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Harmonized European human biomonitoring in small countries: Challenges, opportunities and lessons learned in Cyprus and Luxembourg from the DEMOCOPHES study

Abstract: Background: To advance human biomonitoring (HBM) for policy support in Europe, a harmonized approach was developed (COPHES project, FP7 2009-2012) and evaluated in 17 countries (DEMOCOPHES project, Life+, 2010-2012). Cyprus (CY) and Luxembourg (LU) tested the hypothesis that the COPHES European Protocol is applicable to small countries. Materials and methods: In 2011-12, the European Protocol was adopted and tested by CY and LU for the harmonized biomonitoring of 60 children and their mothers for cadmium, phthalates and cotinine in urine and for mercury in scalp hair in two sampling areas (urban, rural). Results: Both small countries achieved the preset goals for recruitment, sample collection and analysis, which allowed for the first time the assessment of children's and mothers' exposures to the selected chemicals in comparison with other countries. Capacity building was accomplished and communication actions were particularly effective, with both countries taking advantage of their small size to access participants, policy makers, other stakeholders and the press. Time constrains and requirements for capacity building were limiting factors. Conclusion: The COPHES European Protocol for HBM surveys is attainable in small countries. The following elements are fundamental in the design of a harmonized European HBM program, from the perspective of small countries: (a) consultation with and active involvement of the implementing countries, (b) flexibility for national decisions, while not compromising harmonization, (c) elaboration of standardized methods, procedures and documents (d) quality assurance mechanisms, (e) means of training and support.

Keywords: Human biomonitoring, harmonization, environmental health policy, small populations, small countries, DEMOCOPHES, COPHES, lessons learned

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1 Introduction

The exposure of humans to harmful chemicals has been the subject of regulatory and public concern, since many diseases are linked to environmental exposures. For example, tobacco smoke is a known human carcinogen [1]; several phthalates are plausibly endocrine disruptors, affecting reproduction [2,3]; lead and mercury impair neurological development [4]. Traditionally, efforts to control public exposure to environmental stressors focused on regulating the levels of harmful chemicals in different sources such as the food chain, the environment and consumer products. Advancements in analytical chemistry have enabled measurements of low levels of toxic chemicals or their metabolites in human specimens [5]. This methodology, known as human biomonitoring (HBM), can provide the "body burden" i.e. the total amount of a certain pollutant in the human body at a given point in time, since it integrates the exposure to the pollutant from all sources and can be valuable for the validation of public health policies (for example see [6]).

Many countries have no experience or limited experience in HBM surveys (ex. Austria [7]), whereas some countries or regions have mandated HBM surveys (ex. USA [8]; Canada [9,10]; Germany [11,12]; Flanders in Belgium [13]). Variations in the focus and design of the different HBM surveys, however, prevent comparisons of the results and restrict the use of biomonitoring data for policy support. Other difficulties include knowledge gaps on the implications of biomonitoring data for human health and challenges related to communication, ethical issues and quality assurance of the chemical measurements. All these aspects may even be more relevant in small countries, where relevant resources and experiences may be limited.

In this frame, the European Commission announced in the European Action Plan on Environment and Health 2004-2014 an action for the development of "a coherent approach to biomonitoring in Europe" [14]. The culmination of the efforts that followed was the implementation of two complementary European projects, designed to test the hypothesis that a framework for harmonized European HBM can be developed and implemented in the diverse European countries: COPHES ("Coordination to Perform Human Biomonitoring on a European Scale", FP7, 2009-2012) aimed to reach a consensus on the most feasible and evidence-based approach to perform standardized HBM in Europe, by bringing together experts and representatives from 27 European countries; DEMOCOPHES ("Demonstration of a study to Coordinate and Perform Human biomonitoring on a European Scale", LIFE+, 2010-2012) aimed to demonstrate the feasibility of this approach across Europe, in a pilot survey carried out simultaneously in 17 countries (Belgium, Cyprus, Czech Republic, Denmark, Germany, Hungary, Ireland, Luxembourg, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland and United Kingdom). The participating countries varied enormously in size. With regards to population, the largest country (Germany, population ca. 80.5 million) is 150 times bigger than the smallest country (Luxembourg, LU, population ca. 0.5 million); with regards to area, the largest country (Spain, area ca. 504 thousand km^2) is 195 times bigger than the smallest country (LU, area ca. 2.6 thousand km^2). The second smallest participating country (with respect to both population and area) was Cyprus (CY).

A prerequisite for the elaboration of a successful European HBM survey is that it must be attainable in all Member States (MS), including the smallest ones. At the onset of the COPHES and DEMOCOPHES projects, very limited data were available on the feasibility and applicability of HBM surveys in small countries, where specific constraints may hamper the successful implementation. LU and CY tested the hypothesis that small countries can attain harmonized European HBM surveys at national level through: (a) their active involvement in the elaboration by COPHES of a harmonized "European Protocol" for HBM and (b) the application of this European Protocol, in the frame of DEMOCOPHES, for a pilot harmonized European HBM study.

This paper presents the challenges, successes and lessons learned in CY and LU during the testing of the COPHES European Protocol for the DEMOCOPHES pilot harmonized European HBM survey in 2011-2012. The overall results show that the European Protocol is feasible in small countries. In an attempt to provide a useful roadmap for future studies, the paper employs a holistic, systematic approach of discussing every element of the European Protocol and summarizing the most important lessons learned.

