Data analysis and integrated interpretation</u>'

The COPHES/DEMOCOPHES twin projects allowed to for the first time collecting in a harmonized way comparable human biomonitoring data and information from questionnaires across Europe, and a unique dataset was obtained of exposure biomarkers from more than 4000 individuals (children and their mothers) from 17 European countries. In this context WP4 developed strategies for harmonised analysis and interpretation of the data at the individual level, the national level and at the European level, to provide guidance and central programs for data analysis and to support the countries in data analysis and interpretation. WP4:

-Provided an overview of existing practices of data analysis in cross-sectional HBM-studies in the EU.

-Provided support to the DEMOCOPHES countries for:

•Formatting and processing biomarker data and data from questionnaires

•Statistical analysis to obtain information on the distribution of the biomarker values in the population and in subpopulations in each country

•Interpretation of results at the individual level and at country level

-Performed the central analysis of the biomarker data at the European level

•Create a central database for analysis of the biomarker data at the European level

•Calculate distribution of the biomarker values in the EU population

•Calculate 'European exposure values' for each biomarker in mothers and in children

•Statistical analysis to obtain information on determinants of exposure

•Comparison of biomarker levels of each country with the 'European exposure values'

•Interpretation of biomarker results including health based relevance

•Linkage of aggregated environmental data with human biomonitoring data

-Reported on use of INSPIRE (GIS and other ENV data) in HBM surveys

-Evaluated the harmonisation process and provide recommendations for future analysis of EU wide human biomonitoring surveys

Work Package 5 'Communication and dissemination'

The overall aim was to develop a dynamic communication strategy for the dissemination of results and communicate key messages to all stakeholders: study participants, general public, and policymakers. The communication strategy encompassed each stage of the project from the planning, inception, through implementation and final conclusion and recommendations for a future European-wide HBM project.

Objectives of this strategy were to:

-promote public awareness of human biomonitoring

-develop communication tools including a web presence and promotional material for the project tailored to the needs of the different stakeholders

-ensure transparency and openness towards stakeholders

-inform about results and their significance to public health

-deliver a tested communication strategy for future European HBM studies

Work Package 6 'Training and Capacity building'

Training and capacity building identified needs for training, developed training modules for the different aspects of the HBM survey, supported the training activities required, and evaluated the methods developed and tested.

More specifically the objectives of this WP were to:

-identify training requirements in MS in different survey related areas both for partners in the project and the users.

-develop training modules for all aspects identified as priorities and promote their use in a coordinated manner among practitioners and other stakeholders.

-coordinate an efficient and well justified training work programme using the training materials and evaluate its effectiveness.

-promote knowledge and experience exchange inside and outside (DEMO)COPHES.

-provide training material and accomplish a help-desk function.

Work Package 7 'Horizon scanning and link to other research projects'

Biomarker development is progressing continuously. This includes the research on new non-invasive matrices but also the research related to effect biomarkers, susceptibility markers and new emerging pollutants. The newest results in biomarker developments were fed into COPHES through extensive contacts with ongoing EU and international projects and programmes and by organising workshops in connection with relevant scientific meetings.

In particular the work package aimed to:

-Assess future inclusion of new biomarkers (effect markers, non invasive markers, -omics, emerging pollutants, etc) into HBM surveillance studies through linkage with other national, EU and international programmes.

-Identify upcoming research and development points from new projects.

-Provide an overview of relevant existing scientific research on effect markers, non invasive sampling, and -omics in the EU and worldwide, and prepare general guidelines for possible application of these markers for HBM survey activities.

-Establish close collaboration with major scientific journals covering HBM topics and organise and participate in relevant workshops.

Work Package 8 'Support for sustainable EU HBM programme (policy support) '

It is widely accepted that HBM can be used to support policy making, to evaluate policy effectiveness and to promote more comprehensive health impact assessments of policy options. But improved use including better access for secondary use and better comparability of monitoring data at European scale are considered as key parameter for an effective use of HBM as policy tool. Integrating HBM as a tool in new EU policy is considered necessary, and identifying its most effective use is seen as a priority.

Against this background the objectives of WP 8 were in particular to identify major obstacles, requirements, and policy needs, and to develop recommendations for future use of HBM as a tool in policy making. This included an assessment of authorities and stakeholders perspectives for relevant steps of HBM studies, the identification of long-term requirements in an organisational context (including the possibility to liaise with the Health Examination Survey), identification of option to link HBM to the existing regulatory frameworks, and intensive discussions with stakeholders and authorities on a European approach.

The aim of the work package was to develop recommendations and a draft concept for current and future HBM activities in Europe, and to provide an estimate of costs, benefits and resources needed for a sustainable framework with a special focus on a comparison between the current situation and a harmonized approach.

Project Results:

Besides the protocol, which was jointly generated by Work Packages 1-6, the project provided the following key results:

-Support to the conversion of the European protocol into national protocols and the implementation of this national protocol in all DEMOCOPHES countries.

-An intensive interlaboratory comparison investigation (ICI) including capacity building of European laboratories, complemented by an external quality assessment scheme (EQUAS) involving major reference laboratories worldwide to ensure a maximum data comparability and quality.

-Validated analysis methods and list of reference laboratories

-Guidelines for data processing and management

-A report on the use of INSPIRE

-A project website addressing the general approach of a harmonized European HBM as well as the specific aspects of the first European pilot study.

-Modules for training and capacity building

-A tested strategy for future European HBM studies

-Reports on possible use and application of non-invasive sampling, and on state of the art of Omics and metals related to HBM and prospects for COPHES/ DEMOCOPHES

-Conclusions on the feasibility of a harmonised European HBM with lessons learned and next steps for harmonisation

-A concept for a sustainable European HBM framework and policy recommendations for future HBM.

