



**Human biomonitoring survey  
assessment of prenatal exposures to mercury  
using biomarkers in cord blood, maternal urine and hair**

**The first survey protocol**

2017

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## 1. Background

Mercury is recognized by WHO as one of the top 10 chemicals or groups of chemicals of major public health concern. Its toxicity to human health has long been known, and the toxic effects of different forms of mercury extensively studied (1).

Elemental and methylmercury are toxic to the central and peripheral nervous systems. The inhalation of mercury vapour can produce harmful effects on the nervous, digestive and immune systems, lungs and kidneys, and may be fatal. The inorganic salts of mercury are corrosive to the skin, eyes and gastrointestinal tract, and may induce kidney toxicity if ingested.

All humans are exposed to some level of mercury. Most people are exposed to low levels, often through chronic exposure (continuous or intermittent long-term contact). However, some people are exposed to high levels of mercury that can cause acute poisonings.

Fetuses are most susceptible to mercury. Methylmercury exposure in the womb can result from a mother's consumption of contaminated fish and shellfish. It can adversely affect a baby's growing and developing brain and nervous system, which leads to disorders of cognitive functions, memory, attention, language, and fine motor and visual-spatial skills later in life (2, 3).

Human biomonitoring (HBM) is an effective and reliable tool to assess cumulative exposure to environmental pollutants and is an essential element in a strategy aiming to integrate health and environmental policies. Biomonitoring data directly reflect the total body burden (or biological effect) resulting from all routes of exposure, and inter-individual variability in exposure levels, metabolism and excretion rates. Determination of mercury levels in human tissues, such as hair, blood, nails, milk and urine, is recommended for assessing population exposure to mercury and its compounds (4). The results of biomonitoring-based surveillance can be used for planning and assessing the effectiveness of risk prevention measures.

To protect human health and the environment from anthropogenic emissions and releases of mercury and mercury compounds the Minamata Convention was adopted as the global legal instrument (5). According to the Convention, the health sector is responsible for identification of population groups exposed to mercury and its compounds. HBM can be used by national governments to assess exposure to mercury for identification of populations at risks.

Since the period of in-utero development is the most vulnerable stage, in terms of long-term adverse neurodevelopmental effects of mercury, characterization of prenatal exposure is critical for evaluating the public health impact of mercury, and for assessing the public health benefits of reducing exposure. A harmonized approach is necessary to ensure provision of reliable and comparable results at national, regional and global level.

The basic intent of this document is to provide guidance for countries in constructing a national protocol for the monitoring of human exposure to mercury. This document was developed based on the outcomes of an international experts meeting held in Bonn, Germany on 24–25 June 2015 (6). A number of other meetings and expert discussions provided important input to this methodology development.

The protocol comprises recommendations on survey design, recruitment and fieldwork, dealing with biological materials, data management and communication, and ethical considerations.

## 1.1. Scientific evidence and international consultations

This document is based on scientific information on mercury biomonitoring and health effects collected by WHO, including the following: *Guidance for identifying populations at risk from mercury exposure* (2008)(4); *Mercury and Health* fact sheet (2016)(1); *Mercury exposure and health impacts among individuals in the artisanal and small-scale gold mining community* (2014)(7); documents on the work of WHO in coordinating the development of standardized protocols for HBM surveys on mercury, and planning pilot testing in volunteer countries, under the mandate of the Parma Declaration commitments to reduce early life exposure to environmental pollutants (8); and the *Report on information on harmonized systems for measuring mercury body burden* (2011)(9).

In April 2012, at a meeting in Catania, Italy, WHO experts discussed the overall approach, biological matrices and indicators for assessment of prenatal exposure to mercury for development of a harmonized approach to mercury HBM (10). Women who had just delivered a child were agreed as the target population, and scalp hair, cord blood and urine as the matrices for assessment of prenatal exposure to mercury during last three months of pregnancy. (10). The approach proposed by the experts was agreed by the representatives of WHO European Region Member States at the Second Extraordinary Meeting of the European Environment and Health Task Force (EHTF), The Hague, Netherlands, 31 May–1 June 2012 (11).

The discussion continued during a number of forums including: the special session “Protecting human health from negative impact of mercury: from science to policy” at the International Conference on Mercury as a Global Pollutant (14–19 June 2015, Jeju, Korea)(12); the session “Human biomonitoring as an instrument for assessment of exposure to mercury” at the meeting of representatives of the European Member States “Health sector involvement in the implementation of the Minamata Convention” (24–25 June 2015, Bonn, Germany)(6); the international technical experts workshop “Harmonized approach to biomonitoring of human exposure to mercury” (26 June 2015, Bonn, Germany) (unpublished minutes); and during the session “Exposure assessment and health effects” organized by the National Institute for Minamata Disease, Japan, WHO Collaborating Centre for Studies on the Health Effects of Mercury Compounds at the Fifth Conference on Prenatal Programming and Toxicity (14–16 November 2016, Kitakyushu, Japan)(13).

International Ethical Guidelines for Health-related Research Involving Humans (2016) prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with WHO laid the basis for the ethical requirements included in the protocol (14).

## 2. Aims and approach of the survey

The primary objectives of the survey are to provide the data needed for the development of a global mercury monitoring plan, and baseline data on prenatal exposure to mercury in different population groups. The survey implementation will:

- extend the knowledge on baseline levels and sources of human exposure to mercury;
- characterize the level and distribution of prenatal exposure in different population groups in participating countries, and particularly in hotspots (it is recognized that the survey can be used in a wide range of countries, with different food consumption patterns and environmental levels of mercury; however, it is not primarily intended to compare levels of mercury in people among countries, but rather to serve as an instrument to examine exposure levels within countries over time);

- identify risk factors for exposure from different sources of mercury;
- assist countries in the implementation of the Minamata Convention and development of effective measures to prevent the negative impacts of mercury on human health, and especially in vulnerable groups;
- provide analytical tools to monitor progress towards implementation of specific goals of the Minamata Convention (the WHO methodology involves assessment of exposure in a set of participants at a certain moment in time; such a cross-sectional survey is expected to be repeated at regular intervals, e.g. every five years).

The objective of this protocol is to provide a uniform framework for all activities and tasks associated with the collection, analysis, assessment and reporting on prenatal exposure to mercury. This has to be applied consistently in all participating countries of the WHO regions to ensure comparability of data. Due to the differences in governance, culture and ethics, a rigid scheme of mandatory operational procedures to completely fit all participating countries does not seem optimal. Participating countries might need to adjust certain elements of the core WHO protocol to their realities, to choose only a subset of the proposed biomarkers, which are most important in the national context, or to add other biomarkers to address national priorities. However, participating countries are encouraged to adhere to the protocol as closely as possible.

Through expert recommendations and technical meetings, WHO has developed the following approach:

- Recruitment will be conducted during antenatal visits and exceptionally at maternity hospitals.
- Participants will be enrolled using a set of defined inclusion and exclusion criteria (legal adults, living in the catchment area of the hospital, live birth, etc.).
- A standardized questionnaire will be administered to participants to assess potential sources of exposure.
- The survey will use non-invasive sampling only (maternal hair, urine and cord blood); standard operating procedures (SOPs) for no risk sampling are provided by WHO.
- National surveys will involve a capacity-building component, to enable analysis of samples in domestic laboratories; methodological support will be provided by WHO, its temporary advisers and reference laboratories.
- Proficiency test and duplicate quality control samples will be analysed in reference laboratories, to ensure comparability of the results from different countries.

The protocol has been developed to be applicable globally for assessment of population exposure to mercury.

### 3. General principles

The following underlying principles should be considered when applying this protocol to developing a national protocol for monitoring of exposure to mercury:

- Sampling of biological material (hair, cord blood and urine) should not harm or pose an undue burden on recruited women.
- Safeguarding the confidentiality of information should be assured.
- Ethical standards, including prior informed consent, should be respected.
- The protocol should be practical, feasible and sustainable.
- Emphasis should be placed on proficiency.

- Quality assurance of results should be independently confirmed.

### 3.1. Roles and responsibilities of WHO and participating countries

Both WHO and participating countries have roles and responsibilities in the application of the protocol.

The role of WHO in the protocol application is:

- to submit and get approval of the protocol from the WHO Research Ethics Review Committee (ERC) and to communicate modifications of national protocols to the ERC, requesting approval before their implementation;
- to organize a training for national coordinators and laboratory analysts on the survey design and implementation;
- to develop and provide participating countries with training materials and SOPs for sampling of biological material, mercury analysis, and creation of national databases, as well as to develop and provide an eligibility screening form and a questionnaire to be completed by the survey participants;
- as an owner of data collected in the national pilot surveys, to gather the data from countries and to store them in a consolidated global database; to analyse the data gathered through the survey implementation, and to report on the level and distribution of the exposure to mercury at national, regional and global scales to interested governmental and nongovernmental stakeholders (including experts and academia) at an international level;
- to provide technical assistance to countries, if necessary, including in implementation of the survey, interpretation of results and risk communication;
- to update the protocol on a global level before each round of mercury HBM, if necessary;
- to coordinate the quality control process to ensure the quality of laboratory analysis of mercury in participating countries.

The role of participating countries in the protocol application is:

- to adapt the WHO protocol to national realities and to obtain approval from national ethics committees;
- to communicate any modifications in the WHO protocol to WHO before the survey implementation;
- to fully comply with the protocol principles when implementing the mercury HBM survey;
- to train the field staff involved in the survey implementation including, but not limited to, interviewers, maternity hospital staff, those responsible for collecting biological samples, those responsible for the storage and transportation of biological samples, laboratory analysts, those responsible for data handling and database creation, etc.;
- to collect data on exposure to mercury in target population groups; to fully comply with WHO SOPs on analysis of mercury in human scalp hair, cord blood and urine including non-invasive sampling procedures;
- as an owner of the national data, to collect and store the data in a national database;
- to analyse national data on the level and distribution of exposure to mercury and to report the data to interested governmental and nongovernmental stakeholders at the national level;
- to report on the application of the protocol and to submit the national protocol to WHO;
- to report to WHO on results obtained in the survey, conducted according to the WHO protocol.

## 4. Developing a national protocol

The guidelines are intended to assist the national coordinator in developing a national protocol to meet the aims of the survey. The national coordinator should be responsible for overall planning and implementation of the survey in the country, assisted by the appropriately trained field and laboratory staff. In particular, the national coordinator should assure that the survey meets all national ethical requirements for studies involving human subjects. If the national coordinator does decide to modify the national protocol, any changes should be communicated to the WHO team, who will communicate them in good time to the WHO ERC, requesting approval of the modifications before they can be implemented. Any deviations from the protocol may unintentionally result in the reduced reliability or comparability of data at regional and/or global level. The national coordinators are encouraged to follow the WHO protocol as strictly as possible.