2 Methods and Results

The different tasks related to the design and implementation of the pilot European HBM survey and the relevant lessons learned are described below and are summarized in Table 1.

Table 1. Summary of the lessons learned in the small countries Cyprus and Luxembourg from the first harmonized European human biomonitoring survey.

Tasks	Subtasks	Lessons Learned
Study design & preparation of the National Protocol in harmonization with the European Protocol	Definition of study population, recruitment strategy, national methods and related QC aspects for sampling / storage and national communication plan. Preparation of questionnaires (translations, cultural adaptations, specific questions) and a handbook for national implementation of the study. Elaboration of a national quality assurance program to ensure EU comparability of the results, prerequisites for outsourcing chemical analyses, if applicable. Elaboration of a statistical analysis plan and guidelines for country specific analysis of HBM data (source identification/relevant exposures) and of a scenario for translation of HBM data and interpretation into policy advice. Formatting of the national database, to ensure compatibility with EU database. Quality-control (QC) checks to ensure harmonization of the National Protocol with the consensus European Protocol.	Committed European Commission support is important for harmonized European HBM surveys. Continuous, active collaboration of all participating countries is necessary for the realization of a feasible, harmonized approach and quality checks ensuring harmonization must be enforced. Harmonization requirements must be clearly defined from the beginning and must be attainable by all participating countries. National decisions, which do not compromise harmonization, should be possible for effective and efficient implementation and for addressing national priorities. Standardized procedures and documents, for all aspects of the study, are necessary. Minimum performance requirements for laboratory methods must be defined in the study protocol. Mechanisms of external performance assessment are essential. It is necessary to predefine agreed rules and regulations related to property rights and cross-border sharing of personal data. As time constrains and requirements for capacity building can be limiting factors, providing opportunities for training and support and sufficient time for implementation are important considerations.
Instruments for national implementation	Designation of a National Management Unit for harmonized national implementation and for coordination at EU level. Designation of a Survey Office, if different from the National Management Unit.	Linking to state institutions may facilitate prospective use of data for policy support and in connection to this, can assist the process of attaining political support for the study. For efficiency, it is important to build on existing infrastructure and to plan for sustainability. By design, small countries may be privileged in coordination actions, in promptly identifying, diagnosing and remedying problems and in accessing policy makers.
Approvals & other necessary preparations	Submission of the study proposal to the national ethics committee(s). Notification of the privacy authority. Organization of adequate insurance, if required by national law. Approvals for recruiting in schools, if applicable.	Obtaining all necessary approvals may be time- and labour- consuming, depending on national requirements and processes. Availability of centrally developed standardized documents, which can be adapted for national use, is valuable.
Sampling, recruitment & sample collection	Information and training of field workers. Sending of collectors to the persons in charge of sampling. Recruit participants according to defined criteria. Collect specimen samples and questionnaire data and send the specimen samples to the designed laboratories according to predefined method (with sample encoding for anonymity). Upload the questionnaire data in the national and European database and cleaning of the databases, according to defined QC steps.	Care must be exercised to avoid preanalytical contaminations (through appropriate and properly prepared sampling vessels, proper sampling and sample storage until transfer to the laboratories). Addressing the participants needs and requirements (timing, placing of meetings, addressing concerns Proper training of fieldworkers is essential. The availability of a "CAPI" (computer assisted personal interviewing) interface is very useful for the collection of questionnaire data and for data uploading in the associated database, but the high associated cost may be a limiting factor for its use.

continued **Table 1.** Summary of the lessons learned in the small countries Cyprus and Luxembourg from the first harmonized European human biomonitoring survey.

Tasks	Subtasks	Lessons Learned
National sample handling, chemical analysis and long-term sample storage	Method adaptations and participation in external quality assessment schemes. Sample analyses according to quality assurance requirements and uploading of results in national database and EU database, for each of the assessed biomarkers. Implementation of storage policy, including possibility of biobanking.	Multi-centre, quality-assured chemical analysis is feasible, but cost amortization requires the analysis of a large number of samples. It is possible to build capacity at national level, which may be exploited for additional investigations according to national priorities. The cost, ethical constrains and preanalytical requirements associated with the long-term storage of specimens in biobanks and potential associations with existing biobanks must be considered in the study design. The financial and capacity limitations related to biobanking, may be hindering factors in small countries. Cost-effective options for (cross-border) outsourcing of some analyses may be useful, provided they confirm to preset requirements of quality assurance, ethics and personal data protection.
National data analysis and integrated interpretation	Statistical analysis of data at national level. Statistical analysis of data at EU level in association with EU experts. Interpretation of the results at national and European level and preparation of reports, including recommendations for policy.	Harmonized statistical analysis and interpretation at national level, in addition to central EU analysis of the data, is essential for best possible exploitation of the results for policy support. Centrally prepared codebooks, guidelines and training for statistical analysis and interpretation at national level are important.
Communication and dissemination at national level	Communication to participants at recruitment (communication materials, etc). Communication of general information throughout the project to participants, stakeholders and general public on website or in other places. Communication of the individual results and recommendations to the participants, if they so wish. Communication of the aggregated results and recommendations to policy makers at national level.	A holistic, transparent communication strategy is important for stakeholder acceptance and best possible exploitation of the results. Small countries can be especially effective and successful in communication actions, such as: involving policy makers, authorities and community representatives; establishing more direct and personal contact with the study population and actual participants; achieving publicity. Communication with participants must be well planed, focused and respectful. Personal results must be put into context, with opportunities for questions and private consultation, for those who choose to receive them. It is beneficial to seek wide publicity, by involving high level officials and getting TV / Radio / Press / Internet coverage. This publicity can be very beneficial right before the recruitment stage and after the completion of the study.