-Links to ongoing other EU and international projects (such as PHIME, ECNIS, NewGeneris) and institutions (such as WHO, EEA and UNEP)

-Reports evaluating lessons learnt from DEMOCOPHES,

-Reports on feasibility of a EU framework and programme, and on HBM biobanking on the European scale

-Summary reports on sampling, recruitment and sample collection, data analysis and integrated interpretation

In the following a description of the tasks and achievements made by the individual Work Packages is provided:

Work package 1 'Operational EU HBM framework'

Development and coordination of EU pilot study project protocol: a step by step approach

In order to prepare a first discussion document, information on past, currently ongoing and planned HBM and other surveys was collected in the EU Member States by elaborating a questionnaire to be filled in by all national partners of COPHES. The national focal points within DEMOCOPHES were crucial persons in the procedure of obtaining complete and accurate information. This information allowed i.e.

(1) identifying key experts in the countries;

(2) to build a network of experts;

(3) to identify similarities and discrepancies within and amongst countries; and

(4) to identify needs for training and exchange of capacities.

The European protocol was developed by COPHES but an extensive exchange system was set up with DEMOCOPHES and the national focal points, in order to maximize practicability and efficiency. Texts and tools prepared were at regular intervals proposed and discussed with DEMOCOPHES. Subsequently comments and amendments were added to the work in progress. This exchange process allowed taking into account as much as possible the national particularities and concerns. At the same time the construction of the COPHES consensus protocol was based on the information on already existing experiences, knowledge and infrastructure within EU countries as collected by the questionnaire. This step by step approach supported a maximal harmonisation amongst participating countries, allowing however to respond to specific local concerns and requests. (See also D 1.2 First discussion document and presentation of discussion document to MS/HBM programme leaders and D 1.3 Adapted version of discussion document and protocol (so-called consensus protocol and presentation of consensus protocol). WP1 also provided specific advice and support on ethics and data protection.

When the modification of the final EU protocol to national protocols started, a template for reporting on the conversion from the European protocol to the national protocols was developed by DEMOCOPHES and COPHES, aiming at collecting in a structured way all key relevant information on modifications to the European protocol at national level. This allowed to follow up in a common framework the state of the implementation in all participating countries, to exchange on 'good ideas and practices', to take note of deviations from the EU Protocol (acceptance of older mothers, use of web based questionnaire…) and to identify some concerns/questions encountered (CAPI, the SES stratification, length of the face to face interview, list of Phthalate metabolites, guidelines for national web pages…). Overall reporting showed that the implementation went smoothly in all countries. Only

minor national modifications as compared with the EU Protocol were reported. The COPHES protocol team evaluated the procedures adopted in each country and the risk for major difficulties impacting on the harmonized interpretation of the data. A first overall evaluation was made by WP1, followed - if needed - by a more in depth analysis of specific items by the respective WP's. A letter was sent to all national coordinators including comments and recommendations if applicable.

The implementation of the pilot study in the DEMOCOPHES countries was supported through direct contacts, trough a help desk, and trough training activities reported under WP6. Consultation and advises were also frequently provided through direct contacts between the National Focal Points (NFP), the DEMOCOPHES coordination, and the relevant WP1 -6 teams. When results of sample analyses became available, a series of teleconferences was organised together with the DEMOCOPHES coordinators in June 2012 to support the communication of the individual results to the study participants. This provided the opportunity for the NFP to ask questions on practical aspects and to exchange experiences.

After the first analysis of internal exposure and questionnaire data by WP4, a workshop was organized (11-12 July 2012, KULeuven University Faculty Club) to discuss the first EU level results of the pilot study, identify remaining questions, inconsistencies and problems, and to prepare key messages for further dissemination. Also the preliminary scientific programme of the Cyprus final COPHES/DEMOCOPHES Conference organised under the Cypriot Presidency of the EU Council on 23-24th October 2012 was discussed. Additional exchanges on these topics followed during the next months at several occasions (see D1.5 Workshop to discuss preliminary results and to prepare reporting of results to a wider audience).

The further dissemination of the exposure results of the pilot study is still ongoing at national and at European level trough workshops and publications. The relevance of the data for policy aims is already shown by the use of the DEMOCOPHES mercury data in a publication on the economic benefits of methylmercury exposure control in Europe (Environmental Health.2013, 12:3), at the moment UNEP will meet to discuss the measures to control pollution. Also, COPHES partners supported WHO for the development of a standardized methodology for a HBM survey in maternities with analysis of total mercury in maternal hair samples.

Conclusions on feasibility of a European framework and programme

The pilot study showed that comparable results could be obtained in 17 European countries (UK, SK, SE, RO, PT, PL, LU, DE, CZ, CH, HU, BE, CY, IE, SI, DK, ES), all implementing the same study protocol, with some adaptations. HBM data and questionnaires informed on exposure

to a limited set of pollutants (Hg, Cd, cotinine, phthalates and in 6 countries BPA). A European network was built, exchanging information, expertise and experiences, providing first training facilities at several levels. Therefore a European approach is considered feasible. Sufficient harmonization can be achieved to successfully conduct HBM-studies on an EU scale. A key challenge in determining common approaches is (preliminary) summarized as the need for finding the right balance between a rigid structure allowing maximal comparability and a flexible approach increasing feasibility. Also, a strict Quality assurance and Quality control system is needed to guarantee comparable and reliable results. However, combining this with a system that aims at capacity building for chemical analyses might prove very difficult and too time consuming to fit with the demands of a HBM survey programme.

Capacity building should not compromise strict criteria for laboratory selection. To allow a HBM campaign to exert its full potential, a broad communication approach from the very start is considered essential and must include social science strategies. A EU level communication strategy/plan and communication material is needed, well adapted to the target groups but allowing adaptations to the national situations.

In order to develop a sustainable system at European level, adequate decision making processes need to be developed and adequate funding secured. This requires political support by Member States and the European Commission. At the moment initiatives are ongoing to obtain such support at several levels. WP8 developed a concept for a sustainable framework. At the same time several European countries expressed their willingness discuss further on possibilities to explore the potential of a common use of Human Biomonitoring data produced at regional, national as well as transnational level for supporting and evaluating policy.

