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Biomonitoring-based indicators of exposure to chemical pollutants

Report of a meeting

Catania, Italy

19-20 April 2012

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ABSTRACT

The WHO European Centre for Environment and Health (ECEH) is coordinating the development of biomonitoring-based indicators for efficient monitoring of Parma Declaration commitments to protect children from chemical hazards. This technical meeting in Catania, Italy, was co-funded by the Sicilian Regional Government. The meeting involved 38 biomonitoring experts from 15 Member States who worked together with Sicilian specialists to define a list of biomarkers for the proposed WHO survey in the general population and inhabitants of areas contaminated by the petrochemical industry. Meeting participants agreed that the proposed survey should focus on pregnant women who will be recruited from hospital maternity wards. After evaluating a large number of chemicals using a set of pre-defined criteria, meeting participants defined a list of high priority biomarkers for further evaluation, methodology development and pilot testing in a region with chemical pollution problems, such as Sicily.

Keywords

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Background and preparation of the meeting

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. The Parma Declaration specifically recognized pregnant and breast-feeding women as target population groups for actions aimed at identifying and reducing environmental risks as far as possible by 2015.

In Parma, the Member States also committed themselves to developing a consistent and rational approach to human biomonitoring (HBM) as a complementary tool for evidence-based public and environmental health measures. HBM characterizes the body burden of pollutants from all sources of exposure. The application of this approach in environmental health surveillance is increasing in Europe and worldwide. The demand for more high quality biomonitoring data is rising in many areas of work in environment and health.

In order to enable efficient monitoring of the progress towards these goals, the WHO European Centre for Environment and Health (ECEH) has been coordinating the development of biomonitoring-based indicators. A WHO technical meeting in November 2010 identified early life exposure to mercury and polybrominated diphenyl ethers (PBDEs) as the most relevant biomonitoring-based indicators of exposure supplementing the HBM-based indicators blood lead level in children and dioxins in human milk, which have already been implemented in WHO's European Environment and Health Information System (ENHIS). It was stressed that the existing data collection programmes should be utilized to the maximum extent possible for the proposed indicators. Specifically, PBDEs are included in the existing WHO-sponsored survey of persistent organic pollutants (POPs) in human milk.

At the same time, meeting participants agreed that new data collection would also be necessary in order to close existing data gaps and produce good quality, internationally comparable human biomonitoring data characterizing exposure to mercury. This would enable monitoring of the effectiveness of the legally binding international agreement on mercury, the Minamata Convention, as well as related Parma commitments.

In close collaboration with the Consortium to Perform Human Biomonitoring on a European Scale (COPHES), WHO has developed a draft standardized 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. The proposed survey would include two arms to characterize exposure distributions in the general population and in highly exposed subpopulations.

The September 2011 WHO technical meeting reviewed and approved the proposed survey's design, detailed protocols and standard operation procedures. That meeting also agreed that the scope of the proposed human biomonitoring survey should be expanded to include other biomarkers of exposure to priority pollutants. This would enable using synergies in fieldwork and characterize exposure to several pollutants using a cost-effective approach. The September 2011 meeting formulated a preliminary set of criteria for selecting additional biomarkers but left more detailed discussions for future meetings. It also specified the need to

further develop a survey in exposure “hot spots” and to identify opportunities for pilot testing and validating the proposed approaches.

Such opportunities may exist in Sicily where WHO Europe is conducting an exposure assessment project which is co-funded by the Government of Sicily and supported by the European Network on Contaminated Sites and Health. Objectives of this project include the development of health impact assessment methods and their application in contaminated areas, particularly at petrochemical industry sites, taking in account human exposure to contaminants from air, soil, drinking-water and food. The project has identified a need for fuller integration of human biomonitoring in epidemiological studies and risk assessment.

The Sicilian Regional Government generously provided funds for the current WHO technical meeting in Catania.

Summary of meeting discussions

Meeting participation

The meeting was attended by 38 technical experts, including 21 WHO temporary advisers from 14 Member States and the USA, 11 observers from Sicily and 4 WHO technical officers. The list of Participants is available in Annex 1. Meeting participants were identified using several approaches as described below.

WHO temporary advisers

Invitations were sent to technical experts in the areas of chemical safety and human biomonitoring who are involved in the COPHES project as well as those who are involved in existing national human biomonitoring programmes or biomonitoring surveys.

Observers

Sicilian specialists from local public health departments, universities and NGOs who are involved in addressing local environmental health issues related to the petrochemical industry and other local sources of pollution were invited to attend the meeting as observers in order to share their knowledge and discuss a potential pilot survey in Sicily. Another goal was to inform local experts on the most advanced existing national and international biomonitoring programmes, and share knowledge on approaches to HBM-based surveillance.

WHO staff

WHO technical experts, from the European Centre for Environment and Health (ECEH) in Bonn, Germany, WHO country office in Belgrade, Serbia, and WHO headquarters in Geneva, Switzerland, who are involved in the development of HBM-based surveillance methods were identified by WHO management.

Meeting objectives and organization

The main objectives of the meeting were (i) to develop a set of biomarker selection criteria; (ii) using these criteria, to identify additional human biomonitoring-based indicators to be included in the proposed biomonitoring survey; and (iii) to agree on an approach for characterizing exposures to selected pollutants in industrially contaminated areas using Sicily as an example. The first part of the meeting was devoted to reviewing major classes of environmental pollutants, the use of human biomonitoring data in support of decision-making, and existing national and international biomonitoring programmes and biomarker selection processes. Technical presentations at a plenary session provided background information on the specific situation in Sicily and the on-going WHO project there, as well as the proposed WHO biomonitoring survey in hospital maternities, including information about its methodology and design. Selected national biomonitoring programmes that can serve as examples of good practice for the selection of biomarkers, survey design, and the use of data in support of policy-making were also presented.

Meeting participants agreed upon criteria for selecting biomarkers for the two exposure arms of the proposed WHO survey, identified environmental pollutants to be included in the proposed WHO survey and selected appropriate exposure biomarkers to characterize exposure distributions in the general population as well as in highly exposed subgroups living close to industrially contaminated sites.

The meeting reviewed existing practice and latest scientific knowledge of participants for the general population arm, and reviewed technical documents prepared by local Sicilian participants for the determination of additional biomarkers for a hypothetical HBM survey in contaminated areas in Sicily.

In-depth discussions took place in two working groups which focused on the two arms of the proposed biomonitoring survey: working group (WG) 1, “General population survey in maternity hospitals: selecting additional biomarkers for assessing perinatal exposure to environmental toxicants” and WG 2, “Selection of biomarkers and survey design for exposure hot spots and heavily exposed population subgroups”. The list of working group assignments is presented in Annex 2.

WG 1 focused on selecting additional biomarkers for assessing perinatal exposure to environmental toxicants in the general population arm in maternity hospitals. The tasks for the first day were to define a set of biomarker selection criteria and compile a preliminary list of chemicals and biomarkers. The tasks for the second day were to discuss each biomarker and agree on a short set of high priority biomarkers.

Discussions in WG 2 (simultaneous Italian interpretation was provided) focused on the selection of biomarkers and survey design for three contaminated areas in Sicily and pollutants emitted by the petrochemical industry. The objectives of the working group were to: identify major pollutants for areas contaminated by the petrochemical industry, discuss the relevance to public health of each pollutant and select a list of biomarkers (BM) for petrochemical industry contamination hot spots. The group was also asked to agree on evaluation criteria, to propose and agree on target population(s) and recruitment criteria, as well as to agree on tentative survey design parameters and assess feasibility, relevance, and pilot testing from a country perspective.

Discussions in WGs were followed by concluding plenary sessions where meeting participants discussed the results from working groups and agreed on a provisional set of biomarkers for further development and presentation for the consideration of the European Environment and Health Task Force (EHTF).

Dr. Ludwine Casteleyn and Dr. Elena De Felip served as chair and co-chair respectively at plenary sessions. Dr. Anke Joas served as a rapporteur at plenary sessions and in WG 2. Dr. Argelia Castano chaired WG 1 and Ms. Geraldine McWeeney served as its rapporteur. Dr. Greet Schoeters chaired WG 2. This meeting report was compiled by the WHO secretariat using detailed notes from the rapporteurs and incorporating comments from meeting participants on the draft version.

Plenary session presentations

Background information

Background information, purpose and expected outcomes of the meeting

At the 5th European Ministerial Conference on the Environment and Health in Parma, Italy (2010), the Member States made commitments to protect children, pregnant and breastfeeding women from toxic environmental pollutants including carcinogens, mutagens, reproductive toxicants and endocrine disruptors. The Member States also committed themselves to developing a consistent and rational approach to human biomonitoring to assist evidence-based policy actions. The Parma Declaration also calls on the WHO Regional office for Europe to assist Member States in the development of internationally comparable environmental health indicators.