2.1 Study design and objectives

2.1.1 Challenges and Opportunities

The COPHES and DEMOCOPHES projects presented two small countries, CY and LU, with the opportunity to become involved in the design and implementation of the first harmonized European HBM survey and facilitated the first ever comparisons of exposures of mothers and children from different European countries to selected chemicals: cotinine, cadmium and selected phthalate metabolites in urine [15-17] and mercury in scalp hair [15,18]. On an optional basis, LU additionally assessed bisphenol A (BPA) [19], parabens and triclosan in urine.

2.1.2 Implementation

A "European Protocol" for a harmonized European HBM pilot survey was developed in the COPHES project, through

a close collaboration of experts with MS representatives, by taking into consideration the wide variability of European countries with regards to prior experience, existing infrastructures and capabilities. The European Protocol described the survey's objectives, which were defined based on the available budget, time constrains and factors such as health-based prioritization, known exposures in susceptible populations, bioaccumulation potential, analytical capabilities and ability to collect and analyze relevant matrices. On these grounds, the pilot survey investigated a limited number of biomarkers in non-invasive matrices from a small number of participants per country, coming from two populations of interest (children of elementary school age and women of reproductive age). On an optional basis, countries could include additional biomarkers (bisphenol A, parabens, triclosan) under the condition that this will not interfere on any level with the harmonized biomarkers. The European Protocol also provided standardized procedures for all aspects of the work (for details see [20-26]).

CY and LU tested the European Protocol simultaneously with 15 other larger countries in the DEMOCOPHES project, co-financed by all participating countries and the European Commission. Each country adopted the European Protocol for national use. The National Protocols were approved by COPHES to ensure that cross-border harmonization was not compromised. The National Protocols provided detailed specifications and procedures for the implementation of the harmonized survey in the country: a communication plan and associated communication materials [24]; standardized procedures for sampling and interview conduct [22]; laboratory and method requirements [23,26]; a statistical analysis plan [15]. All communication materials were translated in the national languages (for CY: Greek; for LU: German and French. Luxembourgish was not obligatory or demanded). Questionnaires were locally validated prior to use (tested for understanding, perception and effectiveness). With regards to their communication strategies, both CY and LU took advantage of the short communication lines, which are typical of small countries, to access and involve policy makers, potential participants, the mass media and other stakeholders.

2.1.3 Lessons Learned

The availability of European Commission funding for this study was very important for both CY and LU, since a common limitation faced by entities trying to engage in such initiatives in small countries, is the lack of committed national funds. Consultation with MS was necessary during the development of the European Protocol to ensure its applicability across Europe. The thoroughness of this protocol and a mechanism of support and supervision were necessary tools to ensure successful implementation. It was important to define the protocol's critical components, which cannot be changed, and allow flexibility in non-critical components for the best possible national implementation. The short communication lines typical of small countries can and should be exploited, such as in obtaining stakeholder acceptance, which is a critical consideration for studies involving human subjects, such as HBM. An example of this was demonstrated in LU, where after a press conference by the Minister of Health, there was increased interest of the general public to participate.

2.2 Instruments for Implementation

2.2.1 Challenges and Opportunities

A National Management Unit (NMU) had to be established for (a) coordination and information exchange with the Central Management Unit at EU-level, (b) the elaboration of the National Protocol and (c) the management of a national consortium for the implementation of the pilot study at national level. This challenge created opportunities for capacity building.

2.2.2 Implementation

In LU the national consortium was unique, since it encapsulated a public research centre (Centre de Recherche Public (CRP) – Gabriel Lippmann, (since 1.1.2015 Luxembourg Institute of Science and Technology, LIST) serving as NMU for the pilot study), a public organisation (Laboratoire National de Santé (LNS)) and a Non-Governmental Organization (Initiativ Lievensufank).

In CY, the national consortium involved two departments of the Ministry of Health, the State General Laboratory (SGL) and the Medical Services and Public Health Services (Larnaca Hospital). Participation in DEMOCOPHES provided the opportunity for the establishment of a new, sustainable infrastructure for HBM actions in the country, through the formation of a HBM Laboratory at the SGL. The HBM laboratory served as the NMU, with the overall responsibility for the coordination of the work of an interdisciplinary team of civil servants and hired personnel, consisting of chemists, medical doctors, trained fieldworkers and a statistician.

Larnaca Hospital served as the Survey Office.

The implementing units in both countries are recognized authorities in public health, with significant research history in the field of environmental health, background in HBM the years preceding the COPHES/DEMOCOPHES projects [27-32] and extensive experience in methods validation and quality assurance. Furthermore, their association to the Ministry of Health of their respective country proved to be a valuable asset, particularly with regards to policy implications and communication actions.