One of the demands during discussions leading to Action 3 of the Action plan included 'obtaining preliminary reference values of selected biomarkers from all participating Member States'. Reference values for environmental pollutants are established at national level in several countries. The number of samples obtained in the DEMOCOPHES study is too small to be representative and the data obtained do not fulfill the scientific criteria for a "reference" base. For the further development of a common European HBM approach that would allow the generation of EU reference values, the current effort needs to be expanded to:

(i) measuring exposure to a larger amount of substances; and

(ii) using data obtained for a suitable reference population, representative for the European population.

The substances to address will have to be identified through a transparent process of prioritization. For emerging substances methods need to be developed and also for this prioritization is needed, through a transparent process. More harmonised approaches in EU HBM can support the development of reference values at EU level that might be the basis for actions and policies envisaging higher environmental equity. They can determine whether a person or group has an unusually high exposure and identify population groups that merit further assessment of exposure sources or health effects (See also D 1.6 Report on results of Demonstration /pilot study and on feasibility of a EU framework and programme, also including in its part II an overview and analysis of ethical aspects).

Numerous presentations to an audience of various stakeholders were done and are reported in the COPHES overall list of Dissemination activities and Publications.

Work Package 2 'Sampling, recruitment and sample collection'

Information from relevant existing cross-sectional HBM-surveys from BE, CZ, DE and FR were combined with results of ESBIO and of the Implementation Group to develop recommendations for the conduct of the Pilot Study DEMOCOPHES and for a future EU-wide harmonized survey. The objectives referred to the issue of recruitment and field work which included the study design, study population, selection of participants (=sampling), recruitment including exclusion and inclusion criteria and occupational exposure. Issues of field work included questionnaires for the interviews (way of questioning, modules of questionnaires) and the collection of urine and scalp hair samples. Furthermore aspects of all issues were connected with quality assurance.

Based on the before mentioned information (Deliverable 2.1) advantages and disadvantages for selected items of each WP 2 issue were discussed and recommendations for DEMOCOPHES developed and first perspectives for a future EU-HBM shown (Deliverable 2.2). Within the course of COPHES and with the input of the DEMOCOPHES countries these recommendations were further elaborated. Detailed Standard Operation Procedures (SOPs) were compiled. Recommendations and SOPs built the basis for the national DEMOCOPHES conduct.

DEMOCOPHES countries reported back their experiences with the SOPs, the questionnaires and the overall conduct of participant selection, recruitment and field work including sample collection. These experiences were evaluated to extract lessons learnt (Deliverable 2.3) which lead to refined considerations for a future EU-HBM surveillance programme (Deliverable 2.4).

Following lessons learnt for selection of participants, recruitment, field work and sample collection can be extracted from DEMOCOPHES:

Selection of sampling locations and participants: A European definition for urban and rural is missing. Therefore based on national decisions the countries selected two sampling locations due to population density or number of inhabitants representing the upper and the lower degree of urbanization. For the selection of the children it was recommended to get the addresses via inhabitant registries or contact children via schools. The majority of the countries chose the school approach, so the school approach is recommended for an EU-HBM survey on children aged 6 to 11 years.

The SOP for the recruitment procedure was very detailed. Number, contents and time of sending invitations and reminders were fixed. Most countries deviated slightly from the strict schedule and adapted their procedure to national needs; e. g. reduced the number of letters but called the participants instead. These deviations revealed that a frame of recommendations (the contents and not the single steps) for recruitment is sufficient. A recruitment questionnaire was applied to assess inclusion and exclusion criteria. It showed that a very clear and early description and communication of exclusion criteria is advisable (e.g. age of mother, no siblings - already clearly announced in the invitation letter). Convincing people to participate proved to be more difficult than expected. All countries faced a very low participation rate for the participation and also for answering the non-responder questionnaire. Accompanying communication activities (task of WP 5) are crucial to increase the participation rate. If representativeness of the population sample is desired for a future EU-HBM survey, all aspects of participant selection and recruitment influencing representativeness are to be fixed.

The procedures for field work (exact schedule of the visits) and sample collection (also including explanations on urine and hair sampling) were followed in all countries. The recommendation to sign the informed consent directly at the beginning of the visit was a lesson learnt. Some families preferred home visits compared to visits in examination centres, so both possibilities should be offered even if no ambient monitoring is included. The duration of the whole visit of the fieldworkers including the interview with the basic questionnaire, the hair sampling, collection of the urine vessels and the questionnaires on urine and hair sampling, took a median time of 60 minutes - shorter than expected.

The basic questionnaire consisted of six modules

(1) residential environment and residence,

(2) nutrition,

(3) smoking behaviour,

(4) exposure-relevant behaviour,

(5) occupation and

(6) socio-demography, to assess environmental exposure and related questions.

Additionally a background paper for the basic questionnaire was developed, which included information about the background and references of the questions and an interviewer briefing.

The experiences of the interviewers with the basic questionnaire revealed that only some single questions need improvement, especially those based on EUROSTAT classifications (occupation, socio-demography).

The provided CAPI system SOCRATOS was well accepted for data entry but did not meet the needs for being used directly in the face-to-face interview because internet access was constantly necessary which could not always be provided and additionally caused problems with data protection. Despite this, countries voted for a computer based version which could ease the performance or be accessible prior to the visit.

DEMOCOPHES revealed that providing incentives (at least non-monetary), was possible in all countries and that they were valuable instruments to increase the participation rate. Incentives should be offered as far as ethically allowed - and should best be announced in the invitation letter.

All parts of the field work were accompanied by quality assurance measures. The recommendation to produce a national Fieldwork Manual containing all necessary information on the survey and all written materials for the participants was followed in nearly all countries. The offered train-the-trainer session on field work was well appreciated as training of the interviewers was crucial for the success of the survey. Materials provided on this session were used for the national trainings of the interviewers which in some countries were performed very intensively but in others could be intensified. Additionally check lists for internal quality control were provided and several countries used them either for interviewer training or for their internal quality control. External quality control is additionally recommended for a future EU-HBM survey.

The initially planned 3 month period for the conduct of the field work in all 17 countries was prolonged because ethical approvals, data protection issues and participant recruitment needed longer than expected which should be considered for a future EU-HBM survey.