The WHO European Centre for Environment and Health has been coordinating the development of indicators which will enable efficient monitoring of Parma Declaration commitments. It is envisioned that the indicator data will be displayed in the European Environment and Health Information System (ENHIS). In consultations with Member States and technical experts, WHO evaluated the existing biomonitoring-based ENHIS indicators, blood lead levels in children and persistent organic pollutants in human milk. There is a need to improve the geographic coverage and data comparability for the blood lead level indicator. Joint efforts of WHO and Member States have also led to the selection of additional core indicators, early life exposure to mercury and brominated flame retardants in human milk. The latter will be based on the data from the existing WHO survey of persistent organic pollutants in human milk, while the former will require new data collection in most Member States. Working in close collaboration, WHO and the EC-funded COnsortium to Perform Human biomonitoring on a European Scale (COPHES), developed detailed survey design and standard operating procedures for the proposed survey. The survey will have a randomized clustered design with data collection conducted in maternity hospitals. Total mercury will be measured in maternal hair samples. The survey will have two arms to characterize exposure in the general population and heavily exposed populations or exposure hot spots. The remaining open tasks include the identification of additional biomarkers and development of sampling and laboratory analysis protocols, as well as further development of the high exposure arm of the proposed survey.

Sicilian project – assessing health risks associated with chemical contamination from petrochemical industry and other sources

Three areas in Sicily have high levels of environmental pollution due to emissions from the petrochemical industry and other sources: Milazzo-Valle del Mela, Augusta-Priolo and Gela. Each area is heavily contaminated by the existing and historical sources of pollution. The Augusta-Priolo polluted area in south-eastern Sicily is the location of Italy's major petrochemical facilities as well as naval shipyards and a former asbestos-cement plant. It is one of largest contaminated areas in Europe which includes the city of Syracuse and three other municipalities with more than 200,000 inhabitants in total. Gela (more than 100,000 inhabitants) is another heavily polluted site where epidemiological studies have demonstrated adverse health outcomes in the local population. Milazzo-Valle del Mela (more than 50,000 inhabitants) is the smallest of the three contaminated areas with significant pollution levels.

The on-going WHO project in Sicily, funded by the Sicilian Regional Government, is focusing on the assessment of environmental contamination, human exposure, epidemiological analysis, risk and health impact assessments, and health aspects of remediation programmes for contaminated areas. The available information demonstrates high levels of contamination of soil and local foods with heavy metals and organic pollutants. The limited available human biomonitoring (HBM) data also show high body burden of this pollutants in local adults. A major publication summarizing the results of this project is expected to be released in 2012.

Sicily would be an excellent location for pilot testing the proposed WHO biomonitoring survey. Persistent problems with environmental contamination have generated keen interest in local public and environmental health professionals in a comprehensive characterization of population exposure levels. There is a strong interest in Sicily in using HBM to monitor the effects of policy actions. A number of pollutants are present in the environment at levels that can pose risk to public health. At the same time, prioritizing environmental pollutants in Sicily using environmental monitoring data is difficult due to multiple routes of exposure. HBM provides data on the body burden of pollutants resulting from all routes of exposure. Combining HBM data with environmental data would help to guide targeted decision-making and monitor the effects of policy actions in Sicily.

Health risks posed by contamination from the petrochemical industry and other industries are a major environmental health problem in the WHO European Region. Sicily can serve as a pilot region for developing efficient approaches for biomonitoring-based surveillance in support of risk reduction measures. The collection of human exposure data using consistent standardized methodologies would allow comparisons of exposure levels within Sicily and with other location in the European Region.

International efforts to monitor exposure to chemical pollutants and the use of biomonitoring data in support of international agreements

Due to substantial adverse public health effects of exposure to toxic chemicals, such as heavy metals (HM) and persistent organic pollutants, policy-makers need to develop and implement exposure reduction measures. The United Nations Environment Programme (UNEP) coordinates worldwide actions to reduce emissions and exposure levels, such as phasing out the use of lead in petrol, banning most applications of organochlorine pesticides, such as

DDT, and measures to reduce exposure to second hand tobacco smoke. The use of leaded petrol has been declining steadily. Currently, only six countries remain that still have to ban its use. As a result, there has been an impressive decline in the body burden of lead in around the World. Similarly, coordinated policy actions to reduce the use of DDT resulted in a steady decline in the level of its by-products in humans. HBM was instrumental in stimulating these policy actions and demonstrating their effectiveness. Similar monitoring efforts are necessary to address exposure to other pollutants of global importance, such as mercury, and to demonstrate the effectiveness of targeted policy actions, such as the Minamata Convention.

Methodological issues – laboratory analysis and interpretation of biomarkers data

The European HBM survey COPHES/DEMOCOPHES: organization and selection of biomarkers

The efforts to develop a harmonised HBM survey in European Union countries, to translate results of surveillance into policy options and to adapt effective communication strategies are based on the European Environment and Health Action Plan for 2004-2010. The COnsortium to Perform Human biomonitoring on a European Scale (COPHES) was established in order to develop and test a harmonized approach to human biomonitoring. The COPHES project involved the selection of a set of biomarkers and the development of standardized survey protocols, laboratory and data analysis methods. The on-going cross-sectional demonstration survey DEMOCOPHES involves 6 to 11 years old children and their mothers in 17 EU countries (120 mother-child pairs per participating country). The project utilizes the existing expertise to the extent possible and includes an extensive consultation process with all participating countries. The project uses only non-invasively collected samples and measures the following biomarkers: mercury in hair samples, and cadmium, cotinine and metabolites of phthalates in urine.

The importance of harmonization of laboratory analysis: DEMOCOPHES experiences

Detailed internal and external Quality Assurance/Quality Control (QA/QC) procedures were developed for the DEMOCOPHES survey. These include Inter-Laboratory Comparison Investigations (comparability) and External Quality Assessment Scheme (accuracy and acceptable tolerance range of the results). The implementation of these QA/QC procedures ensures the comparability of results from all participating countries and laboratories. Other quality-related aspects in DEMOCOPHES include detailed standard procedures for the preparation, transportation and use of testing materials. All participating laboratories have to pass proficiency evaluation and quality control tests for each biomarker prior to analysing survey samples. The numbers of laboratories that successfully passed these rigorous tests differed depending on the type of analysis with most laboratories qualifying for analysis of metals (Hg and Cd) and the smallest number of laboratories demonstrating proficiency in the analysis of metabolites of phthalates. The implementation of DEMOCOPHES and its extensive QA/QC programme have contributed to capacity building in participating countries.

Exposure pathways, biomarkers and analytical methods – organic pollutants

Most organic pollutants can be analysed using gas chromatography (GC) or liquid chromatography (LC) coupled to mass spectrometry (MS). During the last three decades, the sensitivity of these methods has improved remarkably. On top of that, the selectivity has improved dramatically due to the introduction of multidimensional GC (GCxGC), and triple quadrupole and time-of-flight mass spectrometers. The current instrumentation enables using human biomonitoring as an early warning system. Identifying new emerging contamination issues at level which are still far below the health effect levels can support pro-active policy actions and prevent adverse public health impacts. Human milk, blood or cord blood can be used for analysis of polychlorinated biphenyls (PCBs), dioxins, organochlorine pesticides, brominated flame retardants, perfluorinated compounds and organotins. Urine samples can be used for analysis of bisphenol A (BPA), organophosphates, metabolates of polyaromatic hydrocarbons (PAH) and phthalates. Variability in results depends on the matrix (highest for urine, medium for blood, lowest for milk), and on the type of compound (lower for highly lipophilic compounds and higher for more polar compounds and their metabolites). Environmental monitoring coupled to HBM is necessary to quantify contributions of different exposure pathways. For example, recent research demonstrated that the main route of exposure to brominated flame retardants is inhalation of house dust rather than ingestion of contaminated food. It was also shown that neonatal exposure to phthalates (e.g., bis(2-ethylhexyl)phthalate [DEHP]) occurs mainly through the use of plastic medical devices.

Heavy metals – pharmacokinetics, endocrine disrupting and developmental effects of early life exposure

Cadmium (Cd), arsenic (As), mercury (Hg), and lead (Pb) are endocrine disrupting chemicals (EDCs). It has been shown that exposure to these heavy metals is linked to gonad dysfunction, adverse effects on the hypothalamus-pituitary-gonads axis resulting in the early onset of puberty, testicular injury due to disruption of blood-testis barrier, cancer and sexual function. Arsenic exposure significantly alters the signal transduction mechanisms of the estrogen receptors impairing pubertal growth and sexual maturation. Sicilian children living in the industrially contaminated areas Augusta-Melilli-Priolo, Gela and Milazzo-Valle del Mela are exposed to heavy metals through contaminated air, water and soil. The situation warrants further evaluation of body burdens of these pollutants and investigation of their potential effects on the endocrine system and development.