2.2.3 Lessons Learned

Since HBM surveys are multidisciplinary, costly and challenging, the need for efficient use of resources, building on existing experience and infrastructure and planning for sustainability is essential for small countries. It is also important to use their small size to their benefit, where possible. Since the study may convey important policy implications, it should be linked to state institutions, but at the same time it must be transparent and open to stakeholder involvement to gain acceptance. The involvement in the study of institutions and individuals widely respected in the community is important for its acceptance.

2.3 Approvals and other necessary preparations

2.3.1 Challenges and Opportunities

As HBM involves human subjects, the study protocol must receive ethical approval and Privacy Authorities must be informed about the type of data collected. Participants may need to be insured. The overall timing is strongly dependent on meeting dates of responsible authorities.

2.3.2 Implementation

In CY, the Privacy Authority was notified and the National Protocol was approved by Cyprus National Bioethics Committee. The Bioethics committee required the appointment of a professional in the same field of research as the study, permanently based in Cyprus, but not affiliated to the research team nor involved in the study, to receive complaints and other concerns on behalf of the participants. This role was fulfilled by a well-respected, senior state physician, involved with the administration of a Department of Pediatrics. All forms and documents directed to study participants had to be submitted in Greek, along with the approval of the Ministry of Education for recruitment in schools. Written consent of mothers and the assent of children were necessary. Since the study did not involve invasive sampling, it was not necessary to obtain insurance for the participants.

In LU, the National protocol was approved by the National Research Ethics Committee (CNER). All the documents for participants had to be submitted in both German and French for approval, while the scientific documentation could be submitted in English. Following the submission of all relevant documents, the overall approach was presented in person by an involved senior scientist to the CNER during their meeting. The Commission Nationale pour la Protection des Données (CNPD) was informed about the type of data collected in order to comply with the relevant national regulations. Written consent of participating mothers was necessary. Even though the study did not involve invasive sampling, it was necessary to obtain insurance for the participants as this is a legal requirement in LU.

2.3.3 Lessons Learned

Completing these preparations, which are critical to the integrity of the study, may take time. This applies to all countries, not just the small countries ones. Smaller countries may have an advantage over larger countries due to their simpler organization and the shorter communication lines typically in place. For example, ethical approval in CY and LU is granted by a single National Ethics Committee, whereas in larger countries, ethics approval may be required at several levels (entity / regional / national). For maximum efficiency, it is valuable to have relative standardized documents available in the European protocol to assist the process.

2.4 Sample populations and sampling areas

2.4.1 Challenges and Opportunities

To ensure harmonization with the European Protocol, the pre-defined criteria for the sampling areas and sample populations had to be carefully maintained. The target populations were children (6-11 years of age, equally distributed by sex and age) and their mothers (up to 45 years of age). Additional inclusion criteria included a minimum of 5 years residence in the sampling region and fluent use of the national language (for LU: Luxembourgish or German or French; for CY: Greek). Exclusion criteria

included a different main residence for mother and child, any major co-morbidities or residence beyond the designated sampling area of interest [22]. CY and LU had to recruit a total of 60 mother-child pairs, which was half than the relevant goal set for the other 15 larger countries implementing DEMOCOPHES. Participants had to be randomly selected, but under the preconditions of the study, it was not possible to select participants on a strictly representative basis in each participating country.

In each country, the mother-child pairs had to be equally distributed in two independent sampling areas, one urban and one rural, representing the two extremes of degree of urbanization.

2.4.2 Implementation

Participants were successfully selected according to the criteria defined in the European Protocol.

In CY, both the size and the population density of a community served as criteria of the degree of urbanization and input from the Statistical Service of the Republic of Cyprus proved valuable. The urban area was the capital city of Nicosia and the rural area was the village of Frenaros. In LU the capital Luxembourg Ville and two smaller suburban cities (Bettembourg, Schifflange) in close vicinity to Luxembourg were defined as cities while the rural area was north of Luxembourg Ville in the area within Luxembourg dominated by agricultural landscape.

2.4.3 Lessons Learned

The two urbanization extremes of the small countries deviated considerably from the biggest EU countries. Such differences across European countries need to be kept in mind, as they may have an effect on data interpretation. Clearly defined criteria for participation and areas of sampling are very important. For pan-European studies, these definitions must be harmonized and study objectives must be applicable to all countries.

2.5 Recruitment

2.5.1 Challenges and Opportunities

The study design called for random selection from a pre-defined population, which is a pre-requisite for extrapolation of the results to a wider population. Since participation was voluntary (self-selected population), it was important to avoid a high-degree of non-participation. The fact that the target population included children of primary education level and that primary education is mandatory in Europe, created an opportunity to recruit in schools. Alternatively, population registries could be used. All communication materials needed to be available in the local language(s).

2.5.2 Implementation

Population registries were inapplicable in CY and LU at the time of DEMOCOPHES. Both countries chose to recruit participants through schools. In CY, it was necessary to receive permission from the Ministry of Education to access participants through schools. A total of 2 primary schools (one in the urban sampling area and one in the rural) were used. CY had one of the highest participation rates among the 17 countries (Table 2). In LU schools in participating municipalities were approached via the local environmental counselor. Schools that decided to participate were free to either send a letter to the parents via post or hand the letters to the pupils.