The harmonized performance of the DEMOCOPHES participant selection, recruitment and field work was finally a success. 15 of 17 participating countries were able to involve the predefined number of 120 mother-child pairs, one country recruited 100 pairs and one 21 pairs. Therefore it can be concluded that the European consensus protocol and adjacent SOPs on participant selection, recruitment and field work including the questionnaires are a very valuable basis for developing a future EU-HBM survey.

Work Package 3 'Sample handling, analysis and biobanking'

WP3 tasks have been developed at different stages throughout the project. During the preparatory phase WP3 has contributed in the preparation of the study protocol used as guideline and basis for future steps later on. The specific contribution of WP3 to the protocol was the development of the Standard Operating Procedures (SOPs) for pre-analytical and analytical phases.

The SOPs dealing with pre-analytical aspects were:

-First - morning urine sampling

-Scalp hair sampling

-Sampling Packing and shipment

-Sample reception and registration

In addition to the SOPs, a training course focused on urine and hair sampling was done by members of WP3. Both, SOPs and the training courses, have allowed a harmonized way of sampling in all participating countries. A harmonized sampling is the basis for harmonized HBM data.

The analytic phase was also supported by WP3 with the development of SOPs for the analysis of the target biomarkers in COPHES/DEMOCOPHES. The SOPs included as part of the European protocol were:

-Mercury in hair by AAS

-Cotinine in urine by GC-MS

-Phthalates in urine by LC-MS/MS

-Creatinine in urine by Jaffé

-Cadmium in urine by ICP-MS

In the test phase, the work of WP3 was focused in the establishment of a concept for the QA within an EU HBM network. Firstly, an inventory of potential participating laboratories was done in close collaboration with NFPs and WP1. The inventory gave a first overview of the capacities, characteristics and a first rough picture on the experiences of the laboratories that would perform the analysis of the DEMOCOPHES samples.

Then, a Quality Assurance Unit (QAU) was established by the members of WP3 (ISCIII and IPA). This central QAU was responsible for all questions on analytics and offered the possibility to have a global view on all quality aspects in the field of chemical analysis.

The QAU organized an Inter-laboratory Comparison Investigation (ICI) and an External Quality Assurance Scheme (EQUAS). Control material for those four exercises (2 ICI, 2 EQUAS) was prepared by QAU based on pooled native samples. The control material was extensively tested for stability and homogeneity before distribution to the laboratories that participated in the exercises.

Thanks to the 3 rounds of ICIs performed throughout 2011, the analytical methods and their application were harmonized and therefore the comparability of the analytical results of the participating laboratories was improved. The newcomers in the field of HBM had the opportunity to test the performance of the new established methods in those exercises.

During the EQUAS (2 rounds, 2011-2012) the accuracy of the results of participating laboratories was tested. In this exercise, 16 renowned and experienced laboratories worldwide served as reference laboratories in the COPHES/DEMOCOPHES EQUAS.

COPHES/DEMOCOPHES ICI/EQUAS exercise involved more than 50 laboratories (participating laboratories across Europe and reference laboratories worldwide) and the preparation and shipment of more than 600 samples of control material.

During the implementation of the exercise different web-conference were done in which the participants had the opportunity of discuss the results, share experiences and knowledge as well as have the support of the QAU to resolve technical problems. Therefore, the ICI/EQUAS has served not only as an exercise to ensure comparable results but as a training and capacity building activity as well.

The results of the ICI/EQUAS exercise were used by the COPHES coordination team to established criteria for the selection of qualified laboratories. WP4 guided the discussion based on their knowledge on statistics. Since some of the laboratories started analysing some parameters just before the beginning of the COPHES project not all laboratories were able to meet the high quality criteria of the COPHES project in that short time. Only laboratories that successfully participated in at least one ICI and one EQUAS for both concentrations was regarded as qualified in the quality assurance exercise. A list of qualified laboratories for each parameter was elaborated by WP. This list can serve as a starting point for further European HBM activities in the future.

The pre-analytical and analytical SOPs, the data of the inventory of the potential participating laboratories, the results of ICI/EQUAS, the list of qualified laboratories, etc. in sum, all works developed by WP3 are available in the deliverables defined in COPHES protocol as mandatory for WP3:

-D3.1 Define methods for sampling specimens, including choice of collectors, conditions of handling, preservation, sending, holding in bio-banks and QC aspects for the biomarker selected.

-D3.2 Report on existing activities for biobanking in the EU - (under responsibility of WP2)

-D3.3 Define methods for analysing samples (SOPs) inside and/or outside MS.

-D3.4 Inventory of EU Reference Labs for different chemicals/biomarkers/matrices.

-D3.5 Establish a concept for a periodical program for the QA within an EU HBM network.

-D3.6 Support the project website with information on validated methods, database of EU reference Labs.

-D3.7 Report on the feasibility of HBM biobanking on the European Scale and adapted general guidelines for processing and storing human specimens - (under responsibility of WP2)

In addition to these deliverables, an extra one was developed after the Workshop on Quality of Analytical Data in HBM, organized by WP3 the 30th November 2011 in Brussels during the European Week on HBM:

-D3.8 Workshop on Quality of Analytical Data in Human Biomonitoring - Presentations for the workshop held during the European Week on HBM, Brussels December 2011.

In addition to the specific tasks defined within WP3, it has collaborated with other WPs for interpretation of the European-wide HBM results, supported the project web-site, elaborated the study protocol and other common documents, in the organization of training and communication activities, etc.

Work Package 4 'Data analysis and integrated interpretation'

WP4 focused efforts on the development of strategies for harmonised analysis and interpretation of the data at the national level and at the European level. The use of aggregated environmental and health data was explored to complement the information which can be obtained from the human biomonitoring surveillance network.

In the light of the identified preferences and needs of the project and DEMOCOPHES countries, the choice was made to develop central guidance and programs for data analysis and data interpretation at the national level, which allowed countries to build expertise for analysing their own data. A protocol was established to allow the national teams to obtain country specific information on the distribution of the biomarkers in their study population. Countries were instructed to get aggregated data of the studied chemicals in the environment and in food.