## 5. Survey design

The survey involves mothers of newborn children recruited during antenatal visits, or at maternity wards if it was not possible to recruit during antenatal visits. The randomized clustered design of the survey allows assessment of prenatal exposure to mercury in the general population and in exposure hotspots, such as areas contaminated by industrial emissions or areas with high levels of consumption of contaminated foods (for example, fishing communities for methylmercury exposure). It is very important to involve the community and local representatives in the survey from an early stage, so as to ensure support for the survey and proper communication of healthy behavioural habits to pregnant women to prevent avoidable exposure, if necessary. The proposed community involvement strategy is in Annex 5.

The survey of general population exposure to mercury involves representative samples of women at randomly selected maternity hospitals. Depending on the country size and variability in conditions, the survey design can involve spatial stratification, which involves random selection of maternity hospitals within predefined administrative or geographic regions.

The survey of high-exposure populations in hotspots involves samples of women who are known or suspected to have high levels of exposure to mercury and/or its compounds.

This document provides a detailed description and sample size justification for the general population and high-exposure surveys. Countries, which have geographically defined populations with high levels of exposure to mercury are advised to conduct the high-exposure survey and the general population survey (in order to have a national basis for comparison, or to develop “reference values”, defined as typical exposure levels in the general population of the country). A detailed approach for selecting maternity hospitals in high-exposure areas, and criteria for recruiting highly exposed individuals should take into account local conditions.

The proposed survey design includes a limited set of biomarkers. Affordability and feasibility were important biomarker selection criteria as the survey is intended to be applicable in the majority of countries.

The minimum recommended sample size for the general population survey is defined below, based on the experience of the European project COPHES/DEMOCOPHES, and selected national HBM surveys. Individual countries might opt for larger sample sizes, as well as for including additional biomarkers and sample matrices.

## 5.1. Target population

The target population is mothers who have just delivered a child.

All efforts should be made to gain consent from women during antenatal care visits. In cases where women do not have an antenatal care visit during the two weeks before delivery, they can be contacted in maternity hospitals shortly before or after the birth.<sup>1</sup> The following criteria should be applied to determine whether a woman can be recruited and consent given at the time of delivery:

- low level of stress (no fear at childbirth)
- normal development of the childbirth process
- satisfactory physiological condition of the mother
- satisfactory physiological condition of the fetus
- no severe pain
- no emergency signs (15).

Survey interviewers should briefly describe the objectives of the survey and ask the women if they are interested in participating. If a positive answer is provided, the interviewer, using an eligibility screening form (Annex 1) should conduct a brief interview to check the eligibility of the candidate. If eligibility is confirmed, the interviewer should explain the purpose of the survey, specific activities and risks, and present the informed consent form (Annex 2). If consent is provided, the interviewer should then collect exposure information using the standardized questionnaire (Annex 3), obtain medical and anthropometrical data from the medical records, and collect a sample of scalp hair (following relevant SOPs). Samples of urine and cord blood should be collected by the medical personnel in due course, depending on specific rules and procedures in the maternity ward (following relevant SOPs).

Since the survey aims to characterize prenatal exposure to mercury, maternity hospitals are the preferred recruitment venue due to the availability of medical records and because they may be the easiest place for sampling hair, cord blood and urine, especially in those countries where mothers spend several days in hospital after delivery. However, collection of hair and urine samples, and interviews can also be conducted in other settings, such as at home within two weeks after the delivery.

It is important to collect all relevant information on factors that may affect exposure to mercury (e.g. age, nutritional habits, occupation, socioeconomic status, education and use of chemicals and/or mercury-containing equipment at home).

## 5.2. Selection of hospitals and number of participating mothers

### 5.2.1. Number of participants in the general population survey

The International Federation of Clinical Chemistry (IFCC), endorsed by the International Union of Pure and Applied Chemistry (IUPAC), Clinical Chemistry Division, recommends the measurement of biomarker values in at least 120 individuals per group for the determination of baseline values (hereafter called “reference values”). The reference interval is defined as the 0.95 central interfractile interval, or the interval between the 2.5 and the 97.5 percentiles of the distribution (16).

<sup>1</sup> No more than two weeks after delivery.

Clustered design reduces the cost and improves logistical feasibility but requires a larger sample size due to the loss of statistical efficiency. A factor of 2 is used to increase the IFCC recommended sample size of 120 to 240 participants, based on the existing literature (17). This sample size estimate takes into account the clustered design of the proposed survey (samples from the same maternity hospitals are not statistically independent). It is recommended that samples are taken from 10 additional participants in case some participants drop out of the survey. Thus, 250 women is a minimum recommended sample size for each cross-sectional HBM survey in the general population.<sup>2</sup> Based on the data on variability in mercury levels in hair samples in women from Flanders (18), a sample size of 250 women can be assumed to be large enough to demonstrate a 27% change in the geometric mean mercury level between a baseline survey and follow-up cross-sectional surveys in a different set of women in the same country, at the conventional level of statistical significance and with 80% study power. This effect size is relevant in view of differences between countries and temporal changes in mercury levels already reported in the literature.

It is recommended that at least 10 maternity hospitals be selected for the general population survey. It is also recommended that an equal number of mothers are selected in each maternity hospital, for example, 25 mothers each from 10 randomly selected maternity hospitals.

### 5.2.2. Number of participants in the high-exposure survey

It is feasible to use the above approach to recruit pregnant women in high mercury exposure areas, where the population is high enough and the number of births is sufficient. In small contaminated areas with a small number of annual births, a survey involving women in maternity hospitals may require a longer enrolment period.

As with the general population survey, it is recommended that the statistical power be calculated to determine the minimum number of participants that would allow detection of statistically significant differences between the hotspot population and the general population or reference values. If power calculations are not possible, the number of participants in the high-exposure survey should be as close as possible to the number in the general population survey, for a stronger statistical analysis of the results.

### 5.2.3. Identification of high-exposure areas

For mercury exposure, proximity to the sea or other substantial water bodies can be used as a criterion for site selection. In countries having access to the sea, it can generally be assumed that fish consumption and exposure to methylmercury are higher close to the sea. In other countries, regions with large fresh water bodies with substantial fisheries may exist.

Emissions of inorganic mercury from industrial sources are another relevant consideration for the identification of exposure hotspots. The participating countries should choose locations for the high-exposure survey using appropriate information sources. General guidance is provided by the United Nations Environment Programme (UNEP) and WHO (4).

For the high-exposure survey, delimitation of the area of industrial hotspots or contaminated areas should take the following factors into account:

- size, location and other pertinent characteristics of active pollution sources of concern;

<sup>2</sup> The sample size calculation can be changed for other specified populations when the data on variability in mercury level in hair samples become available.

- historical contamination of the area (presence of polluting activities in the past);
- concentrations of mercury in environmental samples (air, soil, surface water or sediment, groundwater, locally produced food) exceeding health-based guidance values and/or high consumption of contaminated local food products;
- health complaints by inhabitants or documented elevated rates of conditions related to mercury;
- meteorological and geographical characteristics of the area (e.g. wind direction, topography) in relation to the source of emissions.

If no environmental measurements are available, validated dispersion models utilizing information from geographical and meteorological conditions can be used to imply a high-exposure scenario (e.g. downwind from an air polluting facility; downstream (or downgrade) from a hazardous waste disposal site).

The area of interest should be carefully selected.

### 5.3. Criteria for enrollment of mothers

With regard to the selection of potential participants, the recommended inclusion criteria are as follows:

- women at least 18 years of age (legally adult);
- live birth;
- normal term delivery (at least 37 weeks of pregnancy);
- singleton pregnancy;
- living in the catchment area of the maternity hospital (general population) or in the selected survey area (high-exposure group) for the last three years and for most of the time during the last three months of pregnancy (spending not more than two weeks outside the area);
- hair at least 3 cm in length on the back of the head.

Immigrants should not be excluded as long as they have sufficient language ability in the interview language(s) and meet the other eligibility criteria.

A potential occupational exposure will not be considered an exclusion criterion.

The recommended exclusion criteria are as follows:

- women younger than 18 years old;
- delivery before 37 weeks of pregnancy;
- still-birth or delivery of a lifeless child;
- not a singleton pregnancy (twins, triplets, etc.);
- living in the catchment area of the maternity hospital or in the selected high-exposure area for less than three years before delivery;
- living outside the selected high-exposure area for more than two weeks during last three months of pregnancy;
- having hair shorter than 3 cm on the back of the head;
- not having sufficient language skills to understand information about the survey, the informed consent and other relevant information;
- women with mental disorders.

Individual countries may develop additional exclusion criteria:

- women with hepatitis C, malaria, HIV and other contagious conditions, according to the relevant national regulations;
- women having lacerations during child delivery;
- women having complicated pregnancy.

However, it is recommended that the above list be followed as closely as possible to ensure the international comparability of data.

#### 5.4. Project follow-up: medical surveillance of people with high mercury concentrations

The main objective of the HBM survey is to generate data on the levels and distribution of prenatal exposure to mercury, in connection with different potential sources of mercury exposure, and to develop a global plan for mercury monitoring.

Elimination of mercury sources is the most important follow-up measure to reduce exposure and the associated health risks. In order to reduce exposure from industrial or environmental sources, the authorized governmental regulatory authorities, for example environmental protection agencies, need to be involved. For the reduction of exposure to methylmercury, public and individual advice, including dietary recommendations and guidance, based on the available scientific knowledge (19), should be made available to exposed groups. Monitoring of fish contamination with mercury should be established to control potential exposure.

The health impacts of mercury depend on its form and the level of exposure. Exposure to mercury vapours can cause acute and chronic kidney disorder. People chronically exposed to high concentrations of inorganic and organic mercury develop neurological symptoms.

If a high level of mercury is observed the survey coordinator should ensure that:

- for individuals with a high level of mercury in their urine, their doctors are contacted and a check-up of renal system functions is advised and arranged upon the woman's request;
- for individuals with a high level of mercury in their hair and blood, their doctors are contacted and a visit to a neurologist is advised and arranged upon the woman's request.

However, it is unlikely that such clinical cases would be detected through the HBM survey.

An individual medical follow-up should be considered on a case-by-case basis, only for mothers with a confirmed high level of mercury. Additional investigation of potential sources of exposure should precede risk communication and planning of protective measures.

Neurological and cognitive development surveillance could be considered for children delivered by mothers with a very high concentration of mercury, within the first control at three months from delivery. It could be framed within the usual surveillance programme for newborns.

The national survey coordinator is responsible for contacting mothers with high mercury concentration and/or their doctors and advising on neurological examination of a child.