Both countries successfully recruited and sampled the preset goal of 60 mother-child pairs, with 100% completion rate, in terms of both questionnaire replies and sample suitability for further analysis. With regard to response rate, results are presented in concise form

Table 2. Recruitment response rate for each of the 2 smallest DEMOCOPHES countries

VARIABLE	CYPRUS	LUXEMBOURG
Number of schools contacted	2	3
Number of invitation letters distributed in total	497	1253
Number of reply cards received in total	462	84
Number of positive replies	212	84
Percentage of positive reply cards out of all invitation letters spread	42.7	6.7
Number of positive replies that were indeed eligible to enter the study (based on inclusion / exclusion criteria)	103	84
Number of final participants	60	60

in Table 2. Once a family was contacted via the school registry, a reply card was provided for positive or negative feedback (with regard to study participation) while there was also an option to contact the researchers for further details. If a positive card was received, the researchers would then use a "responders' questionnaire" to confirm eligibility and, if so, include the family in a candidate participant list. A "non-responders questionnaire" was used to assess potential selection bias [22].

In the case of CY, due to excessive offers of eligible families for participation, random number selection was subsequently used to shortlist the 60 final participants. The experience from LU indicates that sending invitation letters via regular post results in higher participation than handing the letters to the pupils. Schools using postal service had a positive feedback between 4.8 to 5.3% while the latter resulted only in 1.8% of positive answers. Although representativeness was not a concern in DEMOCOPHES, the collected 120 samples would correspond to a sample size of about 2.3/10,000 inhabitants for LU and 1.4/10,000 inhabitants for CY (the part of the country under the effective control of the government) (Table 2).

With regard to resources used, LU used 4 and CY 2 field workers, thus making the ratio of volunteers (families) to fieldworkers particularly manageable (1:15 for LU and 1:30 for CY). The total available budget for DEMOCOPHES implementation (coordination, organization, recruitment, sampling, analysis and dissemination) was similar for both countries.

2.5.3 Lessons Learned

It is important to allow for flexibility and national decisions for best practice, as long as comparability of results is not compromised. Showing consideration for people's concerns and time is important. School-based recruitment is an attractive option for studies involving school-age children and carries added benefits, such as higher participation rate, involvement of teachers and school principals, inclusion of HBM in the health promotion curriculum already applied by schools and non-biased target population coverage [25].

2.6 Fieldwork, Sampling and Biobanking

2.6.1 Challenges and Opportunities

Biological material and relevant personal information had to be collected with the fieldwork, using standardized procedures for proper communication, interviewing and sampling under tight deadlines. Since pre-analytical imprecision (improper sample collection, transportation and / or storage) can cause serious bias [2,33,34], standardized procedures had to be followed to ensure proper sampling and sample handling prior to analysis [23,26]. Biobanking of collected urine for a total of 10 years was required by the study design, to enable the investigation of additional biomarkers in the future.

2.6.2 Implementation

The fieldwork took place between October and December 2011 in all DEMOCOPHES countries. Four "specimen sampling questionnaires" (urine questionnaire for each of the child / mother and hair questionnaire for each of the child / mother) were used for quality assured sampling of morning urine samples and scalp hair samples from participating mothers and children. Relevant individual data had to be collected through a "basic questionnaire" answered by the mothers on behalf of themselves and their child. The questionnaire addressed potential exposure pathways, the participants' environment, nutritional habits, smoking behavior, occupation and related socio-economic characteristics. All study questionnaires were developed by the Federal Environment Agency (Germany) within the frame of COPHES and were adopted for national use in each implementing country [22,25].

Within the frame of COPHES, a computer assisted personal interviewing ("CAPI") system ("SOCRATOS") was developed by VITO (Belgium) specifically for the DEMOCOPHES pilot HBM survey and was made available to all participating countries. Access to SOCRATOS required internet connection.

In CY, the fieldwork was carried out by two trained fieldworkers, one in each sampling area, during home visits arranged according to participants' preferences. The study questionnaires were completed using "Pen and paper", because it was not possible to ensure internet access during all home visits. The responses were subsequently uploaded on SOCRATOS, which allowed (a) easy creation of the questionnaire database, (b) cleaning of the data and (c) uploading the data to SPSS or Excel for the subsequent statistical analysis. No incentives were given. The fieldworkers were in close contact and cooperation with the chemists of the SGL to ensure proper sample collection, handling and timely delivery to the lab. Particular attention was given to proper pre-sampling procedures and sample handling and storage

until analysis, in line with the European Protocol, to ensure sample integrity. Difficulties were encountered with relation to the identification and purchase of suitable containers, which had to be ordered from abroad. Aliquots of urine samples are stored, with the consent of participants, at the SGL for future use.

In LU, the fieldwork was carried out by four trained fieldworkers, one in each sampling area during home visits arranged according to participants' preferences. The national stakeholders had the feeling that the use of a CAPI would be considered as impolite by the interviewees due to lack of eye-contact and therefore the interviewers used pen-and-paper, with subsequent uploading on SOCRATOS. No incentives were given. The fieldworkers were in close contact and cooperation with LIST and LNS to ensure proper sample collection, handling and timely delivery to the lab. Particular attention was given to proper pre-sampling procedures and sample handling and storage until analysis, to ensure sample integrity. Aliquots of urine samples are stored at the LIST, with the consent of participants, for future use.