Review of selected national biomonitoring programmes: selection of biomarkers, survey design, lessons learned and the use of data in support of policy-making

Biomonitoring surveys in Flanders: evaluation and support of policy

The Belgian region of Flanders is one of the most densely populated and industrialized regions in Europe. It includes a number of industrially contaminated areas. The Flemish human biomonitoring programme involved consecutive rounds of monitoring with characterization of the exposure distribution in the general population and identification of reference values as a first step and subsequent focus on monitoring in hot spots. The first cycle of this program (2002-2006) demonstrated that living in areas with different environmental pressure yields a different fingerprint of pollutants in the body hence

indicating the importance of region based environmental policies and priorities. In the first cycle of the program, about 4600 individuals of 8 different geographical areas were recruited including mother-child pairs, 14-15 years old students and adults between 50 and 65 years of age. In the second cycle of the human biomonitoring program (2007-2011), a participatory process was used to select two exposure hot spots. The survey produced reference data for biomarkers in the general population. The survey involved 200 school students, 200 adults and 250 mother-child pairs who were recruited using a stratified random sampling scheme. The exposure biomarkers included metals, classical persistent organic pollutants, perfluorinated compounds, brominated flame retardants, musks, bisphenol A, metabolites of phthalates, parabens and pesticides.

To summarize, the programme developed procedures for the identification of hot spot areas. The results of HBM were compared with health-based guidance values or biomonitoring equivalents (BEs). Detailed recruitment procedures, approaches to data interpretation, communication, procedures for selection of biomarkers and the use of HBM data in policy-making can be used as a resource in further efforts to develop a HBM programme for the European Region.

Use of HBM in environmental health surveillance in Germany

The objectives of the German monitoring programme include the generation of representative data on exposure to environmental pollutants, identification of relevant exposure pathways and vulnerable groups, development of pollution prevention and exposure reduction strategies, monitoring of temporal trends, policy follow-up and evaluation of policy effectiveness, identification of emerging risks and characterization of exposure distributions in the general population and vulnerable groups. Overviews of the histories and approaches of the German Environmental Survey (GerES) and the Environmental Specimen Bank (ESB) were presented. Selection criteria for substances included: toxicological properties, potential impact on children's health, relevance for environmental policy, widespread exposure, reliable sampling procedures, validated analytical methods and costs of monitoring.

The presentation discussed future priorities for prioritization of biomarkers in the light of the implementation of Registration, Evaluation, Authorization and Restriction of Chemicals (REACH). It reported that 120 substance groups had been identified as relevant. These include phthalates, flame retardants, perfluorinated and fluorinated compounds, cosmetics ingredients, musk fragrances, sensitizing agents, benzothiazoles, substances that are included in the SVHC (Substances of Very High Concern) Candidates List [REACH Art. 57], aromatic amines, metals and metallic compounds, nanoparticles, and contaminants in food, which are currently being prioritized by an expert group. In addition, it reported about the German joint initiative with the chemical industry for HBM method development, aiming at developing standard protocols for monitoring five new substances per year.

National human biomonitoring programme in France: prioritization of substances and selection of biomarkers

The objectives of the French national biomonitoring programme are to characterize exposure of the French population to chemicals in food and environment, and to better understand the determinants of chemical exposures. Two important surveys in this programme are called ELFE (longitudinal) and ESTEBAN (cross-sectional). The presentation focused on the

selection of compounds for the ESTEBAN survey, and in particular on the decision structures (scientific council of national authorities) and selection procedures. Candidate compounds were identified based on feasibility of human biomonitoring, toxicity and relevance (regulations and policy priorities). A preliminary list was then grouped based on chemical properties, toxicity, and analytical techniques leading to 51 groups of biomarkers. A modified Delphi method was used for the prioritization of substances. This iterative method was based on a mailed questionnaire which was disseminated firstly among French and secondly among international experts. Candidate biomarkers were scored using eight criteria: health hazard, exposure levels, social perception, biomarker characteristics, interpretability of the results in terms of health risk, logistic and analytical feasibility, exposure prevention/reduction feasibility, and contributions to closing knowledge gaps. A number of technical meetings have been held for fine-tuning prioritization and ranking procedures and decision-making. Each biomarker was characterized using a statistical summary of individual scoring sheets and ranked in accordance with its total score. The resulting list was presented to different stakeholders for further discussions.

NHANES, the US National Health and Nutrition Examination Survey: goals and challenges

Selection criteria for chemical substances that have been used in NHANES include affordability, availability of adequate analytical methods, easy sampling or availability of sample matrices, toxicological properties, and exposure levels. This randomized survey is designed to characterize the general population. NHANES is a nutrition and health survey with HBM limited to blood and urine samples. Whereas lead, cadmium, and mercury are measured in all samples, other substances are measured in randomly selected subsets of study participants. Communication of individual results to participants only applies to heavy metals. The complete analyses results as well as statistical summaries of survey results are posted online. The selection of substances has been performed via the Federal Registry, enabling any person, entity or corporation to nominate a substance. Specific criteria have also been developed to remove a substance from the survey. NHANES does not provide information about geographical regions, exposure hot spots, or exposure levels in the very young. Therefore, there is a need to supplement NHANES with additional surveys focusing on vulnerable populations.

National HBM survey in Spain, BIOAMBIENT.ES

In Spain, a national HBM survey is linked to occupational health annual exams. This survey was designed to include all types of occupations and to draw a representative sample of the Spanish population. It is conducted at the national level and includes all provinces of Spain. The survey was funded by the Ministry of Agriculture, Food and Environment and carried by the National Spanish Institute of Health Carlos III in coordination with the Prevention Services of Corporación Mutua, the biggest Spanish mutual-profit insurance company. The sample size was almost 2,000 individuals aged from 18 to 67 years. Recruitment started in March 2009 and finished in July 2010. There were four sampling periods in order to cover for seasonal variability in biomarker values. Urine, blood, serum and scalp hair were analyzed for persistent organic pollutants (POPs), cotinine and heavy metals. Questionnaires were administered to collect data on life style and diet. The results of this project will provide data on the body burden of selected pollutants in a representative sample of Spanish working adults. This information will be used to establish reference values for the source population and support regulatory measures.

National HBM survey in Slovenia: legal embedding – the Slovenian chemical act

The presentation focussed on the impacts and implications of a legal embedding of HBM. The national legislation in Slovenia requires environmental and human biomonitoring to be performed in parallel. The objectives of the programme are characterizing exposure to chemicals and its health impact throughout Slovenia, identification of reference (background) values, assessment of spatial differences in exposure, risk assessment, information support to the development of targeted policy measures and monitoring of their effectiveness. A total of 12 areas were selected to represent urban and rural settings, and contaminated sites. Fifty lactating women and 50 men (20 – 40 years of age) from each area (1200 individuals total) were recruited. Data collection involved blood, milk, urine, and hair sampling. Biomarkers involved heavy metals (cadmium, lead, mercury, arsenic and others), PCBs, and clinical markers, such as cholesterol, triglycerides and urinary markers of kidney function. Training at national, regional and local levels was a crucial factor for success of this survey. Major obstacles were budgetary limitations, and low response rates.

National HBM survey in Denmark: inclusion of novel biomarkers

The NewGeneris survey in Denmark involved testing 250 pairs of maternal and umbilical cord blood samples for health effect biomarkers, such as micronuclei, bulky DNA adducts, gene expression and protein expression profiles, CALUX and Comet assays. The presentation also provided detailed information on the strong association between levels of brominated flame retardants in house dust and human milk which were demonstrated in Denmark. The ongoing project, the Danish DEMOCOPHES survey, involves 145 pairs of school age children and their mothers. In addition to the core set of DEMOCOPHES biomarkers, the Danish survey includes analysis of bisphenol A, parabens, triclosan, and benzophenon-3 in urine. A subset of participants also donated blood samples. Biomarkers include POPs in serum, CALUX assay, micronuclei in white blood cells, gene expression assays, metabolomics and toxicogenomics tests. The presentation also provided information on potential applications of data from the Exposome initiative and other investigations to bridge the gap between environment data and health.

Selection of biomarkers and survey design

1. General population arm

Background and proposed survey design

During the Meeting on methodological and organizational issues of monitoring the implementation of Parma conference commitments that took place on 29-30 September 2011 in Bonn, it was discussed and suggested that the WHO survey of prenatal exposure to mercury should have the following characteristics:

- Total mercury in maternal scalp hair as the biomarker of prenatal exposure
- Cross-sectional surveys in maternities (clustered design)
- General population: 240 mothers, at least 10 maternity wards

Biomarker selection criteria

The working group 1 group discussed and agreed on the following selection criteria for additional biomarkers to be incorporated in the proposed survey in the general population:

1. Importance: Prevalence of exposure, health hazards, public health impact and concerns from the public.
2. Justification: The proposed biomarker reflects the early life exposure to the pollutant and predicts later health effects.
3. Interpretation: Health based assessment data (interpretation based on scientific literature or national standards) are available.
4. Applicability to policy-making: Source can be or has been identified, and risk management measures are available.
5. Validity and feasibility: The proposed biomarker is valid, realistic in terms of required laboratory capabilities and costs; human and technical capabilities are available or can be developed, and standard operating procedures (SOPs) for pre-analytical and analytical phases are available. The required minimum sample volume is acceptable.
6. Acceptability: Effective political action committee (PAC) and willingness of people to participate, non-invasive, abundantly available matrix for sampling of the biomarker under the survey conditions in maternities.