## 6. Recruitment and fieldwork

The processes of recruitment and fieldwork are described briefly in this section; to understand the processes in detail it is essential to also consider the respective SOPs (Annex 4).

## 6.1. Fieldwork management

Fieldwork is the responsibility of the participating country. Each country decides on the organization of the fieldwork, including the following:

- using the standardized methodological documents provided by WHO as a starting point to prepare the SOPs, fieldwork manual and other documentation in a national language;
- training field personnel and supervising their work;
- selecting maternity hospitals;
- obtaining necessary permissions from regional and local authorities;
- liaising with the local community, identifying and engaging local representatives to promote the survey;
- developing information leaflets for maternity hospitals and for survey participants;
- informing the recruited women, administering informed consent and conducting interviews;
- collecting, storing and shipping samples to the respective laboratories;
- entering the data into a data file and performing preliminary data cleaning;
- analysing national data or submitting the data to a WHO-affiliated data analysis centre;
- communicating the results of the survey to the participants and national public health authorities.

Participating countries can deploy experienced fieldwork personnel or ask the maternity hospitals to perform the work. If the latter option is selected, regular personnel of maternity wards will likely perform the survey tasks in addition to their normal duties, which may adversely affect their performance. To ensure the adherence of hospital staff to the survey protocol, sufficient training, quality assurance and quality control measures must be in place.

## 6.2. Timing of the survey

Exposure patterns, such as fish consumption, may vary by the season. To avoid a seasonal bias, sampling should either take place over the course of an entire year or during a specified season. The former approach may not be feasible for this relatively small survey involving a limited number of maternity hospitals. Therefore, it is advisable to conduct all data collection activities in a specific season.

In the case of a comparison study, sampling in the general population and in the high-exposure group should take place in the same season to allow for the comparison of results.

It is envisioned that this survey will be repeated at regular intervals to monitor trends in exposure. Combining data from several data collection rounds would also increase the power of the statistical analysis of exposure determinants. Follow-up surveys in the same country should use the same schedule (be conducted in the same season) to ensure data comparability. The baseline survey may produce important information on exposures and lead to policy interventions aiming at reducing exposures. Since new policy measures would require substantial time to take effect, conducting a follow-up survey is recommended.

### 6.3. Recruitment, interview, medical data collection and biological sampling

The recruitment of participants starts with distribution of an information leaflet. All efforts should be made to provide information about the survey to women during antenatal visits, and to make the information leaflets available for women to take home. This would give time to reflect on taking part in the study and would reduce the burden of consent process just before or after delivery. The leaflet can also be provided before or shortly after delivery.

The leaflet should give information on the survey's objectives, its scope, benefits for the women themselves, and the communication of the results. It should also provide information on the inclusion and exclusion criteria.

The interviewers will need to be present at the maternity hospital. These could be either dedicated survey staff or trained employees of the hospital.

A female fieldworker might generally be a better choice to contact women shortly after delivery. The fieldworker should introduce themselves, and do the following:

- handover the information leaflet (unless it was made available to the woman during one of her antenatal visits), briefly describe the survey and ask whether the woman is interested in participating;
- conduct the screening interview and administer the informed consent form;
- collect the data on exposure, socioeconomic status, etc. using the questionnaire (it is preferable to do this in an interview rather than to leave the questionnaire with the woman for self-administration);
- collect a hair sample;
- arrange for the collection of urine and cord blood samples, strictly following the procedure recommended by WHO for sampling (note: if the recruitment is conducted after the delivery, it may be necessary to collect cord blood and urine samples prior to recruitment; if the woman is not eligible or does not agree to participate, the collected biological samples should be immediately discarded; samples must not be delivered to the analytical laboratory and analysed prior to obtaining informed consent; samples will be collected in the hospital and stored before shipment to an analytical laboratory; the national coordinator of the survey should ensure that only samples from consenting women are shipped to the analytical laboratory for an analysis);
- obtain medical data on the woman and her child, including ICD-10 codes of diseases and conditions during pregnancy and delivery: nephropathies (N00-N16); polyneuropathy and encephalopathy (G50-G99); complications of labour and delivery (O60-O75) and delivery (O80-O84); and basic anthropometrical measurements of the infant (weight and height);

such information could be used in the further analysis of the data on mercury concentration in biological matrices and the questionnaire data, and to facilitate formulation of exposure- and risk-reduction recommendations.

#### 6.4. Questionnaire

All survey forms will have to be translated into a national language or another principal language of the area. The participating countries may also need to adapt the questionnaire to the local cultural attitudes, lifestyle patterns and education level of the participants. It is recommended that a computerized system be used to assure correct transfer of the questionnaire information into the data management system.

Preliminary questionnaire versions in national languages will have to be pilot tested prior to the main survey. As pilot testing is an essential part of developing the questionnaires and national survey protocols, it should be conducted as early as possible.

Screening interviews and obtaining consent (annexes 1 and 2) have to be done prior to administering the questionnaire.

The main questionnaire (Annex 3) can be used to interview the participants at the time of hair sampling. Completion of this questionnaire takes about 20 minutes, if administered by an interviewer. Section A comprises personal information, anthropometric data, ethnic origin, educational level of the family and socioeconomic status. Section B focuses on potential exposure pathways to mercury, and is divided into four parts: (1) occupational exposure, (2) exposure in the residential environment, (3) personal care and lifestyle (e.g. smoking behaviour), and (4) food and beverage consumption.

Personal interviews conducted by trained interviewers are the most commonly used method to collect data on behavioural and nutritional exposure factors. However, this method has a tendency to under-report socially undesirable behaviours (for example smoking). This is known as the “social desirability” bias. On the other hand, interviews have the advantage over self-administered surveys that any misunderstanding can be resolved immediately, which leads to higher data completeness and quality. Training of the interviewers is essential to ensure that the interviews are conducted in a standardized way. The training of interviewers has been shown to improve their performance, particularly in reducing under-reporting of pertinent information.

The participating country is in charge of generating a file with data from the questionnaire and assuring data quality using a template developed by WHO. National survey coordinators are responsible for developing SOPs for data handling and data quality control procedures, and for conducting pilot testing and evaluation of these procedures prior the beginning of a national survey.

The national coordinator should retain questionnaires from all the respondents until the end of the study and they should be kept for future reference. Retention of all records should conform to national requirements and international norms concerning confidentiality. The national coordinator should complete a summary of information form about mothers donating samples. They should also provide scanned copies of the questionnaires to WHO upon request.

#### 6.5. Training of fieldwork staff

To ensure standardization of processes, the training must be strategic and organized as far in advance as possible. Training should involve a range of fieldworkers engaged in survey implementation, including interviewers, hospital staff, those responsible for collecting samples, those responsible for sample transportation and laboratory analysts.

A train-the-trainer approach may be the most cost-effective, which utilizes the exchange of knowledge and experience to minimize costs.

Establishing a technical help desk during the survey, starting from the moment the general protocol is adapted to the national situation, might increase consistency and promote adherence to survey protocols. The help desk could be available through a central website supporting the survey. It should provide answers that have been formulated by experts in the field in a timely manner.

If trained hospital personnel conduct interviews in addition to their regular duties, then additional motivation might be needed.

It is envisioned that the survey will involve reference laboratories. Technical assistance in the form of training of laboratory technicians will be provided to individual countries when necessary upon their request.

## 6.6. Quality control measures

Quality control with respect to fieldwork and training of the project staff should be considered by the national coordinator. It is in the interest of all partners involved that the fieldwork is controlled and checked. To avoid errors, it is recommended that checklists including all important steps of the procedures are used. In addition, field visits by supervisors and from experts not directly involved in fieldwork are recommended.

## 7. Biological material

### 7.1. Overview of biomarkers for assessment of exposure to mercury

#### ***Justification for the selection of biomarkers of prenatal exposure to organic and inorganic mercury***

In population-based HBM surveys, non-invasive matrices are preferred for assessing exposure to mercury in order to maximize the response rate. The selection of biological matrices for assessing human exposure depends on the mercury compounds (organic vs. inorganic), exposure pattern (chronic or acute) and time of sampling after the exposure (4).

#### ***Maternal scalp hair***

Exposure to methylmercury is reflected in the level of mercury in scalp hair (4). Once incorporated into hair, mercury does not return to the blood, providing a good long-term marker of exposure. Mercury in maternal hair (close to the scalp) is a proxy of fetal mercury exposure (20). Mercury concentration in 3 cm of scalp hair taken close to the scalp shortly after delivery reflects the exposure of the fetus during the last three months of pregnancy. However, the concentrations of mercury in hair can change to a certain extent due to the changing growth rate of hair (21).

Hair-mercury concentrations can be affected by several factors, including hair colour and variable growth rates (20). Previously conducted studies have shown that total mercury in maternal hair is a predictor of long-term neurotoxic effects in children (22), despite some studies reporting inconsistent results, particularly when assessing the effects of exposure to low mercury levels (23).

Mercury levels in populations consuming a very small amount of fish are normally below 0.5 µg/g in hair; in populations with moderate fish consumption total mercury in hair varies from below 1 to 2 µg/g; while people with frequent consumption of fish (once or more per day) may have mercury levels in hair exceeding 10 µg/g. The United States Environmental Protection Agency (US EPA) reference dose of 0.1 µg methylmercury per kilogram of body weight per day corresponds to approximately 1 µg/g mercury in hair in people with low fish consumption.

More recent calculations resulted in an adjusted biological limit corresponding to 0.58 µg/g in hair, the validity of which is supported by recent studies of developmental neurotoxicity at exposure levels close to the background (24).

A tolerable limit proposed by WHO corresponds to a hair-mercury concentration of approximately 2.5 µg/g, which takes into account the possible compensation for methylmercury toxicity by beneficial nutrients in seafood. Due to the ease of collection and handling, maternal hair-mercury level is one of the most widely used biomarkers of prenatal exposure to methylmercury in population studies.

#### ***Cord blood***

In contrast to hair, the presence of mercury in blood represents short-term exposure to organic and inorganic mercury, and does not provide information on long-term exposure and its variations (4). Total mercury concentrations in cord blood are proportional to methylmercury concentrations in hair. As a biomarker of prenatal exposure, mercury in cord blood is preferable, as it provides information on both the exposure of mothers and prenatal exposures of their children (25). Mercury in cord blood may have a stronger association with neurobehavioural deficits in the child compared to mercury in maternal hair (26). Concentrations of total mercury in cord blood of individuals who do not eat fish are normally in the range of 0.5–5.0 µg/L. In cases of high fish consumption, values higher than 10 µg/L are frequently occurring. The reference value for mercury in cord blood based on the US EPA's reference dose is 5.8 µg/L. Mercury levels in cord blood and hair are recommended biomarkers of prenatal low-level methylmercury exposure due to its selective transfer through biological barriers such as blood, hair and placenta (27–29). Cord blood is a non-invasive matrix, but should be collected by the nurse after birth.