2.6.3 Lessons Learned

Small countries have the advantage of easier coordination of fieldwork and timely delivery of the sample to the survey office on a personal basis. The availability of a fieldworker manual and proper training of fieldworkers are important. Training should provide the study background, objectives, design, communication and how to perform effective interviews, how to perform home visits and proper sampling. Mock interviews and sampling on volunteers prior to first project appointments are critical. Accommodation of participant's schedule and respect for their time, wearing professional gear (IDs, Sample bag with project identifying logos) are important. Generally, the lower throughput of surveys in small countries, in combination with the high cost associated with engaging in CAPI, typically paves the way for the use of pen and paper. Both CY and LU used a combination of "pen and paper" and "CAPI" for their fieldwork. This hybrid process was beneficial, but time-consuming. From the perspective of small countries, a centrally developed CAPI, which would be made available to implementing countries, could greatly assist the fieldwork in future European surveys. Efforts to eliminating pre-analytical bias should in addition to the training of fieldworkers for proper sampling, include guidelines and assistance related to avoiding potential external contamination. This assistance could be provided by a reference laboratory or a technical working group of experienced laboratories. For future surveys, it may be considered to purchase and prepare sampling vessels centrally and distribute them to the national survey centres.

Banking of specimens must follow national ethical requirements, which may involve verification of consent of participants for any future use. Proper conditions for biobanking are important to define in the study protocol and potential association with other existing national biobanks may be considered. The cost of long-term storage of specimens at the appropriate temperature needs to be considered. Future use of specimens must consider the possibility of variations in the analytes of interest due to prolonged storage or thawing.

2.7 Analytical Measurements

2.7.1 Challenges and Opportunities

Since quality assurance of the analytical measurements is vital in any HBM program, the European Protocol described essential laboratory performance requirements and envisioned the assessment of performance through interlaboratory comparison investigations (ICI) and external quality assessment schemes (EQUAS) [23,26]. The unique challenges inherent to biomonitoring applications, such as potential external contamination and measurements at very low levels are also opportunities for capacity building [35]. Capacity at national level is important for potential applications of HBM to targeted investigations, according to national priorities. Both LU and CY were faced with the challenge to develop methods and prove their performance in order to qualify for the analysis of their national samples, as was the case for laboratories in all participating countries. Where national capacity was not available and could not be built, arrangements had to be made for the analysis of samples in qualified laboratories abroad.

2.7.2 Implementation

The national laboratories in both countries had extensive experience in analytical testing, method validation and good laboratory practice.

At the onset of DEMOCOPHES, the CY SGL was accredited according to ISO 17025:2005 for several scopes, but not for HBM applications. In the frame of DEMOCOPHES, a method was refined for the "determination of cotinine in urine by GC/MS" [32] and a method was developed for the "determination of cadmium in urine by ICP/

MS". Both methods were validated and approved by the COPHES Quality Assessment Unit, through successful participation in ICI and EQUAS exercises [26]. Analyses for phthalate metabolites and creatinine in urine, and of total mercury in scalp hair, were analyzed in qualified collaborating laboratories, as originally planned. Transfer of knowledge on phthalates analysis was accomplished through a training visit in the collaborating laboratory. Time constraints were a big limiting factor.

For LU analytical methods were refined and quality assured by participation in the ICI and EQUAS exercises by the two participating laboratories (LNS – creatinine, cotinine, cadmium, mercury; LIST - BPA). Phthalates were outsourced due to a lack of competence on the national level at the time of the analyses required to be performed. Also for LU time constraints were crucial.

2.7.3 Lessons Learned

DEMOCOPHES demonstrated that despite difficulties, it is possible to build capacity at national level, which may open possibilities for additional investigations, according to national priorities. Capacity building and analysis of the samples from 60 mother–child pairs required for DEMOCOPHES in the small countries, resulted in similar costs compared to the analysis of 120 mother–child pairs in the bigger countries. Cost amortization requires the analysis of a large number of samples. If national funding in a small country is limited, external funding may be a prerequisite for the country to participate in large HBM surveys.

For a Europe-wide HBM survey, which involves analytical measurements in multiple laboratories, in addition to the accuracy of the results, it is important to set minimum performance criteria (limits of detection and quantification, variation and other statistical parameters) of laboratory methods in the study protocol. The availability of reference standards and a forum for the exchange of technical expertise is valuable for method development and validation. Performance assessment is important for confirming the accuracy of laboratory measurements, including pre- and post- analytical laboratory procedures. A mechanism to support national laboratories in capacity building is necessary. This could be in the form of a reference laboratory, which could arrange trainings and / or a technical working group.

2.8 Data management / interpretation

2.8.1 Challenges and Opportunities

A precise statistical analysis plan and specialized support by a centralized office is important with regards to capacity building and harmonized implementation. A central European database must be created, where the national data of each participating country must be uploaded for statistical analysis at European level. For this reason, the laws and procedures which regulate the transfer of data across national borders must be thoroughly evaluated before a project starts (see also [36]).