The criteria were selected in the light of policy-making and were used for the evaluation of each biomarker (chemical substance and sample matrix). The proposed biomarkers were scored X (low), XX (medium) or XXX (high) for each criterion. The biomarkers were then classified as low, medium or high priority based on the combination of individual scores.

Target population and recruitment criteria for the general population arm

In order to perform a comparable and traceable recruitment, it is essential to have well defined inclusion and exclusion criteria for the population samples. With regard to the selection of potential participants, the proposal for the WHO survey hence recommends criteria that were further specified and confirmed by the group. Based on the discussion it was agreed that women who were to be included in the survey should be aged between 20 and 40 years. They should have had live births (still births are excluded), and they should have been living in the catchment area of the maternity hospital for the last five years (for assessment of exposure to persistent pollutants). The survey participants should have not travelled outside their area of residence for more than two weeks during the last three months of pregnancy (for assessment of exposure to short-lived pollutants).

It was decided that immigrants should not be excluded as long as they had sufficient language proficiency in one of the official languages used in the country/area. A potential occupational exposure was decided to not be considered as an exclusion criterion, in order to give a realistic picture about the average contamination of a representative population sample.

Meeting participants stressed that the results from a survey in maternities should not be extrapolated to the general population of women as exposure patterns may differ.

2. High exposure arm – survey in exposure hot spots

General considerations

Meeting participants agreed to focus on the development of an HBM survey for contaminated areas of Sicily. Such survey is expected to serve as an example of the application of HBM to characterize cumulative population exposure in areas contaminated by the petrochemical industry. It is envisioned that the survey would help local authorities and public health professionals to monitor the effects of policy actions targeted at curbing emissions and reducing population exposure, and help to inform the local population. While assisting the Sicilian Region of Italy to address local environmental health issues, WHO would develop and potentially pilot test an approach which will be used in many countries of the WHO European Region. The Sicilian Regional government, which generously funded this meeting of technical experts, would benefit from WHO-coordinated contributions of international experts and, by enabling this work, would contribute to the wider international community.

List of major pollutants in industrial hot spots in Sicily

The selection of pollutants and biomarkers started with reviewing the available data on major environmental contaminants in Sicily. Previously conducted environmental monitoring surveys have demonstrated that a broad range of organic and inorganic pollutants are found in the three contaminated areas in Sicily (Table 1). The meeting participants developed a set of evaluation criteria and discussed each pollutant and potential biomarkers that can be used to characterize human exposure.

Table 1. List of environmental pollutants in Sicilian exposure hot spots.

Inorganic substances	**Organic substances**
Arsenic	Benzene, toluene, ethylbenzene and xylenes (BTEX)
Cobalt	Vinyl chloride
Hexavalent chromium	Hexachlorobenzene HCB
Mercury and its compounds	Hydrocarbons with less than 12 carbon atoms
Lead and its compounds	Hydrocarbons with 12 or more carbon atoms
Copper	Polycyclic aromatic hydrocarbons PAHs
Zinc	Polychlorinated dibenzodioxins and dibenzofurans PCDDs/PCDFs
Cadmium	Tetrachloroethylene (PER)
Nickel	Trichloroethylene (TRI)
Vanadium	1,2-Dichloroethane (EDC)
	Polychlorinated biphenyls (PCB)

Biomarker selection criteria

The selection of biomarkers for the high exposure arm of the proposed survey started with the development of evaluation criteria for the above pollutants and associated biomarkers. Meeting participants agreed on primary and secondary criteria as described below.

Primary criteria:

- existence of validated biomarker(s)
- toxicological potential and health hazard
- availability of an appropriate sampling matrix that can be used in maternity settings
- existence of health based guidance values
- manageable sample volume
- affordable cost of laboratory analysis.

Additional (secondary) selection criteria:

- magnitude of exposure
- availability of environmental/health information
- existing capacities to conduct laboratory analysis
- specificity of the biomarker
- link to industrial pollution sources
- trans-placental transport of contaminant from the mother to the foetus in light of the decision to use the maternity approach for the hot-spot survey in accordance with the general population study approach
- vulnerability during the in-utero development phase.

Further discussions are necessary in order to develop final scoring and ranking procedures, and to finalize the list of biomarkers. Meeting participants agreed that the list of biomarkers would in practice be developed for each contaminated area or region, and that it will have to be tailored to specific exposure situations. Developing a single list of chemicals and biomarkers fitting all hot spots contaminated by the petrochemical industry would be problematic because of a wide variety of industrial processes and pollutants.

It was noted that investigations should not focus exclusively on industrial emission as naturally occurring chemicals can add to overall toxicity and health risks. On the other hand, it would need to be taken in account that naturally occurring chemicals cannot be eliminated from the environment, while industrial emissions can be reduced. Aspects of regional environmental background contamination were considered as an important criterion to also be taken into consideration for the elaboration of the hot-spot study design. (See below.)

It will be necessary to formulate an affordable short list of core biomarkers for which WHO will provide standard operating procedures and coordinate technical support. In addition, biomarkers will need to be categorized by predominant emission sources in order to generalize the recommendations developed specifically for Sicily to the entire WHO European Region. In this context, it is crucial that the recommended biomarkers be easily interpretable and that the selection criterion for chemicals be further assessed.

Target population(s) and recruitment criteria

Meeting participants discussed potential target populations for the proposed hot spot survey keeping in mind the advantages of using a harmonized design with the general population survey in maternities. The suitability of this approach for hot spot areas where the population and annual number of births may be rather small was a main concern. As occupational exposures are predominant in some hot spot areas with operational industries, it may be

advantageous to include fathers, or even whole families. Another approach considered in light of costs, ethical aspects and feasibility, was recruiting adolescents or younger children via schools. The latter approach received slightly more support from the meeting participants. The deciding factor, however, was the need to be consistent and match the design of the proposed general population survey in maternities. It was also determined that the contaminated areas in Sicily are large enough, with a sufficient number of births, to allow for the recruitment of mothers through maternities. Thus, recruiting mothers in maternities was also recommended for the hot spot survey, at least in Sicily and other regions/countries with sufficiently large populations living in exposure hot spots.

Survey design for exposure hot spots

The meeting also discussed the selection of appropriate reference areas for the hot spot survey. The following three options were evaluated for their feasibility:

1. Compare distributions of biomarker data in highly exposed population (exposure hot spot survey) and the reference population (general population survey)
2. Assess associations between proximity to emission sources and exposure levels
3. Assess temporal relationship between emission levels and body burden of pollutants

For Option 1, it was suggested that a national survey in the general population would provide reference data for surveys in exposure hot spots. An alternative suggestion was to use a reference population from the same region in order to avoid confounding due to potential regional differences in background levels of exposure. Specifically, exposures to some metals are different in Sicily due to the Etna volcano which affects local geochemical conditions. Thus, it was recommended that a general population survey in the Sicily Region should provide the basis of comparison for a survey in Sicilian exposure hot spots. Meeting participants also discussed if it would be better to have a separate reference population for each hot spot area. This approach is epidemiologically sound but it is associated with greater costs. Defining a separate control area for each contaminated area would also be problematic because these large contaminated areas cover a substantial portion of Sicily.

Option 2, linking the distance from a source of emission with body burden of pollutants is problematic due to potentially complicated spatial patterns of environmental pollution, which are affected by prevailing winds and, for the contamination of water bodies, transport with water flows. The presence of various exposure pathways including local foods further complicates the situation. The available data from one contaminated area of Sicily also do not support a simple association of exposure with the distance to the source. However, meeting participants agreed that it would be advisable to collect data on the place of residence of survey participants to enable optional analysis of spatial patterns.

Option 3 was not considered viable due to a cross-sectional design of the proposed survey and other methodological limitations.

3. Review of potential biomarkers for both survey arms

Based on the environmental monitoring data for exposure hot spots in Sicily and information on priority pollutants in the general population, meeting participants compiled two preliminary lists of pollutants for the two survey arms. Some pollutants, such as non-persistent organic chemicals emitted by the petrochemical industry, were discussed at the hot spots working group only, while others, such as cotinine and parabens, were discussed only in relation to the general population arm of the survey. Many pollutants, however, were discussed in both working groups. In addition, meeting participants discussed biomarkers of health effects. Such biomarkers can be used to assess combined effects of multiple pollutants with similar target organs or systems. The results of working group discussions were presented and further discussed at concluding plenary sessions. The combined list of biomarkers of exposure and health effect is presented below. For further details, see Annexes 3 and 4.