#### ***Maternal urine***

Urine is the matrix of choice for assessing exposure to inorganic and elemental mercury (30, 31). In an occupationally non-exposed population, the number of amalgam surfaces was found to be associated with urinary mercury (32). In the general population, urinary mercury can be elevated also due to high fish consumption, as a consequence of demethylation and excretion of inorganic mercury and partially also due to limited excretion of methylmercury through urine. Urine is a non-invasive matrix, is easy to collect and is commonly used to assess exposure to elemental and inorganic mercury, particularly in occupational health settings where biomonitoring of random spot urine samples is routinely practiced.

Due to wide variability in urinary excretion rates among individuals, as well as the great temporal variability in urine composition within individuals (33), the results should be expressed per gram of creatinine or adjusted for the specific gravity. Concentrations of total mercury in urine of non-exposed individuals are normally in the range of <0.1–5.0 µg/L. In cases of non-occupational

exposure to inorganic and elemental mercury, values of up to 10 µg/L have been reported, while workplace exposures can result in levels higher than 50 µg/L. The health-based German HBM I,<sup>3</sup> which corresponds to the concentration of total mercury in urine below which adverse health effects are not expected, is 7 µg/L, or 5 µg/g creatinine; the German HBM II value that corresponds to the concentration above which there is an increased risk of adverse health effects in susceptible individuals of the general population is 20 µg/L, or 25 µg/g creatinine (34).

### 7.1.1. Choice of the matrices for the survey and sample collection

The literature provides adequate evidence that mercury in maternal hair (close to the scalp) is an appropriate biomarker of fetal mercury exposure (26). Moreover, this biomarker has been used to show an association between prenatal mercury exposure and long-term neurotoxic effects in children (22).

Human hair has the advantage of being a non-invasive matrix that is easy to collect through a simple procedure that requires minimal training of survey personnel. Hair samples can be transported and stored in a zipper bag or a paper envelope at room temperature (35). Hair samples have been used extensively in studies of methylmercury exposure from fish consumption (36, 37).

Once incorporated in the hair, mercury remains there, providing information on exposure during the hair growth period. Most mercury in hair is in the form of methylmercury, especially among populations that consume fish. It is an accurate and reliable method to measure methylmercury intake levels. The relevant SOP for analysis of mercury in hair, provided by WHO to the national coordinators, describes in detail the place on the head for collecting hair samples, the amount of hair to be collected and the principles of sample storage.

Cord blood can be collected by the nurse after birth and does not cause any pain to the mother or baby. Mercury levels measured in cord blood reflect exposure of the fetus to mercury and its compounds. A detailed description of the collection of cord blood is given in the relevant SOP for analysis of mercury in cord blood, provided by WHO to the national coordinators. The procedures described in this SOP are only suitable for mercury.

Urine is another non-invasive matrix, which is easy to collect. Urinary concentrations of pollutants, including mercury, can be influenced by the composition of urine. Therefore, creatinine levels or special gravity should be measured as well. The results for primary biomarkers are expressed as adjusted for the creatinine content or special gravity measurement results. Urine collection is described in detail in the SOP for analysis of mercury in urine, provided by WHO to the national coordinators.

For the collection of cord blood and urine samples, appropriate containers should be used to prevent background contamination. Prior to sample collection, the batch of containers for urine and blood should be tested for the presence of interfering chemicals. The containers for the collection of cord blood should contain ethylenediaminetetraacetic acid (EDTA) to inhibit blood coagulation.

## 7.2. Transportation of samples

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<sup>3</sup> These values are based on the German Environmental Surveys (GerESs), nationwide population surveys that have been carried out in Germany periodically since the mid-1980s.

In preparing samples for transportation, the national coordinator or fieldworker must ensure that samples will not be destroyed or lost during transportation and that any person coming into contact with them will not be infected.

Hair samples do not require any special transport conditions; they can be transported at room temperature. However, it should be checked that the corresponding documents, including a sheet listing all samples, is sent in the package and information on any event that occurred during sampling that could affect the sample, has also been included.

Cord blood and urine samples must be kept at 4°C until their arrival at the laboratory, where they will be aliquoted and analysed or stored until analysis. Alternatively, the samples can be aliquoted and frozen in the maternity ward, and then transported to the laboratory under proper conditions. Furthermore, urine and cord blood samples must be transported in compliance with the relevant shipping regulations for biological material.

### 7.3. Preparation of samples

A specific form will be used to document the sampling, labelling, processing and shipping of the samples.

Detailed instructions for hair sampling and sample pre-analytical treatment can be found in the SOP for analysis of mercury in hair.

The cord blood samples should be aliquoted (at least two aliquots) to enable mercury analysis in the national laboratory and the reference laboratory.

Urine samples should be aliquoted (at least three aliquots) to enable mercury and creatinine analysis in the national and the reference laboratories.

### 7.4. Analysis of samples

The 250 individual samples of each matrix (scalp hair, cord blood and urine) should be collected within the framework of the pilot surveys. Analysis of scalp hair contamination with mercury should be performed by all countries. A second matrix should also be chosen for analysis, either cord blood or urine. The national coordinator is responsible making this selection, based on an initial assessment of exposure sources and the validity of HBM results. Ideally, all three matrices should be analysed in the pilot survey.

Analysis of samples should be performed following the relevant SOPs, developed by WHO: in cord blood and urine using cold vapour atomic absorption spectrometry (CVAAS), and in scalp hair using thermal decomposition-gold amalgamation-atomic absorption spectroscopy. An alternative SOP was developed by WHO for laboratories that have access to instruments with flow injection analysis and gold amalgamation, processes that would be followed by either CVAAS or cold vapour atomic fluorescence detection.

Ideally, the laboratory that performs the analysis should be located in the country, but the main emphasis should be on analytical proficiency, as demonstrated by adequate quality assurance procedures and confirmed by the successful participation in inter-laboratory study.

## 7.5. Standardization

Results of the measurements must be analytically comparable between laboratories. To ensure this, each national survey must follow the SOPs for sampling and analytical methods, and develop procedures for quality assurance and quality control that cover the pre-analytical phase. The availability of appropriate reference materials (samples with a certain level of mercury) supports internal quality assurance. External quality assurance should be done through international inter-laboratory comparison investigations (ICI).<sup>4</sup>

A proficiency test of the analysis of total mercury in cord blood and urine can be organized by WHO, using freeze-dried samples as well as a mirror analysis of 20 samples of each biological matrix.

## 7.6. Storage of samples remaining after the mercury analysis

Human biological material is valuable for different purposes in medicine and biology, including investigation of environmental determinants of diseases. Biological samples remaining after the mercury analysis can be stored and used for other purposes, for example, to analyse their contamination with other chemicals, such as heavy metals or organic pollutants.

However, the storage of biological samples (particularly blood) and their future use should comply with the legal requirements regulating their use for purposes other than the mercury survey (38).

The storage of human biological samples should follow the same principles that regulate the management of the national biobank (39) (this legislation should be referred to in the national survey protocol). The same regulations should be applied also to small biorepositories comprising biospecimens in laboratories.

Laboratories that will store remaining biological samples should have an appropriate governance structure regulating the following items:

- to which legal entity the material is entrusted;
- how authorization from the donor is obtained;
- how the donor can retract this authorization;
- in which circumstances donors need to be recontacted;
- the procedure for determining whether unsolicited findings should be disclosed, and if so, how they should be managed;
- how the quality of the material is controlled;
- how confidentiality of the link between biological specimens and personal identifiers of the donors is maintained;
- who may have access to the materials for future research;
- which body may review research proposals for future use of the material;
- the appropriate mechanism for keeping donors informed of research outcomes;
- to which other sources of personal information the results of analysis on biological materials may be linked; which type of research will be pursued;
- which types of research will be excluded or included;
- to whom any benefits from the research are expected to accrue;
- appropriate mechanisms for keeping participants informed of research outcomes;

<sup>4</sup> ICI is a measure to harmonize analytical methods and their application so as to improve the comparability of analytical results. ICI is carried out before the laboratories begin to analyse the samples.

- how the rights and welfare of individuals from whom the materials were collected are not adversely affected.

The person whose materials are stored must authorize future use by signing a biobanking consent form (Annex 2).

Basic national legal requirements are listed below:

- The storage must be operated by a public agency or institution with a mandate for storage of biological materials according to national legislation or other legal acts.
- The samples must be used for research purposes only. Personal samples and data may be transferred within the domain of science only to the extent that this is necessary for the research purposes.
- The limitation of use to a specific purpose must be structured by statute or contract in such a way that it applies not only to the person responsible for the samples' storage, but also all people who have access to the samples and data.
- Inaccessibility to all non-research third parties and appropriate prohibition on use must be guaranteed.
- No storage and use of samples can be considered without permission of a national ethical committee.
- The sample-related data must be anonymized and in this form stored or transferred to other research. The connection between pseudonymized data and identifying data of the donor (name, address, telephone number, etc.) may only be made by authorized individuals who are bound to secrecy. External agencies and organizations must be subject to a prohibition on the use of personal data obtained with the use of biomaterials.
- The donor should know the specific research purpose for which samples and data materials will be used (for example, for biomonitoring of chemical pollutants). Personal data may be collected and used only for a purpose specified in advance. If storage of materials is considered in the frame of this survey, this information should be included in the informed consent form.
- The stored samples must be used for a limited period of time defined by the project purpose, and duration of existence of the samples and data shall be agreed with the national ethical committee. The donors should be informed about it.
- The donors should have the possibility at all times to obtain information on the research activities and results.
- The use of samples and data must be fully documented.
- The storage conditions must meet appropriate technical requirements (temperature regime, etc.).

If the requirements above cannot be met, samples should be destroyed after the analysis and confirmation of the results.

## 8. Data management, analysis and evaluation

### 8.1. Data management

Data generated during the fieldwork will need to be further processed and merged in order to allow for final evaluation and results. A database will combine the laboratory data files and the questionnaire database. The database is constructed as a matrix with one row per subject and all

separate variables in columns. The data from each participant are identified by a unique identity number (ID number). Please see the following example:

ID number	Variable name	Matrix	Biomarker	Unit	Data source
XXXXX	HM_HG	Hair Blood Urine	Total mercury	ng/mg	Lab result

Ideally, the data will be stored in a uniform format in all participating countries. WHO will develop and provide the data management and storage format. Information on the structure of the database, including variable names, formats, units and rules for handling missing values or values below the limit of quantification, will be included in a codebook.