At the same time anonymized European biomarker data were centrally processed, analysed and interpreted. A statistical working group was installed to develop a statistical analysis plan and agreed on confounders and covariates, stratification, rounding, how to handle missing values and values below the limit of detection. Variables were coded and categorised if needed.

Data management and data quality control included the use of a Computer Assisted Personalized Interview (CAPI) tool to allow that the information from the centrally developed questionnaire was loaded directly into a harmonised database. A software program for quality control of all data was developed and provided to the national focal points to control their database before uploading them in a central European database.

Characteristics of the population and distribution of the biomarker data in the population were analyzed at the country level and at the European level. The detailed results at the country level are available in the national reports of the DEMOCOPHES project. At the European level, information was obtained on the distribution of biomarker levels (urinary cadmium, cotinine, phthalate metabolites, bisphenol A and mercury in hair) in the 17European countries. Data on bisphenol A were obtained in only 6 countries; data on some phthalate metabolites (MiBP, MnBP) in 13 countries and cadmium measurement in 16 countries. The geometric mean (with 95% confidence intervals) and 90th percentile were calculated for each biomarker separately in children and in mothers and were named 'European exposure values'. The European exposure values were compared with available health based guidance values. After adjustment for confounders, average exposure values in each country were compared with the mean of the 'European exposure values' by means of a weighted analysis of variance. Multiple regression analysis was used to identify significant environmental, geographical, personal or life style related parameters which influence the biomarker level.

In addition to the information provided by the countries, environmental data were collected from EU databases available through EFSA, FAO, UBA and EEA.

Results

-Data from 1844 mothers and 1844 children between 6 and 11 years of age were collected between October 2011 and January 2012

-For the first time European exposure values were calculated as weighted geometric mean and 90th percentile. All countries were weighted in such a way that they contribute for 120 participants, except for Cyprus and Luxemburg who contributed for 60 participants. The average values but not the P90 values were adjusted for selected confounders.

-Biomarker values showed a large variability in the population and between the countries

-Exposure of the general population in Europe was well below the current health based guidance values. Very few participants had values which were higher than the health based guidance values.

-The biomarker levels in children were highly correlated with the levels in their mother, especially for mercury and cotinine, which may indicate a common environmental factor that influences the biomarker level.

-Younger children (5-8 yrs) had higher levels of mercury, cotinine and phthalates (except MEP) compared to older children (9-11 yrs). This emphasises the importance to give specific attention to the younger age group.

-Environmental and life style factors significantly influenced the biomarker levels: fish consumption was an important predictor for levels of mercury in hair from mothers and children; exposure to tobacco smoke was a predictor for urinary cotinine levels in mothers and children; exposure to tobacco smoke increased urinary cadmium levels in mothers, personal care products, use of PVC in floors/walls, ice cream, chewing gum influenced levels of different phthalate metabolites in urine.

-After adjustment for known modifying factors, social class (represented by the highest educational level of the family) had a significant influence on each of the biomarker levels. This influential factor may hide underlying determinants of exposure not yet discovered.

-Country specific aggregated data on chemicals in the environment and in food, made available through EU databases, or collected within countries were linked with the biomarker data. Despite limited statistical power due to lack of data several associations confirmed hypotheses between internal exposures and external sources. The country specific average exposure values for urinary cotinine in both mothers and children were significantly related to the smoking legislation of the country. Air emission data of cadmium at country level and calculated mean cadmium uptake through food were borderline significantly correlated with urinary cadmium concentrations in mothers. Total consumption of aquatic organisms, as reported by the DEMOCOPHES countries, was a significant predictor of mercury levels in hair in mothers and in children.

Conclusion

For the first time European exposure values could be calculated, however since not all European countries were included and since the study sample was not fully representative for each country, the values cannot be considered yet as 'European reference values'. Countries differed in their biomarker profiles and showed elevated levels for different biomarkers. The information reported by the participants on their environment and life style allowed to identify factors that influenced the biomarker levels and hence indicate the leverage for intervention. Data were often not available for all countries limiting the statistical power. It is expected that better geographical description of biomonitoring sampling sites could improve data linkage.

Work Package 5 '<u>Communication and dissemination</u>'

Key results:

D 5.1 COPHES II internal publication guidelines (month 2)

D 5.2 Communication strategy (month 5)

D 5.3 Communication plan and tools (month 12)

D 5.4 Web presence: both secure and open sites (month 1-36)

D 5.5 Leaflets and other promotion material for the project

D5.6 Communication material during the project (month 1-30)

D5.7 Delivery of a tested strategy for future European HBM studies (Month 30)

Communication Plan and tools (D5.1 and D5.3)

The Communication Plan addresses each stage of the project and includes dissemination activities. It includes guidance on communication campaigns and communication materials. The plan covers the three main stages of a biomonitoring project: the recruitment and sampling, sample collection and final dissemination of results. During the course of the project there have been many dissemination activities, using the flyers, posters and leaflets developed by COPHES and numerous oral presentations given by many members of the consortium. Publication guidelines were developed for the use of consortium members and members took every opportunity to present and promote the work of the group to Policy makers, the press, the public as well as scientific and other stakeholder audiences.

Web presence (D5.4)

The COPHES website http://www.eu-hbm.info was a central platform for dissemination of information and progress throughout the course of the project. The site is linked with its sister consortium DEMOCOPHES but care are has been taken with updates to the design of the website to ensure that the separate identity of each project is protected. The project website was developed and updated on a regular basis. This site includes pages for each aspect of the project as well as key links to meetings, conferences, and other web sites of relevance to human biomonitoring in general. The site has a 'standard' format which has been adopted for all communication material, this has enabled COPHES to have a brand-identity which is distinctive and will be sustainable.