Heavy metals

Arsenic

Arsenic is a well-known genotoxic carcinogen which can also cause kidney damage. Arsenic is an important pollutant because of a high prevalence of exposure, potentially severe health effects, and high level of concern from the public. Natural and anthropogenic sources of arsenic have been identified, and risk management measures are available.

Arsenic can be easily measured in blood, cord blood, hair and urine using validated analytical methods. Quantities required for chemical analysis are small and costs are relatively low. There are health based international reference values for the interpretation of biomonitoring data. The maternal hair or urine biomarkers are well suited to reflect early life exposure, which is predictive of long-term health effects. The biomarker is valid, realistic in terms of laboratory capabilities and costs. Validated SOPs for sampling and analysis are available; human and technical capacities are available, and the matrix is readily available in the required quantity. Of note, it may be difficult to distinguish between an environmental and industrial origin. For appropriate assessment and interpretation, the meeting recommended integrating HBM results with information about major up-take pathways and sources.

For the general population arm, arsenic in maternal urine scored high for all selection criteria except interpretation. The indicator might be most suitable for exposure monitoring in areas with high levels of naturally occurring arsenic or industrial hot spots where it was classified as a high priority biomarker. Measuring arsenic in cord blood is an alternative approach.

Hexavalent chromium

Hexavalent chromium is an important carcinogen and the most toxic form of chromium. Total chromium can be measured in urine as a biomarker of exposure to hexavalent chromium. The biological half-life of chromium in urine, however, is very short. If blood or cord blood samples are used, chromium can be measured in red blood cells (RBCs). However, the above biomarkers of exposure to hexavalent chromium are not sufficiently validated. Effects of high level exposure to hexavalent chromium can also be identified during untargeted screening using genotoxicity biomarkers.

Due to its carcinogenicity, chromium was identified as a high priority biomarker for the exposure hot spot arm. This biomarker would be most relevant for hot spots contaminated by emissions from cement plants. However, exposure is not exclusively linked to industrial emission sources. Therefore, it is necessary to integrate HBM results with additional information from environmental monitoring.

Inorganic Mercury

For assessing exposure to inorganic mercury, urine is considered to be the preferred matrix. Given its toxicity, inorganic mercury received a high priority ranking for the exposure hot spot survey. The cost for chemical analysis of total mercury in urine is relatively low, approximately €20 per specimen. Samples are easily available in the amount necessary for analysis. For the general population survey, urinary mercury scored high for validity and acceptability, but medium for importance, justification and policy relevance. The biomarker is considered relevant for countries that still use dental amalgam. It could also be a good indicator to follow up the implementation of the Minamata Global Treaty on mercury.

Methylmercury

Total mercury in maternal hair is the core biomarker of prenatal exposure to methyl mercury. It was identified and confirmed at a previous WHO meeting. This biomarker was re-evaluated at the current meeting using the newly developed set of criteria. It scored high for all selection criteria including prevalence of exposure, health hazard, public health impact and concerns from the public. The biomarker is well suited to reflect early life exposure and it is predictive of long term health effects. Health based assessment data is available. Of note, there is a limitation in terms of divergent guidance values from different sources. Major sources of emission and exposure pathways have been identified, and risk management measures are available. The biomarker is valid, realistic in terms of laboratory capability and costs. Validated SOPs are available for sampling and analysis procedures are in place. The matrix is readily available in the required quantity. It should be noted that analysis of total mercury is rather inexpensive and that an adequate amount of the required matrix is available for assessing exposure to methyl mercury which accumulates in hair.

The hair mercury biomarker reflects exposure to methyl mercury which is associated mainly with consumption of contaminated fish. Thus, the biomarker is relevant for the general population and for high exposure areas, such as coastal areas with high level of fish consumption. There may also be a situation with local contamination of the aquatic food chain in industrial exposure hot spots. The indicator is not suitable for assessing exposure to metallic mercury, such as inhalation exposure from industrial sources. For that, urinary mercury is a more suitable biomarker.

Lead

Lead in cord blood and/or a finger stick is a biomarker which has received a high score for all selection criteria including prevalence of exposure, health hazards, public health impact and concerns from the public. The biomarker is well suited to reflect early life exposure and to predict later health effects. Health based assessment data is available, major sources have been identified, and risk management measures are available. The biomarker is valid, realistic in terms of laboratory capability and costs, and validated SOPs for sampling and analysis are available. Human and technical capacity is available, and the required sample volume can be

obtained easily. It is also possible to screen for health impacts of lead exposure using a biomarker for genotoxicity (see below). Blood lead level can be analysed at low cost (< €20 per specimen). If analysed together with other heavy metals, then the cost of analysis may be even lower. The biomarker is recommended for the general population and high exposure arms of the proposed survey. (Note: The indicator of blood lead level in children already exists in ENHIS but the data availability and comparability are unsatisfactory.)

Cadmium

Cadmium is an important pollutant due to its carcinogenic and endocrine disrupting properties. It can be measured preferentially in maternal urine or maternal blood. The biomarkers scored high for importance, justification, validity and acceptability. The prevalence of exposure is high, health hazards are substantial, public health impacts are significant and concerns from the public are pronounced. Required sample volume is small. Health related reference values exist. The biomarker is valid, realistic in terms of laboratory capability and costs, and validated SOPs for sampling and analysis are in place; human and technical capacity is available, and the matrix in general is readily available in the required quantity. Major sources have been identified, but there are limitations in risk management measures, and health based assessment data. Although cadmium poorly crosses the placenta barrier, it can still adversely affect the placenta itself. Due to the placental barrier, levels of cadmium in cord blood are very low. Therefore, maternal blood or maternal urine are most suitable sample matrices. Since it is advantageous to use non-invasive sampling, the urinary biomarker is preferred. This biomarker is well suited to reflect early life exposure and to predict later health effects. Cadmium in maternal urine was classified as a high priority biomarker for both general population and exposure hot spot arms of the proposed survey.

Cobalt

Cobalt can be readily measured in urine with a validated analytical method. In addition, its effects can be detected during untargeted screening via the effect markers of genotoxicity, like most of the other heavy metals. It was discussed that elevated cobalt levels may be difficult to interpret due to strong inter-individual variability. Given less severe health impacts and the limitations in interpretability, cobalt was only attributed a limited priority level by the group.

Copper

Copper was not considered a highly relevant biomarker by the experts due to its strong inter-individual variability and limited health risks. Whereas the substance can in principle be easily measured in urine, no appropriate effect marker has been identified that could be used for untargeted screening methods.

Nickel

The major risk related to nickel exposure is dermal allergies. Given the low severity of health effects, the substance was ranked as medium priority by the group. Of note, it could be easily measured in urine using a validated, inexpensive analytical method.

Vanadium

Vanadium ranked low because adverse health effects are currently not well defined. On the other hand, it was reported that levels in some agricultural areas in Sicily may be 10 times higher than normal. Screening of exposure levels may need to be given further consideration.

Organic pollutants

Hydrocarbons (C1-C20)

Hydrocarbons are the major substances emitted by the petrochemical industry but they are difficult to investigate via HBM due to their very short half lives. Given their low toxicity levels, short chained hydrocarbons were considered of low relevance by the group. Long-chained hydrocarbons are associated with a higher health risk and hence classified as a medium priority substance. Benzene, toluene, ethylbenzene and xylenes (BTEX), together with T, t-muconic acid, in maternal urine were recommended as the most appropriate biomarkers for exposure to hydrocarbons. BTEX could be measured in exhaled air or in urine. An obstacle for its use is the short half life and limited evidence for health relevance and early life exposure. Required urine sample volume is small. Reference values for interpretation of health risks, however, do not yet exist.

Polyaromatic hydrocarbons (PAHs)

Metabolites of PAHs can be measured in maternal urine. Given the carcinogenic and mutagenic properties of PAHs, this chemical group was ranked high by the experts for hot-spot settings. 1-OH-pyrene in maternal urine would be the most appropriate biomarker for PAH exposure. DNA adducts would be the corresponding biomarkers of effect. Due to the short half-life, monitoring of 1-OH-pyrene will only inform about acute exposure. A combination with DNA adducts could inform about prenatal exposure and risks. Required urine sample volume is small. Reference values for interpretation of health risks, however, do not yet exist.

For the general population survey, this biomarker scored high in terms of importance, policy relevance and acceptability, but only medium for justification and validity, and low for interpretation. This biomarker has only limited potential to reflect early life exposure and to predict later health effects. Chemical analysis is complex, with adequate capabilities and expertise existing in only a few laboratories of excellence. The cost of analysis is relatively high.