2.8.2 Implementation

Statistical analysis followed a centrally developed standardized procedure developed by COPHES [15]. Both CY and LU developed their respective national database according to detailed instructions provided in a centrally developed codebook, guidelines for quality control and relevant training. A process was set up to check the quality of the national databases and to merge them into one European database. The statistical analysis included calculation of response rate and non-responder analysis obtained on the basis of the inventory made during recruitment, description of the general characteristics of the study population (i.e. age, gender, anthropometry, social class, etc.) and statistical analysis of the monitored biomarkers.

2.8.3 Lessons Learned

A detailed statistical analysis plan and instructions, a codebook and procedures for quality control, relevant training and a support centre are all very important for the construction of uniform databases across countries and for uniform analysis. Since analytical measurements of biomarkers may be performed by different laboratories, it is important to set up minimum performance criteria for analytical methods in the study design and to establish clear procedures on how to deal with values below the limits of quantification and detection.

2.9 Communication and dissemination

2.9.1 Challenges and Opportunities

As HBM involves human subjects, it is essential to secure stakeholder acceptance. Proper communication with

participants and other stakeholders (policy makers, scientific community, and general public) is essential for the acceptance of HBM studies and for putting the results into context [24]. Small countries may have a strong advantage in this respect, as they tend to have easier access to potential participants, the media (newspapers, TV, radio), but also politicians. The right of participants to receive their results may also be a strong incentive for participation.

The willingness of the Minister of Health (LU) to support DEMOCOPHES in public was important for the success of the recruitment in this country, as the press conference from his office was reported from in practically all media.

Since the conclusion of the COPHES and DEMOCOPHES projects coincided with the Cyprus Presidency of the Council of the European Union (EU), an opportunity presented itself for world-wide dissemination of the project results at a conference within the framework of the Cyprus Presidency. This required the strong support of the CY Ministry of Health.

2.9.2 Implementation

2.9.2.1 Communication Materials

Within the scope of DEMOCOPHES, communication materials were minimally adopted in CY and LU and translated for national use in order to facilitate comparisons across Europe. For LU it was of help that German protocols were available from Germany and Switzerland that only needed minor adaptations for small local linguistic differences due to local habits. LU and Belgium shared the costs for a company translating all documents into French as well as the quality assurance of what was provided by the company. This contributed to an optimal use of resources. Developing and using communication materials directed to the child participant is an excellent idea according to experience from CY (though not developed and applied in LU). Based on the experience of both countries, it is important to keep the communication materials short, simple and to the point.

2.9.2.2 Reporting of Individual Results

In CY, all study participants received their personal results in person. Personal reports with the mother – child results and their interpretation, were handed out in sealed envelopes, in private, after the presentation and discussion of the aggregate results at two different workshops organized in each of the urban (Nicosia) and rural (Frenaros) sampling areas. Participants wishing private consultation were able to receive it.

In LU, participants received a letter with their results together with the invitation for a private information meeting for participants at the LIST in the presence and under the auspices of the Minister of Health. The letter contained the results for all chemicals analysed together with an interpretation.

In both countries, a second sampling was offered to participants in case that sample size did not allow proper measurement (Hg in hair), so that they could obtain their personalized results.

2.9.2.3 Reporting on the study and the aggregate results

Each country developed a national website for the DEMOCOPHES project (www.democophes.org for CY, www.democophes.lu for LU), as demanded by the study design, achieving visitation rates of more than 500 different hits at the time of writing. Highly successful promotion events were organized prior to the recruitment of participants and following the sample analysis. In both countries, the project was featured in the press and on radio and TV. At least one major press conference in each country involved the Minister of Health and other high ranking government officials. The dissemination actions included the participation of government officials, experts, research team members, industry and academia representatives as well as the population of the sampling regions. The study outcomes were disseminated in print and electronic versions for both laymen and health professionals in English and in the national languages.

The first public discussion of the COPHES and DEMOCOPHES results and preliminary conclusions took place in the frame of the Cyprus presidency of the Council of the European Union at the international conference “Human Biomonitoring: Linking Environment to Health and Supporting Policy”, in Larnaca, Cyprus on October 22-25 of 2012 [37]. The conference brought together scientists, policymakers, nongovernmental organizations, industry representatives and authorities from 30 countries and 3 continents and included oral and poster presentations and round table discussions. The Cypriot Minister of Health opened the conference and made press statements. The major highlights and conclusions of the conference were announced in press releases on the presidency webpage (Cyprus Presidency of the Council of the European Union 2012). The conference was additionally featured as a local event in “Open Days 2012” of the “Committee of the Regions” of the European

Union [38].

2.9.3 Lessons Learned

Communication materials should be kept short and to the point. Particular attention should be given to the way participants receive their personal results. It is important to respect participants' privacy, to put the results into context and to allow for questions and individual consultation if the participant wishes it.

Wide publicity should be sought right before the recruitment stage and should involve trusted, high level officials. The timing of publicity events is important. If recruiting in schools, the school calendar should be considered and specialized communication / awareness-raising actions can be envisioned.

"Small" countries may have "big" advantages with regards to communication actions, since they may be better networked, as highlighted by the success-stories of both LU and CY with regards to high publicity and the involvement of high-level respected officials and closer contacts with the study participants.

Although national WebPages received numerous visitations, they were not as highly effective as TV/Radio/Press coverage. In the future, the use of social media could also be considered.