The following have been included on the website:

-A Description of the Study, the services and tools provided

-Minutes and information on meetings

-Updates and news

-Frequently asked questions

-Chart showing the implementation of the tasks for the participating countries

-Legal information on funding

-Links to the national web pages of the beneficiaries

-Summaries on deliverables considering dissemination needs as well as confidentiality aspects

-Restricted access parts for internal study communication (extranet CIRCA)

-A discussion forum accessible for the public, the policy makers and the scientific community

Communication Material (D5.5 and D5.6)

Communication material was prepared for each stage of the project and tailored to the different audiences: participating mother and child; general public; local authorities (health, education); general medical practitioners, paediatricians; policy makers; scientific community; NGOs; the media.

Templates for invitation letters, a general information leaflet, an information leaflet for children, reply card, informed consent and assent form, and letter of thanks etc were all developed and can be used. Other materials which were developed include: Guidance

documents for Schools: How to Engage Participants, Detailed guidance on how to write a press statement, and A Template for a Newsletter.

Communication Strategy and delivery of a tested strategy for future European HBM studies (D5.2 and D5.7)

The strategy is a template for future projects but is not a user manual. It should be recognised that any communication strategy has to be a living document and will vary with the objectives and of course with new technological developments. There should be a concerted effort to increase public participation not only in the project but in the development of the communication material and its content. The same principles apply for the other stakeholders. To this end the tested strategy would put the 'Evaluation and Amendment' of communication at the start of any HBM project so that it is not lost in the implementation of project.

Interactive tools are useful to obtain feedback from the target audiences to evaluate methods of and material for communication. Public focus groups are a valuable means to check whether the material prepared is easily understood and to allow the project to evaluate the effectiveness of the material and strategies.

It should NOT be taken for granted that material produced for a European project is automatically European. Material should be adjusted to take into account social and cultural differences in each of the countries if the study is international. The recruitment rate can be significantly reduced if the material is not tailor made to the audience. The use of focus groups in each participating country is very valuable for a cross border project.

Work Package 6 '<u>Training and Capacity building</u>'

When the COPHES project started, no immediate application of the guidelines for HBM to be developed in the project was foreseen. The start of DEMOCOPHES a few months later made reviewing of the planning for the work package Training and Capacity Building necessary. Planning and progress of the DEMOCOPHES project had to be the driver for this WP 6's efforts.

As a first step training needs of project partners have been identified via an inventory amongst DEMOCOPHES participants during a COPHES/DEMOCOPHES working meeting in Brussels in February 2011.

Based on this inventory and other input, training and capacity building would address in this sequence: the many aspects field work, collection, computer assisted personal interviewing (CAPI), handling and quality control of data collected, statistical analysis by the participating countries, and interpretation of the results, communication and ethical aspects of HBM. Training for laboratory work was seen as more efficiently handled by the WP3, which was responsible for activities related with the analytical laboratory aspects.

Training and capacity building was organised in such a way that the appropriate audience for each discipline from each DEMOCOPHES country could participate. The plan uses training experiences from several COPHES members, and integrates approaches used by EHES.

The WP's responsible for the subject matter, in close collaboration with WP6, developed training modules as presented in deliverable 6.3.

Field workers are a key factor in the HBM process. They collect urine and hair samples which will be analyzed in the laboratories, but field workers also collect information using questionnaires which will enable the interpretation of the analytical results. These data allow for identification of risk groups and for the identification of routes of exposure. It is there of a key interest that field workers have good understanding of the HBM process and the key role the play for attaining the objectives of HBM. It is expected that field workers do not all have enough experience in the English language, therefore representatives of participating countries who will train the field workers have been invited for a two day training session. Subjects identified for training are: principles of HBM, ethical aspects of HBM, administration of questionnaires, personal interviewing, computer-assisted personal interviewing (when appropriate) and urine and hair sample collection and sample storage.

Two two-day workshops were organised for field workers, where two participants from each DEMOCOPHES country were attending.

Countries are responsible for the data collected for HBM through questionnaire administration and laboratory analysis. A standard database lay out was developed by WP4. Training on data collection, quality control of datasets and statistical analysis at a country level was given in two workshops, one in Brussels and later one in Copenhagen. These workshops also offered training in data interpretation, communication in a HBM program.

A help-desk based on the COPHES website has been defined and made operations since December 1. A procedure has been implemented in order to assure prompt response,

involvement of the expertise within COPHES in formulating a reply according to the state-of-the art and the monitoring of questions.

Significant results

-Inventory of training needs amongst DEMOCOPHES participating countries has been made.

-A detailed training program for key aspects of HBM has been developed (D6.3).

-HBM program members from the DEMOCOPHES countries have been trained using the training program. This was a key aspect for the successful conduct the DEMOCOPHES HBM program.

Work Package 7 'Horizon scanning and link to other research projects'

The work of WP7 focused on the organization of a number of workshops discussing latest scientific developments that could be integrated with HBM and close existing gaps and alleviate challenges for use of HBM surveys in environmental health policy.

Workshops on Non-invasive sampling techniques for human biomonitoring took place in Brussels in December 2010. On bisphenol A, triclosan, and parabens, a workshop was held in Brussels, November 1, 2011. Furthermore, an update workshop on 'Omics and metals' was held in Copenhagen, 12-14 March 2012. WP7 also assisted in the scientific organization of the workshop in Cyprus 22-25th October 2012: Human Biomonitoring (HBM) - linking environment to health and supporting policy. Presentations and summaries from the workshops have been uploaded on the website of COPHES.

Presentations and publications

WP7 participated in a number of meetings, workshops and conferences and a number of abstracts have been submitted. WP7 initiated the issuing of two handbooks with many contributions from COPHES partners on human biomonitoring in their countries or on specific substances to be used for national information and each partner received a copy.

Work Package 8 'Support for sustainable EU HBM programme (policy support) '

The HBM and policy team worked towards an improved use of HBM as tool in European and national environment and health policies. It collected information about priorities and needs and established a draft concept for a sustainable framework for HBM.

As the first task, an online exchange platform and discussion forum was established and connected to the project website as deliverable D 8.1. The discussion forum was redesigned and restructured several times, but despite of the efforts made, did not find acceptance within the two Consortia. One reason was the fact that the helpdesk function and a CIRCA interest group and repository were set up as additional communication and data storage tools so that there was a redundancy of competing fora and tools.