Polychlorinated dibenzodioxins & furans (PCDD/PCDF) and dioxin-like polychlorinated biphenyls (PCBs)

Due to their toxicity, endocrine disrupting effects, persistence in the environment and bioaccumulation properties, PCDDs/PCDFs (“dioxins”) and dioxin-like PCBs are of high relevance for industrial exposure settings in particular in relation to metal industry. Uncontrolled waste burning is another source of emissions. These compounds would best be measured in cord blood (plasma) or breast milk. Methods based on GC-MS would provide the best data for human biomonitoring of individual congeners. The CALUX aryl hydrocarbon receptor (AhR) assay could also be used as a screening method in case of a large

number of samples as a mean to reduce analysis costs. Approximately 5 ml of blood are required for the CALUX assay, whereas a larger volume of blood may be required for the congener-specific measurements. Health based reference values exist for individual congeners but not yet for the CALUX assay. These chemicals scored high for the prevalence of exposure, health hazards, public health impact and concerns from the public but they scored low for acceptability of biomarkers. The cord blood or milk biomarkers reflect early life exposure which is linked with long term health effects. Major sources have been identified, and risk management measures are available. The biomarker is valid, but has limitations in terms of laboratory capability and costs, due to the costly, complex and specialized analysis. The large volume sample requirement may be another disadvantage.

Polychlorinated biphenyls (PCBs), organochlorine pesticides, polybrominated diphenyl ethers (PBDEs) and other persistent organic pollutants (excluding dioxins and dioxin-like PCBs)

Persistent organic pollutants (POPs), such PBDEs, organochlorine pesticides and non-dioxin-like PCBs, can be measured in breast milk, blood and cord blood. The cord blood biomarker, which is most suitable for the maternity ward settings, scored high by the experts for all selection criteria except policy relevance (these substances are already banned) and acceptability, where these substances received medium scores. Of note, they have high relevance concerning prevalence of exposure, health hazards, public health impact and concerns from the public. The cord blood biomarker is well suited to reflect early life exposure and to predict later health effects. Health based assessment data is available and major sources have been identified. But given the existing bans and minimization measures, additional risk management actions may not be so easy to take. The biomarker is valid and realistic in terms of laboratory capability and costs. Validated SOPs for sampling and analysis are in place, and human and technical capacity is available. But the required sample quantities are a disadvantage.

POPs are considered an appropriate biomarker for a hot spot arm of the proposed survey, especially in mixed industrial exposure settings, such as those involving the metal industry and waste incinerator facilities. Approximately 5 ml of blood or cord blood are requested for analysis. Health based reference values exist for individual congeners.

Vinyl chloride (VC)

Vinyl chloride is an endocrine disrupting compound which is particularly important in occupational settings. However, validated biomarkers of exposure or effect may not be available. The relevance for early life exposure is low. The chemical was not recommended for general population or exposure high spots arms.

Hexachlorobenzene (HCB)

HCB is a persistent chemical which is a by-product from the production of polyethylene and other chemical processes. Elevated levels of this compound have been detected in the environment. The substance can be measured in breast milk and cord blood, like other POPs. It is of medium relevance for the high exposure arm of the proposed survey.

Tetra- and Trichloroethylene (PER & TRI)

PER and TRI are organic pollutants which are suspected carcinogens with considerable health hazards. These compounds had been used in dry cleaning and metal industry (degreasing) but now are banned. Exposure is mainly through inhalation. Tetrachloroethylene and trichloroacetic acid (TCA), its breakdown product, can be detected in blood. In terms of relevance for hot spot monitoring of early life exposure, however, these compounds scored low due to the lack of validated biomarkers of exposure, and due to their short half-life in the human body.

1,2-Dichloroethane (DCE)

DCE is an intermediate in the production of vinyl chloride and other chemicals. DCE is associated with considerable acute and chronic health risks. The substance is classified carcinogenic for humans and is suspected to be genotoxic. Due to its volatility, inhalation is the major exposure route. In terms of relevance for hot spot monitoring of early life exposure it scored low due to the lack of appropriate biomarkers of exposure and effect, and due to the short half-life of the substance. The substance was not considered for the general population arm as exposures are associated mainly with industrial sources.

Chlorophenols

Cord blood level of pentachlorophenol (PCP) as a marker substance for chlorophenols (mono-, di-, tri- and tetrachlorophenols, MCP, DCP, TCP and TeCP) received high scores for interpretability, policy relevance, and acceptability, and a medium score for importance, justification, and acceptability.

Perfluorinated compounds (PFCs)

Perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA) and other related compounds (PFBA, PFPA, PFHxA, PFHpA, PFNA, PFDA, PFUnA, PFDoA, PFTrDA and PFTeDA) would have to be measured in cord blood or placenta. The biomarker received medium scores for importance, justification and interpretability, and low scores for policy relevance, validity and acceptability. There is not enough information to assess health effects based on biomarker values. Major sources of exposure have been identified, but the availability of data for health based assessment is limited, and risk management measures might not be easy to take. The biomarker is valid, but the complexity of analysis and its high cost reduce the feasibility.

Bisphenol A (BPA)

BPA in urine scored high for interpretation, policy relevance, and acceptability, but it only received a low score for validity and a medium score for importance and justification. This biomarker has only limited potential to predict health effects; chemical analysis is complex, and the cost of analysis if high. Only few specialized laboratories are qualified to conduct these tests. It should be noted that scientific discussions on the prevalence of exposure, health hazards and public health significance of this chemical are ongoing. The biomarker may need to be revisited in the future.

Phthalates

Phthalates, such as bis(2-ethylhexyl)phthalate (DEHP), di-n-butyl phthalate (DnBP), diisobutyl phthalate (DiBP), benzyl butyl phthalate (BBzP) and diisononyl phthalate (DiNP), can be measured as monoester metabolites in urine. The biomarker scored high for importance, interpretation, policy relevance, and acceptability, but only received a low score for validity and a medium score for justification. This biomarker has only limited potential to predict health effects, and chemical analysis is costly and complex, restricting the list of suitable laboratories to a few specialized centres of excellence.

Parabens

Parabens are contained mainly in personal care products where they are used as antimicrobial agents or preservatives. There are clear signs of wide spread exposure in children and mothers, and concerns about potential health effects of parabens. The urinary parabens biomarker was discussed for potential inclusion in the general population arm. However, the biomarker scored low for most criteria. It is not clear if parabens in maternal urine reflect foetal exposure. The long term health effects of early life exposure are also not well established. Thus, health-effect oriented interpretation of biomonitoring data is problematic. These substances, however, are gaining recognition and might be reconsidered in the future.

Non-persistent pesticides

Contemporarily used non-persistent pesticides include organophosphate, carbamate and pyrethroid insecticides, and a variety of herbicides, such as 2,4-dichlorophenoxyacetic acid, atrazine and glyphosate. Some of these compounds are emerging chemicals of concern because they have been associated with neurodevelopmental effects in children. Non-persistent pesticides and their metabolites can be measured in urine. The biomarker scored high for importance, justification, policy relevance, and acceptability, but low for interpretability and validity for the general population survey. There are not enough health based assessment data. Laboratory techniques are rather sophisticated, necessitating the need for specialized analytical training.

Nicotine/cotinine

Cotinine is the metabolite of nicotine, which is excreted in urine. Thus, urinary cotinine can serve as biomarker for smoking and second hand exposure to tobacco smoke in the general population survey. This biomarker was considered for the general population arm and received high scores for all selection criteria except interpretation and validity, for which it received a medium score. This biomarker has some limitations due to limited reference data for health assessments and potential problems with validation of available SOPs. Laboratory capabilities would need to be developed in some Member States in order to produce consistent results.

Biomarkers reflecting biological effects of exposure to chemicals

DNA adducts

DNA adducts can be used to assess the combined effect of complex exposures to chemical mixtures in contaminated areas. DNA adducts should be measured in cord blood to reflect early life exposure. However, the method is not yet sufficiently validated and reference values for evaluation of health risks do not yet exist. In addition, the cost of analysis is high (€ 200-300 per sample) and analysis would require 5-10 ml of blood.

Micronuclei

Mirconuclei may be used as effect biomarkers for a mixture of genotixic chemicals. They should be measured in cord blood to reflect early life exposure. However, the method is not specific, and the results are associated with a high level of uncertainty. If testing for micronuclei were included in the hot spot arm, then it would also need to be included in the general population survey for comparison, as interpretation of absolute values is problematic. The biomarker can only be measured in fresh lymphocytes, which entails the need to have appropriate logistics for analysis within 24 hours of sample collection. In addition, it is costly (roughly € 150). The required sample volume is 1 ml of blood. Reference values for interpretation of health risks do not yet exist.