However, each participating country, in consultation and agreement with the project coordinator in WHO, will choose its software for database management and statistical analysis based on the following criteria:

- suitable for importing data from external data files provided by chemistry laboratories (most commonly Excel or Access files);
- allows input of the questionnaire data;
- sufficient database management functionality;
- capacity to perform statistical analyses;
- possibility to deliver external databases to a WHO database.

Based on experience in other multicentre studies, statistical analysis programs like R, SPSS or SAS meet these criteria and are thus recommended.

Data processing will be conducted in each participating country, while statistical data analysis can be conducted either at the national level or at WHO. The participating countries will transfer the data to WHO for creation of a database at the global level, and analysis of levels and distribution of exposure to mercury at national, regional and global levels.

## 8.2. Statistical analysis

### 8.2.1. Data analysis at the national and the international level (recommended approach)

It is recommended that participating countries conduct statistical analyses at the national level and submit anonymized data for statistical analysis to a central database. The aim of a statistical analysis at the international level is to assess associations between biomarker values and predictors such as age, gender, fish consumption habits, etc. in a pooled dataset. However, in some cases WHO can make its own statistical analysis based on data provided by the national coordinator.

Data analysis will involve descriptive statistics and regression analysis. At the descriptive statistics stage, response rates and distributions of parameters will be evaluated, outliers identified and checked.

The regression analysis stage will involve analysis of biomarker data in relation to predictors. The associations will be studied using univariate and multiple regression models.

### 8.2.2. Data evaluation

The interpretation and evaluation of the HBM results will be dealt with in separate steps. Some of the questions that the HBM survey aims to answer are outlined below:

- Are the observed levels of exposure important/significant in terms of health risk?
- Are elevated exposure levels associated with specific types of exposure source?
- How are specific biomarkers distributed among defined/selected survey population strata/subgroups of the general and exposed populations?
- What is the spatial variability in exposure levels in participating countries globally?

Additionally, it will be valuable to compare the results of the HBM survey with existing data available in the literature.

## 9. Communication

Communication campaigns aim to promote awareness, encourage stakeholder involvement, maximize recruitment and retention, ensure transparency and openness towards stakeholders, and to safeguard translation into precautionary and preventive policy. Apart from providing information to the survey participants, the survey leaders have to provide targeted information to the general public, policy-makers and public health professionals.

Effective communication can help to raise awareness in the population and to stimulate preventive action at the population and individual levels. At the same time, it is important to avoid inducing anxiety in survey participants when corrective actions are not warranted at the individual level.

Three periods of extensive communication campaigns are identified: prior to and at the onset of the sampling period, during the survey, and at the results dissemination stage.

### 9.1. Communication prior to the survey

Measures to enhance recruitment should start before the recruitment itself begins. The recruitment process has two main goals: (1) to recruit individuals that adequately represent the target population; and (2) to recruit a sufficient number of participants to meet the sample size and power requirements. Therefore the initial campaign should start as soon as the protocol is ready.

In order to meet these goals, it is necessary to make sure information leaflets are tailored to the target population. The briefing of policy-makers should start at the same time.

It is important that the participants have sufficient opportunities to ask questions, to encourage uptake and to reduce withdrawal from the survey. The survey information leaflet and other materials should have contact details (including name, address, telephone number and email address of the survey coordinators) and be available for participants. Links to the survey website with a description of the survey, answers to frequently asked questions (FAQs) and information on sources of funding can also be provided.

The information leaflet and informed consent form should provide a brief summary of the survey and its aims, in plain language understandable for a non-professional audience. The leaflet and consent form should also explain what participation means in practice: how long it takes, where it takes place and what it involves. The following list is not exhaustive but gives an idea of the main topics to be covered:

- nature and aims of the survey;
- promise of confidentiality, that the participant's responses will not be linked to their name or any other identifiable information;
- description of what participation means in practice (when, where, who, what);
- inclusion and exclusion criteria for participating in the survey;
- possible risks, inconveniences or discomforts that could reasonably be expected to result from the survey;
- possible benefits for participants (if relevant, as there might not be any direct benefits);
- participating country's institutional contact details;
- information about how the survey leader obtained the potential participant's contact information;
- information about what will happen to the results;
- explanation that participation is always voluntary and that participants can withdraw at any time;
- explanation about how privacy and confidentiality will be maintained over the time data is stored;
- description of data storage in a biobank (if applicable) and possible uses of data in the future.

A withdrawal form should be prepared for any survey subject who decides that they would like to withdraw from the survey. Survey participants may withdraw at any time; they will be asked to confirm their withdrawal with a signature.

## 9.2. Communication during the survey

Communication should continue during the survey implementation, and it is important to react quickly and effectively to any upcoming questions.

To facilitate communication, it is recommended that a contact point be identified (with their name, phone number and email address) to receive and answer questions and queries, as well as to develop FAQs.

## 9.3. Communication of the survey results

Before communicating the result of the HBM survey, careful consideration needs to be given to the assessment of individual and population risks, based on the measured concentrations of mercury and the questionnaire data, as well as on the main goals of risk communication, taking into account different target groups and their needs. The level and distribution of mercury levels and the associated risk determine the main communication aims. For example, if the HBM survey reveals low exposure levels and low or negligible health risks, the main purpose would be to inform participants of the results and to use this as an opportunity to raise awareness and educate. Whereas, if the survey showed a high level of exposure to mercury, communication of results would include more information about health risks and risk-reduction measures, including on preventing exposure and

promoting safer behaviours. It is critically important to distinguish between communication addressed to individuals and to the wider population (e.g. different approaches to risk assessment, recommended risk-reduction measures, and defining of responsibilities of individuals and relevant authorities, etc.) as well as to involve different stakeholders according to their roles and capacities.

In general, the fundamental goal of risk communication is to provide meaningful, relevant and accurate information in clear and understandable terms, targeted to a specific audience. It should facilitate understanding of complex technical issues – such as exposure to mercury, the associated health risks and risk-reduction measures – to bridge the gap between lay people and experts and to help people make more informed and healthier choices.

All stakeholder categories – including policy-makers, health-care professionals, the general public, local communities and individuals involved in the survey – should be included in the mercury risk communication. When communicating the results, consideration needs to be given to the meaning of HBM results, their interpretation at individual and population level, and their potential health relevance (health risk, predictive value of biomarkers, etc.), including communication about uncertainty. Furthermore, communication on available protective and preventive measures at individual and population level, especially in the case of observed high mercury concentrations, is an obligation.

It is crucial not only to prepare clear and understandable messages, tailored to the capacities and needs of the audience, but also to identify the most effective channels to communicate the message (e.g. through publications, mass media, scientific reports, leaflets, lectures, involvement of an expert or a recognized community leader, etc.). It is important to get support from central and local authorities and the medical community.

### 9.3.1. Communication of the survey results to policy-makers, including government health-care and environmental protection bodies

Policy-makers, particularly in the health and environment sectors, should receive a summary of the HBM survey findings with recommendations on further steps and available risk-reduction measures. The summary should include information about the levels and distribution of exposure to mercury in a population, existing and projected health risk at population level, the main sources of exposure to mercury, as well as available and feasible actions and measures to reduce exposure and health risk. Ideally, a preventive action plan should be developed, with a proposed timeline and economic analysis of its implementation. Inclusion of information on good practices could be very useful to demonstrate the potential benefits of implementation of risk-reduction measures. The relevant policy framework at national and international level should provide a context for presenting the survey results and the proposed actions.

### 9.3.2. Communication of the survey results to the general population and communities involved in the survey

Risk-communication messages for the general public and communities should be formulated in a way that avoids misunderstandings and undue concerns. Prior to formulating risk-communication messages the population-level risks should be carefully evaluated, using all information available, and population groups at higher risk (of exposure and health effects) should be identified. A clear distinction needs to be made between interpretation of HBM results at individual and population levels.

The meaning of the HBM survey results should be clearly communicated, focusing on population groups at risk; it should include recommendations on reducing exposure to mercury and/or preventing health risks. An example of this could be fish consumption advice; as much as possible this should take into account local conditions (fish and seafood types, fishing patterns, cultural aspects, etc.) and should be presented in the context of the health benefits of fish consumption.

The public perception of risks might affect the acceptability and the appropriateness of risk-reduction measures. Therefore, it is essential to ensure that the risk-communication process takes into consideration general public perceptions, for example of the risk of mercury exposure associated with fish consumption.

The most effective way to communicate risks is through mass media; for example, as an article in the newspaper, or a programme on regional or local radio and/or television. Involvement of topical experts can strengthen the message and support the recommended risk-reduction measures in certain cases. The use of mass media should allow the message to be presented in a manner understandable to a broad audience, and provide the opportunity to discuss the problem, answer questions and give clarifications. Information about the results of the HBM survey, including on the observed levels and distribution of mercury, should be put in the context of levels of mercury in the ambient environment and relevant safety levels, as well as any accidental mercury exposure, particularly of at-risk populations.

#### 9.3.3. Communication of the survey results to health-care professionals

In cases where high concentrations of mercury are observed, communication prepared for health-care professionals should include general information on mercury and its health effects, the main sources of exposure, principles of diagnosis and treatment, risk-reduction measures and vulnerable population groups, for example pregnant women. Identification of target groups for communication efforts among health-care professionals depends on the population groups at higher risk. These could be paediatricians, gynaecologists and obstetricians, occupational physicians, and general practitioners serving specific communities (artisanal and small-scale miners, fishing communities, etc.). Organization of training for health-care professionals can be considered to help gain support for implementation of risk-reduction measures.

#### 9.3.4. Communication of the survey results to participants

Individual results should be provided to survey participants, except those who do not wish to know their results. In sensitive situations, experts in social sciences and communication might be consulted in order to understand public perceptions and to develop optimal communication strategies.

Prior to communicating the survey results to participants, the following measures are recommended in cases where a high level of mercury has been detected. First, the analysis should be repeated to exclude any mistakes, and to test the samples in a reference laboratory. The next step, after checking the quality of the measurements and confirming the result, is to evaluate risks using all available information on potential sources of exposure and the associated health risks.

When communicating risk-reduction measures, it needs to be remembered that they will differ in cases of exposure to methylmercury and inorganic mercury.

It is important to explain to participants the meaning of their results as clearly as possible. The results can be communicated to the survey participants through direct contact or through their family doctors.

Personal communication with individuals at high risk is the most effective way to discuss the problem and the recommended preventive measures and risk minimizing actions. Involvement of a family doctor and/or family members might be considered, subject to agreement of the participant. It is critical to be prepared to provide clear evidence-based answers to questions about the health effects and medical follow-up, to avoid any misunderstanding or exaggeration of the problem.