As a second tasks key needs and existing practice, expectations, benefits, operational issues and remaining questions related to the use of HBM as policy tool were collected via a questionnaire from competent authorities and other stakeholders. The results of this evaluation have been combined with a comprehensive evaluation of the latest scientific discussion in the field via a literature search and a compilation of major outcomes of the international conferences specifically organised on the topic in the EU throughout 2008 - 2010 (Paris, Parma, Brussels and Berlin) in D 8.2 to provide a comprehensive picture on the status quo and existing requirements and needs for the use of HBM as a policy tool.

In line with the work package objectives major efforts were put into discussions and information exchange with concerned experts from European and national institutions and with stakeholders from NGO and industry, to develop the concept for a future sustainable framework for HBM in Europe. Following the conclusions and recommendations of a first decision makers' workshop on the Use of Human Biomonitoring (HBM) for policy making that took place in Munich on 4 May 2011, two additional meetings with representatives of the European scientific community and the policy consulting committees and with Member States representatives as well as further policy makers (e.g. MEPs), were organised in the course of 2012.

Like the first meeting the European Authorities Scientific Expert Meeting on the Use of Human Biomonitoring as a policy tool in mid and long-term perspective, held in Brussels on 2 February 2012, focused on the potential role of HBM for policy making, its contributions to risk assessment, requirements for an increased role in the future, but it provided a more detailed description of the potential of HBM and a number of suggestions on how to link it to relevant policy areas and how to assign responsibilities.

The meeting resulted in clear recommendations for the development of the proposal for a sustainable HBM framework and the related infrastructural requirements, which was then presented to member State authorities at an international conference From HUMAN BIOMONITORING to European and national policies: meeting the MS representatives, which was organised in Paris at the Ministry of Health on 17 September 2012.

The programmes, abstracts and speakers' presentations are available for download on the project website at http://www.eu-hbm.info/cophes/project-work-packages/wp8-support-eu-hbm-programme . The achieved results are documented in D. 8.3 and in D 8.6.

All three meetings constituted a major basis for the elaboration of the draft concept for a sustainable HBM framework which is (as envisaged) the key outcome of the project work.

The proposed concept aims at integrating HBM in public health or environment and health surveillance, comparable to the approaches followed e.g. in the USA and Canada.

The core pillars of the framework are:

1.An EU HBM suggestion and coordination platform for guidance and decision making

2.A selection procedure for the identification and prioritisation of substances and method development linked to existing EU law and upcoming threats

3.An HBM implementation and enforcement network embedded in Member States.

The platform shall enable information exchange and decision making between competent authorities of the European Union, stakeholders and scientists, in particular as regards prioritisation of substances and biomarker development, survey design and communication issues. The enforcement network should have mutual exchange and close links to an EU guidance unit for protocol development, quality assurance, data management, data interpretation, communication and translation into policy. Clear organisation from the national to the local level, as well as systematic involvement of the national contact person (NFP) in the EU expert network is crucial.

In addition the WP8 team focused on the elaboration of a vision paper on the future use of HBM that put a focus on the research needs and research priorities to arrive at a sustainable framework on the long-term view, and prepared a number of discussion papers related to the potential of HBM in the most relevant areas of environmental and public health policy

such as REACH, the 7th Environment Action Programme, consumer protection policies, or the public health programme 'health for growth'. Further aspects of the work performed in WP8 comprise bilateral contacts and information exchange with Member States and Commission services, participation in public consultations related to the drafting of the 7th Environmental Action Plan, and collaboration with other research projects (e.g. EHES, ERA ENVHEALTH). With the latter aspect WP8 was responding to the recommendation contained to the midterm review.

To support the idea of a harmonised HBM approach within Europe, presentations of the work package objectives and outputs were made at various occasions throughout the project running time as reported in more detail in the COPHES overall list of Dissemination activities and Publications.

Conclusions:

The evaluation of the survey and the scientific discussion enabled a broad and substantial picture on the existing situation of HBM in Europe on one side, and on current obstacles, and requirements for an improved use of HBM as tool for policy making and policy tracing on the other side. The benefit for both, the environmental policy and the public health policy side was re-assured, and the need for a European approach and framework to support Member State activities and to use synergies and reduce efforts and expenses was clearly affirmed.

DEMOCOPHES countries consider it time to intensify collaboration at European and international level and to set up the necessary means for harmonization of practices to optimize the investments made and to increase efficiency.

The major advantages of a European platform are the following:

i) allow overview on all activities that take place and on all interest and proposals (across policies and stakeholders) on the floor,

ii) prevent duplication of efforts and repetition of similar developments and processes,

iii) identification of common opinions/ranking,

iv) sharing developments.

The proposal for a concept for a sustainable HBM framework in Europe has been discussed with interest in the EU and Member States, and first steps have been taken in terms of data sharing and regular information exchange.

Potential Impact:

Action 3 of the EU Action Plan 2004-2010 asked for a more consistent approach to HBM in Europe. It anticipated a step by step approach to test the feasibility of such an endeavour. COPHES, together with DEMOCOPHES, has now developed a functional framework contributing to the definition, organisation and management of a coherent approach towards HBM in Europe, with harmonisation of activities at national level to improve HBM data comparability across the EU. COPHES elaborated a protocol for a pilot study to test out the feasibility of the approach for all aspects of HBM including toxicological analysis, risk communication and strategies to analyse data and interpretation of results, and DEMOCOPHES implemented it. The combined COPHES/DEMOCOPHES effort convincingly showed that comparable results could be obtained in 17 European countries (UK, SK, SE, RO, PT, PL, LU, DE, CZ, CH, HU, BE, CY, IE, SI, DK, ES), all implementing the same study protocol. Some adaptations were made to adapt the protocol to the national situation, without compromising the comparability of results. Therefore a European approach to human biomonitoring is now considered feasible. This result paves the way for further steps e.g. search for combining efforts between the health surveys and HBM surveys at EU level.