Single Cell Gel Electrophoresis assay (Comet Assay)

The Comet assay is a relatively simple and sensitive technique for the detection of DNA damage. It should be performed on cord blood to reflect early life exposure. The method has the major limitation of requiring fresh lymphocytes, which entails the need to have appropriate logistics in place. The cost is relatively high (roughly € 100), the required sample volume is up to 3 ml of blood and reference values for interpretation of health risks do not yet exist.

Standard panel of clinical blood tests (blood count, thyroid function, kidney function)

A haematogram (blood count) and laboratory tests for thyroid and kidney function were considered as supplementary (non-specific) indicators for toxic and endocrine disrupting effects. They would also provide additional information on the health status of survey participants. The idea was to link exposure biomarkers with this effect biomarker. Analysis of all these markers would require less than 1 ml of blood, and could be performed at low cost. Reference values exist for all parameters. The main problem with this test is the lack of specificity to environmental hazards.

4. Summary of biomarker selection discussions

Sample matrices

Meeting participants agreed that the proposed surveys in the general population and in exposure hot spots should involve new mothers recruited through maternity wards (potential exception is contaminated areas with a small population and insufficient number of births;

contaminated areas in Sicily have sufficient population and number of births). It was agreed that the survey should use non-invasive samples which are easy to obtain: maternal hair, maternal urine and cord blood. It was discussed that breast milk could be included in the survey as additional matrix to assess post-natal exposure, but concerns were raised about the disadvantages of this medium. First, sampling of human milk can be more complex than for other matrices. Second, reporting elevated levels of pollutants in breast milk, without the use of effective means of communication or message framing, could give a negative image of breast milk. Third, cord blood can be used for the same purpose without the disadvantages mentioned above. Fourth, sampling of human milk overlaps with the activities of an existing WHO survey of POPs in human milk. Therefore, the group decided to not recommend using human milk sampling in the proposed survey.

General population arm

Using the set of evaluation criteria described above, meeting participants evaluated each chemical and potential biomarkers based on different sample matrices (see Annex 3 for details). The result was a set of biomarkers in three priority groups as described below.

- High priority biomarkers: total mercury in maternal hair, cadmium in maternal urine, cotinine in maternal urine, and lead in cord blood.

- Medium priority biomarkers: arsenic in maternal hair or cord blood, total mercury in maternal urine, phthalate metabolites, PAH metabolites and non-persistent pesticides in urine; and POPs (except dioxin-like substances) in cord blood.

- Low priority biomarkers: bisphenol A, parabens, and pentachlorophenol in maternal urine, dioxins and dioxin-like PCBs in cord blood, and perfluorinated compounds (PFOS/PFOA) in cord blood.

High exposure arm (exposure hot spots)

Meeting participants agreed on a set of evaluation criteria and a preliminary set of biomarkers for the proposed survey in contaminated areas in Sicily as a representative example of European populations affected by emissions from the petrochemical industry and other sources. When compiling this preliminary list, meeting participants took in account that the composition of pollution mixtures varies among the three contaminated areas of Sicily and that the local populations are exposed to pollutants via multiple pathways, mainly through consumption of contaminated local food products and inhalation of contaminated ambient air.

The meeting agreed on the following:

- HBM is a very useful tool for characterizing the population distribution of cumulative total exposure through multiple pathways. The results of a single survey will help to compare populations while follow-up surveys would enable characterization of temporal trends in exposure and assessment of the effect of policy actions aiming to reducing emissions and exposures. The proposed WHO-coordinated HBM survey using standardized methods would also help to address the demand of local communities for high quality reliable information on exposure levels and potential

health risks, and stimulate constructive dialogue between the public and policy-makers.

- It is recommended that the exposure hot spot arm should employ recruitment of mothers through maternities as the default method in order to ensure consistency with the general population survey arm.
- Meeting participants discussed and evaluated a list of chemical pollutants (see Annex 4 for details) and agreed on preliminary rankings. However, further consultations are needed to finalize the short list of biomarkers of exposure in order to control the cost of the proposed survey and provide adequate technical support to ensure the consistency, quality, and comparability of results.
- In light of the complex exposure to a large number of pollutants, health effect biomarkers, such as markers for (i) genotoxicity, (ii) kidney damage, (iii) endocrine disruption, and (iv) combined toxicity may provide additional insights. These analyses, however, are costly and interpretation of results is problematic in the exposure survey settings. WHO will not be able to provide standard operating procedures or technical support for these biomarkers.

Recommendations and conclusions

Specific recommendations on selection of biomarkers

Meeting participants agreed that several outstanding issues will need to be addressed before the start of the proposed data collection activities. The first issue is the harmonization of the recommended list of biomarkers for the general population arm and the hot spots arm. Surveys in the general population would serve as a control group for the exposure hot spots surveys for selected pollutants. Therefore, biomarkers selected for the hot spot survey would also need to be included in the general population arm when warranted. Depending on the local needs and public health priorities, it may also be helpful to include some biomarkers which were selected for the general population survey, such as urinary cotinine, in the hot spot survey. This would help to characterize exposure to a wider range of harmful factors in the population of industrially contaminated areas.

The following biomarkers are recommended for the proposed WHO survey to characterize early life exposure to environmental pollutants:

a. General population arm (clustered random sample of mothers recruited through maternities):
    - High priority: total mercury in maternal hair, cadmium in maternal urine, cotinine in maternal urine, and lead in cord blood
    - Medium priority: arsenic in maternal hair or cord blood; mercury in maternal urine (biomarker of exposure to inorganic/elemental mercury); phthalate metabolites, PAH metabolite (1-OH pyrene) and non-persistent pesticides in maternal urine; POPs except dioxin-like substances in cord blood
    - Low priority: BPA, parabens and pentachlorophenol (PCP) in maternal urine; PCDD/PCDF and dioxin-like PCB in cord blood, and PFCs in cord blood.

High priority biomarkers are recommended for all national surveys. Medium and low priority biomarkers should be further evaluated based on the local/regional priorities and emission sources.

b. High exposure arm (when possible, mothers recruited through maternities):
    - This meeting discussed biomarkers to characterize exposure in populations living in areas contaminated by the petrochemical industry (focusing on contaminated areas in Sicily). Recommendations are preliminary; further discussions with Sicilian stakeholders and pilot testing are warranted.
    - Biomarkers for other types of contaminated sites would need to be identified at future consultations taking in account the local situation and pollution pressure.
    - In addition to all high priority biomarkers for the general population arm listed above, meeting participants recommend monitoring exposure to PAH (1-OH pyrene in maternal urine) and BTEX (BTEX and T,t-muconic acid in urine).

Conclusions

1. The objective of this work is developing a feasible, cost-effective human biomonitoring survey addressing public health priorities in the WHO European Region and enabling monitoring of pertinent Parma Declaration commitments.

2. The meeting involved productive and mutually beneficial discussions between technical experts (WHO temporary advisers) and Sicilian specialists representing local public health institutions and stakeholders. Meeting participants encourage WHO to follow-up on these discussions and explore opportunities for conducting an HBM survey in Sicily. This would provide valuable information to local communities and policy-makers, and would also help to develop a harmonized approach to human biomonitoring for the entire European Region.

3. Meeting participants recommended using regular cross-sectional national HBM surveys to characterize baseline exposure and temporal trends (recommended frequency of surveys is once per five years). The proposed survey should have two arms to characterize exposure in the general population and in populations living in contaminated areas (exposure hot spots).

4. Meeting participants approved the previously developed design for the general population survey, which involves recruiting mothers at randomly selected maternities to characterize prenatal exposures. After considering alternative designs for the exposure hot spots survey, meeting participants also agreed on a similar maternity-based approach.

5. Meeting participants recommended using non-invasive biomarkers for the proposed survey: maternal urine, maternal hair, and cord blood.

6. Meeting participants evaluated and prioritized biomarkers of exposure to pollutants for the general population arm and for the high exposure arm. Follow-up activities shall involve finalizing the list of biomarkers, developing standard operating procedures, questionnaires for assessing exposure sources for each pollutant and survey protocols, identifying reference laboratories and establishing a network of collaborating institutions that would provide technical support to the proposed survey.

7. Three is a strong local interest in a WHO-coordinated HBM survey in Sicily. It is envisioned that this survey would be based on maternities, and include two arms to characterize exposure in contaminated areas and in the general population (the latter will provide the basis of comparison).

8. Meeting participants acknowledged that, in contaminated areas with complex chemical mixtures and exposure patterns, biomarkers of health effects may provide valuable additional information characterizing combined effects of exposure to multiple pollutants. However, interpreting health effect biomarker data remains a challenging task, which makes these biomarkers more suitable for research projects. WHO will focus its limited resources on providing standardized methodologies and technical support for well-established biomarkers of exposure to specific pollutants. It was also recommended to include clinical data on the general health status of the study participants if these data are available and easily accessible.