Communications at the country level and at WHO level should be coordinated and consistent. At the same time, it should allow customized, country-specific messages according to the local context (e.g. country characteristics, concerns). Confidentiality of personal data and testing results needs to be guaranteed. At the same time, all aggregated results can be made publically available, providing that no link can be made to specific individuals.

## 10. Ethics

The survey must adhere to the legal and ethical framework established by international directives, conventions and guidelines, and by domestic laws in participating countries.

Approval of a national ethical committee should be obtained before sampling starts.

The ultimate objective is to guarantee the optimal protection of the rights and dignity of every survey participant (data subject). Special attention should therefore be paid to:

- defining and explaining the specific, explicit and legitimate purposes of the survey to all actors involved;
- asking for written consent (informed, free, explicit, specific and documented) prior to the commencement of research. Informed consent includes:
  - the survey objective;
  - the targeted population and recruitment method;
  - possible risks and benefits to the participants;
  - approval of the survey protocol by an ethics committee;
  - the right to refuse consent or to withdraw consent at any time without giving reasons and without being subject to any form of discrimination;
  - the right to access personal results and the wish of participants to know or not to know their personal results;
  - the procedure for dealing with critically high biomarker values;
  - recipients of the survey data;
  - measures to assure the confidentiality of personal data.

When communicating results at the individual level, explaining their health significance (if known) is extremely important. When further evaluation or intervention is warranted due to a critically high biomarker value, communication at the individual level should involve professional counselling.

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## Annex 1. Eligibility screening form

1. Are you at least 18 years of age?

Yes

No

If no → not eligible, stop the interview politely

2. How many days ago was your delivery (if done after delivery)?

\_\_\_\_ days

If more than 14 days → not eligible, stop the interview politely

3. Do you live in [*the catchment area of the hospital*]?

Yes

No

If no → not eligible, stop the interview politely

4. How long have been living in this area?

\_\_\_\_ years

If less than three years → not eligible, stop the interview politely

5. How many days during the last three months have you spent outside the [*catchment area of the hospital*]?

\_\_\_\_ days

If more than 14 days → not eligible, stop the interview politely

6. Sufficient language ability in the interview language? (assessed by the interviewer)

Yes

No

If no → not eligible, stop the interview politely

7. Hair sampling possible (based on visual assessment – hair length of at least 3 cm on the back of the head)?

Yes

No

If no → not eligible, stop the interview politely

8. Eligible for enrolment?

Yes

No

9. If eligible, consented to participate?

Yes

No

10. Participant gave written consent to (please mark all that apply):

- Hair sample
- Urine sample
- Cord blood sample
- Access to medical records

11. Enrolled in the survey?

- Not eligible
- Eligible but not willing to participate
  
- Enrolled to participate

IF ENROLLED IN THE SURVEY

Name of participant:

---

Home address:

---

Date of admission to the hospital:

---

Date of delivery of child:

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## Annex 2. Informed consent form

The informed consent form should be signed by all recruited women.

Before requesting an individual's consent to participate in research, the researcher must provide the following information, in language or other form of communication that the individual can understand:

- 1) that each individual is invited to participate in research, the reasons for selecting the individual and that participation is voluntary;
- 2) that the individual is free to refuse to participate and will be free to withdraw from the research at any time without penalty or loss of benefits to which they would otherwise be entitled;
- 3) the purpose of the research, the procedures to be carried out by the researcher and the subject, and the aspects of the protocol that are incremental, in that they would not be part of routine medical care;
- 4) for controlled trials, an explanation of features of the research design (e.g. randomization, double-blind), and that the subject will not be told of the assigned treatment until the study has been completed and the blind has been broken;
- 5) the expected duration of the individual's participation and the possibility of early termination of the trial or of the individual's participation in it;
- 6) whether monetary or other forms of material goods will be provided in return for the individual's participation and, if so, the kind and amount;
- 7) that, after the completion of the study, participants will be informed of the results;
- 8) any foreseeable risks, pain or discomfort, or inconvenience to the individual (or others) associated with participation in the research, including risks to the health or well-being of a subject's spouse or partner;
- 9) the direct benefits to participants expected to result from the research;
- 10) the expected benefits of the research to the community or larger society, or contributions to scientific knowledge;
- 11) whether and when and how any products or interventions proven by the research to be safe and effective will be made available to subjects after they have completed their participation in the research and whether they will be expected to pay for them;
- 12) any alternative, currently available, procedures or courses of treatment and their potential benefits and risks;
- 13) the provisions that will be made to ensure respect for the privacy of subjects and for the confidentiality of records in which subjects are identified;

- 14) the limits, legal or other, to the researchers' ability to safeguard confidentiality, and the possible consequences of breaches of confidentiality;
- 15) the nature and sources of funding of the research, the sponsors of the research, the institutional affiliation of the investigators, and financial incentives for the investigators;
- 16) whether it is planned that biological specimens collected in the research will be destroyed at its conclusion, and, if not, details about their storage and possible future use, and that participants have the right to decide about such future use, to refuse storage, and to have the material destroyed;
- 17) whether commercial products may be developed from biological specimens;
- 18) whether the researcher is serving only as a researcher or as both researcher and the subject's health-care professional;
- 19) the extent of the researcher's responsibility to provide medical services to the subject;
- 20) that treatment will be provided free of charge for specified types of research-related injury or for complications associated with the research, and whether there is any uncertainty regarding funding of such treatment;
- 21) whether the subject or the subject's family or dependants will be compensated for disability or death resulting from such injury;
- 22) that the research protocol has been approved by an ethics review committee.

### Informed consent form (proposed template)

CONSENT FORM for participation in a human biomonitoring survey to assess exposure to mercury, a research project carried out by \_\_\_\_\_, with technical assistance from the World Health Organization (WHO).

Dear Madam,

We would like to invite you to take part in a study aiming to assess exposure to mercury. All people are exposed to certain levels of mercury from the environment, but in some cases, for example if a person consumes a lot of fish, lives nearby places where mercury has been used and produced, or works with mercury, exposure levels can be higher, and pose a risk to health. The survey results will be used to advise the government on protective measures and provide advice to you on nutritional and other behavioural habits if high mercury concentrations are revealed in your biological samples.

#### **Purpose**

This study is being conducted to assess your personal and your child's exposure to mercury. Measurements of mercury concentration in your hair, cord blood and urine allow assessment of your personal exposure to mercury, as well as of your child. You will receive individual results; in a case in which high concentrations of mercury are detected, you will receive advice on individual actions to reduce exposure, or recommendations to seek health advice, if needed. Together with you, 250 women will be involved in the survey.

Based on the results of the survey, we will provide data on intrauterine exposure to mercury, assess the level and distribution of exposure, identify the main risk factors of exposure in a population and advise the government on protective measures to reduce exposure if needed.

The survey is supported by the WHO as a part of a global initiative aiming at the development of a global plan of assessment of exposure to mercury and characterization of the global and regional distribution of exposure. It is necessary to plan protective measures and evaluate the effectiveness of their implementation at a global, regional and country level.

## **Background**

Mercury is present in air, soil and food and finds its way into the human body, disturbing biological processes and in some cases affecting our health. When a woman is exposed during pregnancy, mercury can be transferred to the fetus, and affect the developing organs and systems. Prenatal exposure to mercury in high concentrations is linked to an increased risk of certain diseases and conditions in a child. Analysis of biological material from mothers (such as hair and urine) and of cord blood helps to characterize prenatal exposures to mercury and to provide valuable information. This helps to assess health risks at the population level and to support policy interventions aiming at reducing pollution and protecting health. It can also be used to provide recommendations on how to protect you and your child from exposure to mercury and reduce risk in cases of detected higher mercury concentrations.

## **Selection procedure on assessing prenatal exposure to mercury**

Scientifically sound methods to assess prenatal exposure to mercury are well established. The methodology applied in the survey has been developed and is recommended by WHO. It enables an assessment of exposure to mercury during the last trimester of pregnancy, through measuring concentrations of mercury and its compounds in the cord blood, scalp hair and urine. The most valuable data to assess prenatal exposure to mercury can be obtained if samples of biological material are taken immediately after delivery. For that reason, we approach women during their stay at maternity hospitals. If you are interested in getting more information about your and your child's exposure to mercury, and you meet the eligibility criteria, you are invited to participate in the survey.

## **Procedures**

To assess exposure to mercury and its compounds, we will analyse its concentrations in cord blood, scalp hair and urine, following your agreement to provide this biological material. All samples will be collected in a non-invasive manner. A sample of umbilical cord blood will be collected by the midwife at birth; a sample of your hair will be collected by cutting a small strand of hair close to the scalp from the back of your head; and, a spot sample of your urine will be collected in the container provided by survey staff. We will also ask you to answer a questionnaire with a number of questions about your diet, home and work environment, lifestyle and health. This information will help us to learn more about potential sources of mercury. Completion of the questionnaire should not take more than 30 minutes. All procedures will be conducted by trained personnel, who will also be ready to answer your questions.

We would highly appreciate it if you allowed us to access the following information from your and your child's medical records: your child's weight and height at birth, as well as your diseases and conditions during pregnancy and delivery. This information, together with the analysis of mercury

concentrations, will allow the national survey coordinator to provide you with advice on how to minimize your exposure, if necessary.

Furthermore, we would like to request that you allow the storage of remaining biological samples for several more years for potential future research, involving the measurements of pollutants or markers of biological effects of exposure to pollutants. The samples would only be used for non-commercial research purposes, and any future tests would only be conducted after obtaining approval of the national ethical committee, with application of the confidentiality rules described below.

To get more information on how the remaining biological samples would be stored and used, please read the Biobanking consent form (Appendix 1 to this document). After that, please indicate below, whether you agree that your biological samples can be stored for further scientific investigations.

Yes, I don't mind my biological samples being stored and used for further scientific investigations

No, I don't agree that my biological samples can be stored and used for further scientific investigations

The national coordinator of the survey (*name, title, contact details*) may contact you once after mercury analysis is performed, but no later than within three months after the sampling, to provide advice on medical follow-up and on how to minimize risks to your health from exposure to mercury, if high concentrations are discovered in your samples. Please indicate below, whether you agree that we contact you on that matter by phone or email.

Yes, I don't mind you contacting me later for additional inquiry and to provide advice

No, I don't agree that you contact me later for additional inquiry and to provide advice

In any case, you have the option to withdraw your consent to further contact at any time.

### **Voluntary participation/discontinuing participation**

You do not have to take part in this research if you do not wish to do so. Refusing to participate will not affect your treatment at this hospital in any way.