To allow a HBM campaign to having an adequate societal impact and influencing preventive actions at individual and collective level, a good communication strategy is essential. Efforts were set up and are still ongoing at EU level and at national level to broadly communicate the results of the pilot study to all stakeholders. At individual level all study subjects could receive their personal results. For work at national level we refer to the DEMOCOPHES reporting. A final COPHES/DEMOCOPHES conference was held in Cyprus under the theme 'HBM: linking environment to health and supporting policy' where results available so far were discussed (see further under dissemination). A press release was issued and all abstracts were made available in a booklet

The primary aim of the Pilot Study was to test the feasibility of an EU-HBM approach, generating comparable data. Financial means were restricted, and the number of samples was therefore limited. The number of samples obtained in the DEMOCOPHES study is too small to be representative and the data obtained do not fulfil the scientific criteria for a "reference" base. However, the sample is considered to be sufficiently large to allow (minimal) statistical evaluations with preliminary reference values for the groups chosen. Their value has already been shown by the use of the DEMOCOPHES mercury data in a recent publication - anticipating the upcoming UNEP discussions on measures to reduce exposure- on the economic calculation of the cost of the actual exposure of Europeans to this widespread heavy metal.

COPHES also supported activities within WHO Europe to generate comparable HBM data on exposure. The Parma Declaration on Environment and Health, adopted at the 5th Ministerial Conference on Environment and Health in 2010, calls for the intensification of actions by the Member States of the WHO European Region to protect children's health from environmental hazards, such as harmful chemicals including carcinogens, mutagens, reproductive toxicants and endocrine disruptors. HBM-based indicators such as blood lead level in children and dioxins in human milk have already been implemented in WHO's European Environment and Health Information System (ENHIS). In close collaboration with COPHES, WHO has developed a draft standardized protocol and methodology for a survey in hospital maternities to assess prenatal exposure to mercury using total mercury in maternal hair as a non-invasive biomarker of in-utero exposure. Other biomarkers of exposure to priority pollutants would be included at a later stage to use synergies in fieldwork and characterize exposure to several additional pollutants.

For a sustainable system further steps are needed at European level, allowing adequate decision making and guaranteeing an adequate budget. This requires a political will at Member State as well as at European Commission level. When preparing the pilot study, political support was received at several levels through a long process of negotiations. For the future new strategies are needed and at the moment some initiatives are ongoing. Several European countries are willing to explore the potential of a common use of Human Biomonitoring data produced at regional, national as well as transnational level for supporting and evaluating policy. They discussed this topic at a Member States representatives meeting in Paris on September 17th 2012 and at the final COPHES/DEMOCOPHES Conference organised within the context of the Cypriot Presidency of the Council of the European Union, which took place the 23-24th of October 2012 in Larnaca. Member States highlighted the need for a European platform where the Member States and/or experts designated by the Member States would meet with the concerned departments of the Commission and discuss priorities and emerging problems so to ensure better harmonization of practices and comparability of results.

Finally it is to be noted that the pilot study biological samples are stored for a period of minimum 10 years according to the DEMOCOPHES contract, so that further use is possible under conditions yet to be defined.

Socio-economic impacts and wider societal implications

COPHES was a scientific project destined to generate the contextual framework (protocol), quality assurance system and support function for the feasibility study (DEMOCOPHES), wherein the samples were taken. Hence COPHES did not undergo an Ethic Review, but ethical aspects were considered and advice and background documents for the application of ethical approvals were provided in the harmonise protocol. Similarly the project did not involve study participants or human data collection and sampling but provided the study design for sampling of urine and hair, as well as data collection from children and their mothers, therefore requesting DEMOCOPHS countries to collect prior informed written consent. Mothers served as indicators of the exposure of foetuses and infants, in particular for the youngest children, and thus represent a population group in which prevention may be very efficient. The analyses of mothers coming from the same household as the children might also lead to additional insights in exposure sources and pathways.

COPHES comprised processing of data from study participants in its work package four. The processing however was restricted to coded data whereas the primary data allowing for tracking of information was exclusively kept in DEMOCOPHES.

COPHES involved work with students and pupils in terms of invitation to project workshops organised by WP7 and model information material for participating school pupils elaborated by WP5 for DEMOCOPHES. The project website, leaflets, posters and roll-ups were used for dissemination of project information to the scientific community and to policy as described in the chapter related to WP5. In terms of communication to the general public COPHES worked closely with DEMOCOPHES via the website, joined press releases, media, briefing, press articles, flyers and leaflets in English language.

A major European NGO and the key concerned industry association were project partners to ensure direct involvement and close contact with the civil society from the project start. The NGO was not a direct professional in communication and media relation but could contribute with considerable experience in media relations and communication to the public.

Policy makers were addressed and involved during conferences and project workshops, as described in the chapter on WP8. Via the joint protocol and the expert network established and trained, COPHES generated outputs which can be (and partly already are) used by policy makers on local, regional, national, European and international level.

The research in COPHES was largely performed by experienced researchers, with a huge predominance of female experts. This also applies for the work package lead with was female in seven out of 10 cases. The scientific coordination was performed by a male-female duo team. The number of students involved was limited. 21 additional researchers could be financed by means of the project.

Main dissemination activities and exploitation of results

Main dissemination activities throughout the project running time were presentations at conferences. COPHES has organized and co-organized a number of meetings and workshops, participated in workshops, conferences and congresses and submitted in total 230 abstracts and has given 215 oral presentations and 15 posters. COPHES has published in peer reviewed publications and books and will continue these efforts to make sure the results are scientifically disseminated. By the end of the project running time, four articles related to project objectives and HBM related aspects were already published. The majority of publications evaluating project results is expected to be accomplished in the coming month, after the national results related to DEMOCOPHES have been published. As a general rule it is foreseen to have at least one thematic publication related to the results of each work package.

Patent applications have not been made and trademark, registered design or other IPRs were not applied. Being concept oriented science; the project does not have a direct impact on employment. It however, might contribute to creation of new jobs or employment if the recommendations made will be taken on board.

List of Websites:

http://www.eu-hbm.info