9. Meeting participants recommended conducting human biomonitoring in combination with environmental monitoring and food contamination monitoring. This would enable characterizing the contributions of specific exposure routes to the body burden of pollutants.

10. It was stressed that the existing information on environmental contamination in Sicily justifies policy actions aimed at reducing population exposure. The Parma Declaration, which was co-signed by the Italian ministers of Health and the Environment, includes time-bound commitments to eliminate exposure to harmful environmental chemicals. Therefore, the proposed HBM survey in contaminated areas shall be used to monitor progress towards goals set in Parma, and to fine-tune targeted interventions when necessary.

Annex 1. List of participants

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Annex 2. Working group assignments

Working group 1. General population survey in maternity hospitals: selecting additional biomarkers for assessing perinatal exposure to environmental toxicants	**Working group 2. Selection of biomarkers and survey design for exposure hot spots and heavily exposed population subgroups (*Italian interpretation*)**
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	Franco, Giacinto
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	Russo, Alfio

Note: Andrey Egorov participated in both working groups.

Annex 3. Evaluation of chemicals and biomarkers of exposure for the general population

Biomarker	**Importance:** Prevalence of exposure, health hazards, public health impact and concerns from the public	**Justification:** The proposed biomarker s • Reflect the early life exposure to the pollutant • Predicts later health effects	**Interpreta-tion:** Health based assessment data are available (based on scientific literature or national standards)	**Applicability to policy-making:** • Sources can be or have been identified • Risk management measures are available	**Validity and feasibility:** • Biomarker is valid • Realistic in terms of required laboratory capabilities and costs • Human and technical capacities are available or can developed easily • Availability of SOPs for pre analytical and analytical phases • Sample quantity required is realistic and feasible	**Acceptability:** • Effective PAC and willingness of people to participate • Non-invasive and safe to collect	**Comments and justification**
HAIR (MATERNAL)							
Total mercury	XXX	XXX	XXX	XXX	XXX	XXX	Biomarker of exposure to methylmercury. Most relevant for costal countries
Arsenic	XXX	XXX	X	XXX	XXX	XXX	Area based importance
URINE (MATERNAL)							
Total mercury	XX	XX	X	XX	XXX	XXX	Biomarker of exposure to elemental mercury. Relevant for countries which still use dental amalgam. Helpful for monitoring effects of the Minamata Global treaty.
Cadmium	XXX	XXX	XX	XX	XXX	XXX	
Metabolites of phthalates	XXX	XX	XXX	XXX	X	XXX	Justification: predicts later health effects. Validity: not easy to measure – analytical training required
Bisphenol A	XX	XX	XXX	XXX	X	XXX	Justification: linked with health effects later in life. Validity: Difficult to measure - analytical training required

Biomarker	**Importance:** Prevalence of exposure, health hazards, public health impact and concerns from the public	**Justification:** The proposed biomarker s • Reflect the early life exposure to the pollutant • Predicts later health effects	**Interpreta-tion:** Health based assessment data are available (based on scientific literature or national standards)	**Applicability to policy-making:** • Sources can be or have been identified • Risk management measures are available	**Validity and feasibility:** • Biomarker is valid • Realistic in terms of required laboratory capabilities and costs • Human and technical capacities are available or can developed easily • Availability of SOPs for pre analytical and analytical phases • Sample quantity required is realistic and feasible	**Acceptability:** • Effective PAC and willingness of people to participate • Non-invasive and safe to collect	**Comments and justification**
Parabens	XX	X	X	X	X	XXX	Personal care products: sunscreens, antimicrobial agents, preservatives. Scientific concerns about exposure in children and mothers. Gaining recognition.
Non-persistent pesticides	XXX	XXX	XX	XXX	X	XXX	Validity: Not so easy to measure – analytical training required
PAH metabolites	XXX	XX	X	XXX	XX	XXX	Validity: Not so easy to measure – analytical training required
Pentachloro-phenol	XX	XX	XXX	XXX	XXX	XXX	
Cotinine	XXX	XXX	XX	XXX	XXX	XXX	
CORD BLOOD							
Lead	XXX	XXX	XXX	XXX	XXX	XX	Also finger stick can be used
Lipophilic POPs (except dioxins and dioxin-like PCBs)	XXX	XXX	XXX	XX	XXX	XX	Very appropriate for a hotspot situation
PCDDs/PCDFs (dioxins) and dioxin-like PCBs	XXX	XXX	XXX	XXX	X	XX	Validity: complex, costly and specialized analysis

Biomarker	**Importance:** Prevalence of exposure, health hazards, public health impact and concerns from the public	**Justification:** The proposed biomarker s • Reflect the early life exposure to the pollutant • Predicts later health effects	**Interpreta-tion:** Health based assessment data are available (based on scientific literature or national standards)	**Applicability to policy-making:** • Sources can be or have been identified • Risk management measures are available	**Validity and feasibility:** • Biomarker is valid • Realistic in terms of required laboratory capabilities and costs • Human and technical capacities are available or can developed easily • Availability of SOPs for pre analytical and analytical phases • Sample quantity required is realistic and feasible	**Acceptability:** • Effective PAC and willingness of people to participate • Non-invasive and safe to collect	**Comments and justification**
Perfluorinated compounds (PFOS/PFOA)	XX	XX	XX	X	X	XX	PFOS is in the Stockholm Convention; Area based importance, can be hotspot related.

Note: The number of crosses reflects the score for a specific criterion: one cross (X) means low score, two crosses (XX) mean medium score and three crosses (XXX) mean high score.

Annex 4. Evaluation of chemicals and biomarkers for survey in exposure hot spots

Substance	Biomarker (if different from the substance)	Relevance	Health effects	Matrices	Health-based gui-dance value	Cost of laboratory test	Sample volume	Comments and justification
Inorganic								
Arsenic		high	Genotoxicity, kidney damage, cancer	Urine, cord blood	yes	€<50	small	Difficult to distinguish between natural and industrial origin. Important for specific areas due to local geochemistry.
Cobalt		medium	Genotoxicity	Urine	yes	€<50	small	Difficult to interpret due to strong inter-individual variability.
Hexavalent chromium	Total chromium	high	Genotoxicity, carcinogen	Urine, cord blood	no	€<20 for urine; € 50 for blood	small	Biomarker is not sufficiently well established. Elevated levels only expected in areas with cement plants.
Methylmercury	Total mercury	high	Neurotoxicity, kidney damage	Cord blood, hair	yes	€<20	small	Mostly methylmercury in hair; also test urine if exposure to elemental mercury is an issue.
Elemental and inorganic mercury	Total mercury	high	Neurotoxicity, kidney damage	Urine	yes	€<20	small	
Lead		high	Geno-, Immuno-, neuro-toxicity, endocrine disruption	Cord blood, blood	yes	€ 20	small	
Copper		medium	Essential element; toxic at excess doses	Urine	no	€ 20	small	Difficult to interpret due to strong inter-individual variability
Cadmium		high	Carcinogenicity, endocrine disruption, placenta damage	Urine	yes	€ 20	small	Does not cross the placenta barrier
Nickel		medium	Genotoxicity, allergies	Urine, cord blood	no	€<40	small	
Vanadium		low-medium	Genotoxicity	Urine, cord blood	no	€<40	small	Poorly defined health effects

Substance	Biomarker (if different from the substance)	Relevance	Health effects	Matrices	Health-based gui-dance value	Cost of laboratory test	Sample volume	Comments and justification
Organic								
Benzene, toluene, ethylbenzene, xylenes (BTEX)	Unchanged compounds and metabolites (T,t-muconic acid)	medium	Carcinogenicity	Exhaled air, urine	no	€ 30 or more	small	Short half life; need to collect samples shortly after exposure; indicator is relevant to high exposure areas or subgroups.
Polyaromatic hydrocarbons (PAHs)	1-OH pyrene; metabolites	medium	Genotoxicity (DNA adducts), carcinogenicity	Urine	no	€ 100	small	Short half-life; Marker of acute (recent) exposure
Vinyl chloride		low	Endocrine disruption			€ 30 or more		Occupational exposure
HCB and marker PCBs (non dioxin-like)		medium	Endocrine disruption	Breast milk, cord blood	no	€ 100 or more	5 mL blood	HCB – by-product/residue from polyethylene production Elevated levels identified
PCDDs/PCDFs (dioxins) and dioxin-like PCBs		high	Endocrine disruption, carcinogenicity	Breast milk, cord blood	yes	€ 500 for GS-MS analysis	> 5 mL blood	GC-MS analysis requires substantial sample volume. CALUX AhR assay can be used for screening.
Tetra- and trichloroethylene (PER and TRI)	No universally accepted marker	low	Developmental toxicity and teratogenicity	Urine	no	€ 30 or more		Short half-life
1,2-dichloroethane (DCE)	No universally accepted marker	low	Health effects poorly defined	Urine, blood	no	€ 30 or more		Short half-life

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