Also, if you decide to participate in the survey, you will be able to discontinue your participation at any time. All you have to do is to inform the researchers that you no longer want to participate. Furthermore, you can ask for all the samples that you have provided to be destroyed. If you decide to withdraw your participation and ask for the destruction of your samples, please do it before leaving the hospital. Withdrawing your participation will not affect your medical treatment or access to medical services in any way.

The results of the analyses that have already been completed will remain in the survey database and will be used in survey reports.

### **Benefits of the survey**

The results from all survey participants will be analysed collectively to characterize exposures to mercury and to guide policy-makers to make informed decisions for the benefit of public health.

Your results will be compared to health-based guidance values, when they are available. If necessary, you will receive recommendations on how to reduce the level of a pollutant in your body or to avoid future exposures.

You can ask that your individual test results be sent to you or to your doctor. If you choose to have the results sent to your doctor, we will ask you to provide their name and address in writing.

You can also specify to not receive your results if you do not wish to know.

### **Costs**

No costs associated with this study will be charged to the participants.

### **Possible risks**

No risks are anticipated associated with participation in this survey. There is no health risk related to the collection of cord blood. The procedure will not have any influence on the normal delivery procedures. Possible inconveniences are limited to the time you will have to spend on providing the hair and urine samples and responding to the questionnaires. The questionnaires and medical records contain information that can be viewed as sensitive. However these data will be kept strictly confidential. We will use coding and anonymized data at the data analysis stage. Your personal information will only be available to authorized investigators.

### **Confidentiality**

Researchers will process the information from the questionnaires and the samples. Your name and address will be replaced by a code. If the results of this study are published in a report or scientific journal your name will not be mentioned and no information that can identify you will be included in such a report or publication. All information will be treated confidentially in accordance with relevant privacy laws.

### **Information about the survey**

You have the right to ask for additional information about the research project and the procedures described in this document. All reasonable requests for information will be answered by the principal investigator to the best of their knowledge. The researchers will inform you if and when any major changes in the procedures, risks or benefits of this study occur.

Information on the progress of the survey can be requested from the national coordinator (*provide contact details: name, title, position, organization, phone number, email address*). At the end of the survey (*indicate the date*), you will be informed about the biological samples that are still preserved and any potential future use of these samples if you would like to get this information.

### **Explanation of the principal investigator**

The principal investigator is responsible for this research, to be carried out under the conditions described in this document.

Name of principal investigator:

---

Other contact people (*it might be the national coordinator*):

---

I have read the information leaflet about participation in the human biomonitoring survey and want to participate in the survey. I understand the potential risks and benefits of this survey and take part voluntarily in this study. I understand that the information will be kept strictly confidential and that the survey was approved by the independent ethics committee of WHO and of [*national authority hosting the ethics committee*].

Mother's name (printed or written in capitals):

---

Mother's signature:

---

Child's first and last names (if given):

---

Child's date of birth (DD/MM/YYYY):

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### Communication of results

The quality checked human biomonitoring survey results, including concentrations of mercury in hair, urine and cord blood, are expected to be available no later than three months after the sampling. Please indicate below, whether and how you want to obtain your individual results.

- I do not wish to receive my results.  
 I wish to receive my results at my home address:

---



---

- I wish that my results be sent to my doctor.  
 Doctor's first and last name:

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Doctor's address:

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## Biobanking (biorepository) consent form

In everyday life, people are exposed to many chemicals in food, water, consumer products and the environment. Exposure to some of them can be dangerous for health.

Researchers are trying to learn more about exposure of people to chemicals. This can be useful for investigating the sources of chemicals and exposure and revealing links between chemicals and health disorders. Through these studies, researchers hope to find effective ways to prevent the effects of chemicals on human health and protect populations from the negative impact of environmental pollution.

We are asking you to let us store remains of your hair, cord blood and urine so they might be used in these kinds of studies.

You can take part in this storage project or not. This consent form gives information to help you decide. Please read it carefully and take all the time you need to make your choice. Be sure to ask us as many questions as you want. You should know that:

- taking part does not involve any risks
- taking part is voluntary; if you choose to take part, you can discontinue at any time.

No matter what you decide, now or in the future, it will not affect your medical care.

### **The purpose of storage of remains of your samples**

The purpose of the biorepository is to investigate your exposure to other hazardous chemicals, such as heavy metals, organic compounds, pesticides, etc. The material will be used for investigation of exposure to chemicals. No other types of projects, nor commercial enterprises, will be allowed to use your material.

### **What it involves**

If you agree to take part, we will ask you to sign this form. We will store your sample and information in the laboratory of (*please indicate in which institution samples will be stored*), along with those from all the other people who take part. We will not keep your material longer than five years.

We will let researchers from the government, public health centres and universities use the materials stored in the biorepository for approved studies (*if it is known what institutions will be involved, please indicate them*). They have to apply for permission to use the material in their studies and the authorization committee will make a decision about the request. An ethics review will also be conducted. We will not give researchers your name or any other information that could directly identify you.

We may contact you in the future with offers to take part in other research. In which case, a new consent process will be conducted just for those studies.

### **No risks in your participation**

There is no risk related to sampling.

There is a low risk that someone could get access to the data we have stored about you. We believe the chance that this will happen is very small, but we cannot make guarantees.

**All personal information will be kept confidential**

Your privacy is very important to us and we will make every effort to protect it:

- We will remove your name and other identifiers from your sample and information, and replace them with a code number.
- We will keep the list that links the code number to your name separate from your sample and information.
- Only a few of the institution staff (*please indicate who will have access to the biorepository*) will have access to the list and they must sign an agreement to keep your identity a secret.
- Researchers who study your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
- We will not give information that identifies you to anyone, except if required by law.

**Benefits from participation in the biorepository**

You might not get direct benefit from taking part. The main reason you may want to take part is to help researchers to find out more about exposure to chemicals and to help the government to plan and to take measures to protect the population from chemical risks.

There are no costs to you or your insurance. You will not be paid for taking part.

**Information about the research results**

You should not expect to get individual results from research done using your sample. We will inform you if results of the survey reveal threats to your health.

**You can withdraw your participation**

Just call [*number*] and let us know that you would like to withdraw your participation in the biorepository. We will send you a form so you can tell us in writing what you would like us to do with any of your biological samples that we have not already given out for study.

**Consent statement**

I have been informed about the purpose, procedure, risks and benefits.

I voluntarily agree that my biological samples and information can be stored at the biorepository. I understand it may be used in future research to learn about, or prevent health problems.

Someone from the biorepository can contact me once to update my personal information if necessary.

YES

NO

Someone from the biorepository can use my medical record from time to time to get updated information about my health.

YES

NO

Signature of subject

Date

Signature of person obtaining consent

Date

## Annex 3. Main questionnaire for participants

Name of participant	
Medical record number	
Identity number of participant	
Date of interview	Date (day/month/year): __/__/----
Date of child delivery	Date (day/month/year): __/__/----

### A. Personal information

#### A.1. Mother of the child (survey participant)

**A.1.1. What is your ethnicity (or nationality)?**

.....

**A.1.2. Have you had children previously?**

- No
- Yes    How many? \_\_\_\_\_

**A.1.3. What is your education level? Please select **ONE** answer.**

- Primary (completed primary school)
- Secondary (completed secondary/high school)
- Post-secondary (college, university)

#### A.2. Farther of the child

**A.2.1. What is the education level of the farther? Please select **ONE** answer.**

- Primary (completed primary school)
- Secondary (completed secondary/high school)
- Post-secondary (college, university)

#### A.3. Economic status of your household

**A.3.1. How easy is it for you to cope financially? Please select **ONE** answer.**

- Difficult, not always able to afford the necessities
- Income is limited but can afford the necessities
- Live comfortably, but no excess in disposable income
- Stable financial situation, able to afford high-quality products and services

**B. Potential exposure to mercury**

**B.1. Occupational exposure**

**B.1.1. Before your maternity leave/pregnancy, did you have a paid full-time or part-time job?**  
(as an employee, employer or self- employed)

- No
- Yes

*If NO, please go directly to section B.1.5.*

**B.1.2. Have you ever worked in the following industries or sectors? Please mark all that apply.**

Industry type	Never	Less than 6 months	Between 6 months and 1 year	1–5 years	More than 5 years	Any time during this pregnancy
Chemical/petroleum	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Metal smelting	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Metalworking	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Chloralkali plant	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Chemistry laboratory	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Dentistry	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Waste management (general)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Electronic waste management	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Artisanal and small-scale gold mining	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Production of goods that contain mercury, such as traditional remedies, cosmetics, etc.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**B.1.2.1. Please provide the name and address of the industrial enterprise where you were working before/during this pregnancy.**

.....  
 .....

**B.1.3. In your job, did you have contact with the following substances? Please mark all that apply.**

Substance	Don't know	Never	Less than 6 months	Between 6 months and 1 year	1–5 years	More than 5 years	Any time during this pregnancy
Metallic dust	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Mercury	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Amalgam	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Pesticides	<input type="radio"/>						
Fumes from burning coal	<input type="radio"/>						
Fumes from burning electronic waste	<input type="radio"/>						

**B.1.4. If you have worked in any of the previously mentioned industries or have had exposures as listed in the previous questions (you answered YES to any questions in B.1.2–B.1.3), please provide additional information below. Please mark all that apply.**

	Always	Occasionally	No
Did you change work clothes before entering your home?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Did you change work shoes before coming home?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Did you take a shower after your work shift before coming home?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Did you ever bring your dirty work clothes or other contaminated items home?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
If you answered YES to the previous question – Did you wash your work clothes separately from any other clothes?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**B.1.5. During your pregnancy, did your husband/partner or anyone else living in your household work in the following industries/sectors? Please mark all that apply.**

Industry type	Yes	No	Don't know
Chemical/petroleum	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Metal smelting	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Metalworking	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Chloralkali plant	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Waste management (general)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Electronic waste management	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Chemistry laboratory	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Dentistry	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Artisanal and small-scale gold mining	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**B.1.5.1. Please provide the name and address of the industrial enterprise where your husband/partner worked before/during this pregnancy.**

.....

.....

**B.1.6. During your pregnancy, did your husband/partner have regular occupational or hobby-related contact with the following substances?**

Substance	Yes	No	Don't know
Metallic dust	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Mercury	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Amalgam	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Pesticides	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Fumes from burning coal	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Fumes from burning electronic waste	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**B.1.7. If your husband/partner or any other member of your household worked at an industrial enterprise (you answered YES to any question in B.1.5–B.1.6), please provide additional information below. Please mark all that apply.**

	Always	Occasionally	No
Did your husband/partner change work clothes before entering your home?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Did your husband/partner change work shoes before coming home?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Did your husband/partner take a shower after work, before coming home?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Did your husband/partner bring dirty work clothes or other contaminated items home?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
If you answered YES to the previous question – Did your husband/partner always wash work clothes separately from any other clothes?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**B.2. Residential environment**

**B.2.1. Where is your place of residence located?**

- In the city
- In a rural area

**B.2.1.1. In what neighbourhood or residential area do you live?**

- Please provide name of the city/village: .....
- Please provide the name of the area: .....