3 Discussion

For the first time ever, a common protocol was elaborated and shown to be successful, on a pilot scale, for the harmonized biomonitoring of human populations across national borders, including small countries [35].

The development of a coherent, harmonized frame for cross-country HBM must ensure that it can be attained in countries of fundamentally variable sizes, cultures and socioeconomic characteristics. In the COPHES project, this was sought through the involvement of countries of diverse characteristics in the elaboration of a European Protocol for a harmonized HBM pilot survey. The successful implementation of a pilot HBM survey in 17 European countries with this protocol, suggests that continuous, active collaboration of all participating countries is necessary for the realization of a feasible, harmonized approach.

The experience of the two small countries highlighted that it is possible and desirable to allow adaptations of the harmonized protocol at national level, without compromising the comparability of the results. This flexibility (e.g. choosing to recruit participants through population registries or schools, or choosing to assess additional biomarkers) is important for successful and efficient implementation and for addressing national priorities. In association, the protocol must clearly define the essential elements of harmonization. Due to the diversity of European countries, these elements of harmonization must be tested for applicability in all countries.

HBM surveys are complex, costly and demanding in time and resources. Within the scope of a harmonized HBM survey, all implementing countries must apply the same procedures and quality assurance under tight timeframes, which translates to a larger per capita investment for smaller countries. Also, geographically isolated countries may face added challenges and increased costs with regards to shipment of samples and laboratory consumables and travel of personnel to other countries for training and coordination actions. For small countries, the added value of international collaboration can be considerable for overall effectiveness. The DEMOCOPHES experience suggests that the elaboration of the following elements is critical for quality assured, efficient implementation of HBM surveys in countries of variable capacities and resources: validated analytical methods, standardized procedures and documents, CAPI and database software, data storage capabilities, external quality assessment schemes, training and support mechanisms for all aspects of the study, including data interpretation and risk communication.

The DEMOCOPHES experience further suggested that it may be practical to have access to cost-effective options for (cross-border) outsourcing of some analyses, provided that they conform to preset quality assurance, ethical and personal data protection requirements. In addition, the cost, ethical constrains and preanalytical requirements associated with the long-term storage of specimens in biobanks must be considered in the study design, as well as potential associations with existing national biobanks. In this respect, financial and capacity limitations may be more pronounced in small countries. Moreover, the cross-border sharing of data may present difficulties related to restrictions and property rights at national level.

A successful HBM study must adopt a holistic, transparent communication strategy in order to obtain and maintain stakeholder acceptance and to accomplish the best possible exploitation of the results. Small countries have a strong advantage in this respect, due to shorter lines of communication at all levels, which facilitate a democratic process of stakeholder involvement: faster involvement of policymakers, as demonstrated in both CY

and LU with the involvement of the respective Ministers of Health; easier contact with authorities and community representatives; more direct and personal contact with prospective and actual participants. Small countries can also be particularly effective in achieving wide publicity, by involving high level officials and getting TV / Radio / Press / Internet coverage. This publicity can be very beneficial right before the recruitment stage and after the completion of the study.

The implementation of the HBM survey and the exploitation of the results at national level require the assignment of a center to coordinate the different tasks and to serve as the national focal point for international activities. For efficiency, it is important to exploit existing infrastructure and experience and to use the inherent advantages of a small country size for the overall coordination. Since the harmonization of HBM across Europe is expected to escalate its potential to support to policy, both small countries found it important to link their national surveys to state institutions.

HBM initiatives require political support and significant committed funding. Prospective use of the data for policy support can assist the process of attaining political support considerably. Small countries may be particularly effective in gaining access to policy makers and authorities and in keeping them involved. It must be noted, though, that if a country's resources are restricted and/or if other national priorities are more pressing, it may be difficult to obtain funding and political support at national level. The development and testing of a pilot HBM survey in Europe was facilitated largely by European Commission (EC) funding, with co-financing from national sources. The availability of EC funding was important for the involvement of many countries, including the two smallest ones, in this effort.

Through COPHES and DEMOCOPHES, the two small countries CY and LU developed essential capacity for HBM, established connections with other countries and institutions in Europe with shared interests and collected valuable data on the exposure of their populations to selected pollutants. The possibility, for the first time, to compare the exposures of Europeans among countries enhanced the opportunities to raise public awareness on environmental health and escalated the potential of HBM to evaluate current policies (including e.g. the economic benefit of neurotoxicity prevention, [39]).

4 Conclusion

This study demonstrates that small countries can successfully attain human biomonitoring in harmonization with other, much larger countries, thus supporting the hypothesis that a coherent approach to HBM in Europe is achievable. It further provides evidence for the effectiveness of the COPHES approach with regards to the development of a European Protocol for a pilot HBM survey, with the following fundamental characteristics: (a) consultation with and active involvement of the implementing countries, (b) flexibility for national decisions, (c) elaboration of standardized procedures, documents, quality assurance schemes, (d) mechanisms of training and support. The study also highlights that a small country size may be advantageous for communication and coordination actions.

The elaboration of this first pilot European harmonized HBM survey relied in part on the financial support of the European Commission. For this reason, no firm conclusions can be drawn, at this moment, about the extent of commitment of (small) countries to future harmonized biomonitoring activities that may strongly depend on significant national co-financing.

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