**B.2.2. Are there any of the following in the vicinity of your home (up to 2 km)? Please mark all that apply**

	Yes	No	Don't know
Metalworking business	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Waste incineration plant	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Cement production plant	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Chloralkali plant	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Municipal landfill	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Landfill for industrial by-products/waste	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Crematorium	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Mining operation	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Artisanal small-scale mining	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Thermo-power plant	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Electronic waste dismantling	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**B.2.3. What fuel or energy source do you mainly use for cooking and for heating inside your home?** Please mark only one fuel source for each.

Fuel source	Cooking	Heating
Natural gas	<input type="radio"/>	<input type="radio"/>
Coal or charcoal	<input type="radio"/>	<input type="radio"/>
Electric power	<input type="radio"/>	<input type="radio"/>
Wood or biomass	<input type="radio"/>	<input type="radio"/>
Hot water or hot air from central heating system (district heating or central boiler for a multi-apartment building)	<input type="radio"/>	<input type="radio"/>
Kerosene	<input type="radio"/>	<input type="radio"/>

**B.2.4. What is your main source of water for drinking and cooking?** Please select only one water source for each.

Water source	Drinking	Cooking
Public water supply	<input type="radio"/>	<input type="radio"/>
Private well or spring	<input type="radio"/>	<input type="radio"/>
Bottled water	<input type="radio"/>	<input type="radio"/>
Surface water (river, lake, etc.)	<input type="radio"/>	<input type="radio"/>

**B.2.5. Has a thermometer or any other device containing liquid mercury (like a sphygmomanometer) been broken in your home during the last two years?**

- No
- Yes. If yes, how long ago? Please specify below:
- Less than 30 days ago
  - from 30 to 90 days (three months) ago
  - From 91 days to 6 months ago
  - More than 6 months ago but within the last 2 years
- Don't remember/don't know

**B.2.6. Has an energy saving fluorescent lamp been broken in your home during the last three months (90 days)?**

- No
- Yes. If yes, how many days ago? \_\_\_\_\_ days
- Don't remember/don't know

**B.2.7. Has anyone worked regularly with metals in your home in the last three months (e.g. soldering metals as part of do-it-yourself and hobby activities)?**

- No
- Yes
- Don't know

### B.3. Personal care and lifestyle

**B.3.1. Do you have any dental amalgam fillings (dark-coloured fillings)?**

- No
- Yes. If yes, how many amalgam dental fillings do you currently have? .....
- Don't know

**B.3.2. Do you often use chewing gum or habitually chew (leaves/tobacco, etc.)?**

- No
- Yes

**B.3.3. Have you ever smoked cigarettes or other tobacco products in your life time?**

- I have never smoked. *Go to question B.3.5.*
- I used to smoke, but quit prior to this pregnancy
- I was smoking during this pregnancy

**B.3.4. How often did you smoke, on average, before and during pregnancy?**

Frequency	Before	During
Did not smoke	<input type="radio"/>	<input type="radio"/>
Smoked less than once per week	<input type="radio"/>	<input type="radio"/>
Smoked at least once per week, but not every day	<input type="radio"/>	<input type="radio"/>
Smoked daily	<input type="radio"/>	<input type="radio"/>

**B.3.5. How often did you drink alcoholic beverages during this pregnancy?**

- Never
- At least once per month
- At least once per week

**B.3.6. Do you regularly use skin-lightening products?**

- No
- Yes

**B.3.7. Did you use skin-lightening products during this pregnancy?**

- No
- Yes. If yes, how often? *Please specify below:*
  - At least once per day
  - At least once per week
  - At least once per month
  - Less than once per month

**B.3.8. Do you regularly use traditional remedies/medicines that may contain mercury (containing cinnabar)?**

- No
- Yes

**B.3.9. Did you use traditional remedies/medicines that may contain mercury (cinnabar) during this pregnancy?**

- No
- Yes. If yes, how often? *Please specify below:*
- At least once per day
  - At least once per week
  - At least once per month
  - Less than once per month

**B.4. Food and beverage consumption****B.4.1. How often do you eat the following foods? Please mark each category.**

Type of product	At least once per day	At least once per week	At least once per month	Less than once per month
a. Any type of fish/shellfish/sea weed (such as tuna in salad or sandwich, pizza, prawn cocktail, etc.)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
a.1. Fish from shop	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
a.2. Shellfish from shop	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
a.3. Seaweed	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
a.3. Locally produced seafood (any type)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. Cereal and grain products (any type)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b.1. Rice and rice products from shop	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b.2. Bran and germ	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b.3. Locally grown rice	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
c. Meat and meat products (any type)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
c.1. Game meat	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
c.2. Edible offal (liver, kidney, etc.)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
c.3. Chicken	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
d. Vegetables and mushrooms	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
d.1. Wild mushrooms	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
d.2. Leafy vegetables from shop	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
d.3. Legumes from shop	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
d.4. Root vegetables from shop	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
d.5. Locally grown vegetables (your own or purchased at a local market)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
g. Herbs collected locally	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

(including in herb teas)				
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**B.4.2. How often did you eat the following types of fish during the last three months?**

Types of fish	At least once per day	At least once per week	At least once per month	Less than once per month
a. Swordfish, tuna	0	0	0	0
b. Oily fish (sardines, herring, mackerel, salmon, etc.)	0	0	0	0
c. Whitefish, cod, haddock, plaice	0	0	0	0
d. Freshwater fish (trout, perch, others) from shop	0	0	0	0
e. Freshwater fish locally caught	0	0	0	0
f. Shellfish	0	0	0	0
g. Seaweed	0	0	0	0
h. Canned fish	0	0	0	0

## Annex 4. Recommendations on recruitment and fieldwork

### 1. Foreword

These recommendations are intended to be used in the framework of the WHO human biomonitoring survey on exposure to mercury. As such they are part of the survey protocol provided by WHO and give additional information on those steps of the fieldwork survey that are essential to achieve comparability of data. The target population of the survey is mothers giving birth in maternity wards.

### 2. Selection of maternity hospitals

Hospitals which serve exposed population groups should be selected. Contact information, the hospital location, a short description of the hospital activities and other relevant information should be included in the national protocol.

### 3. Selection of participants

All mothers contacted with a proposal to participate in the survey during antenatal visits and those entered in each selected maternity hospital who meet the inclusion criteria will be asked to participate, until the predetermined number of participants (e.g. 250 cases) has been reached.

Not every woman giving birth to a child is eligible. The inclusion criteria include: age at least 18 years; living in the catchment area of the hospital for at least three years; and living in the area for most of the time in the last three months of pregnancy. The child should be alive and delivered at normal term (at least 37 weeks). Immigrants should not be excluded, as long as they have sufficient language ability to understand information about the survey, provide informed consent and communicate with the interviewer. Participants with clinically confirmed mental disorders are recommended to be excluded from the survey. Participating women should have hair longer than 3 cm on the back of the head. Participating countries can define additional criteria based on local conditions (see relevant recommendations).

The response rate is usually a basic characteristic of an epidemiological survey. In this survey, this is not an important indicator and it is up to the national coordinator whether it should be calculated.

The participating country will count and document the following numbers:

- number of women asked to participate
- number of these women fulfilling the inclusion/exclusion criteria
- number of women agreeing to take part
- number of women whose data are used in analysis.

The woman only counts as a survey participant if she gave informed consent, met all inclusion criteria and did not meet exclusion criteria, and has provided most of the required samples and questionnaire data (more specific criteria can be specified in the national protocol). About 80% of the questions in the questionnaire must be answered, including some which are necessary for interpreting data on biomarkers. Examples of such questions related to mercury exposure are those on consumption of fish products and workplace exposure.

## 4. Fieldwork

In each participating country, fieldwork will preferably be performed in the summer and autumn for reasons of standardization.

Each country will decide on the mode of the fieldwork organization. For example, a national implementation team might be established. Regardless of the way in which the work is organized the essential tasks are:

- to notify the authorities about the survey and to apply for ethical approval;
- to prepare fieldwork manuals as brief guidance for fieldwork staff in the national language;
- to translate and validate the questionnaire during a small-scale pre-pilot survey;
- to find qualified interviewers and train them (or to train the nurses of the maternity hospitals);
- to prepare all other written material (information leaflet, informed consent, etc.);
- to provide a help-desk phone number for the survey staff and the participants;
- to supervise the fieldwork, to give help and advice if necessary;
- to organize sample storage;
- to organize the delivery of samples to the laboratory, and to reference laboratories for a mirror analysis;
- to perform internal quality control of fieldwork;
- to evaluate and communicate the survey results;
- to provide the survey database and the national protocol to the WHO unit that performs data analysis and interpretation.

The recruitment and data collection should follow a certain order. First the interviewer introduces themselves and explains the survey. Then they check the inclusion/exclusion criteria and decide whether the woman can be included in the survey. If the mother is eligible, the interviewer gives them the information leaflet and written consent form and asks for their signature. If the woman is not willing to take part she should not be pressured to do so.

The questionnaire is another essential part of fieldwork. The recommended option is to have the questionnaire administered by the interviewer. The interview must be performed in a culturally competent, polite and non-judgmental way. The interviewer must ask the questions verbatim in the predefined order. The interviewer must not push the mother to answer, must not suggest a specific answer and must accept whatever answers she provides.

The procedure continues with taking the scalp hair sample. Again, the examination process will be stopped at this point if the mother does not agree to sampling. Instructions on the correct procedures of hair, cord blood and urine sampling are provided in pertinent standard operating procedures (SOPs). A respectful and careful approach is expected.

### 4.1. Assigning identity numbers to survey participants

To guarantee the privacy of participants, each mother is given a unique code that will be used on all samples and in the database. At the stage of analysis of samples and statistical analysis of data, only this code will be used.

Samples collected during fieldwork are labelled with the identification number. Labels will be attached to the side of the containers. Each aliquoted tube will also have a label with the participant's code.

For the different samples and aliquots additional digits can be added to the identification number.

## 5. Interviewers

The number of interviewers a country may employ depends on the organization of the fieldwork. Interviewers and all people involved in the fieldwork need to be trained. The training should consist of a theoretical module, in which the survey objectives and necessary theoretical background information are provided, and a practical module covering the sampling of scalp hair and performance of the interview. The training will be based on the SOPs and the modules and presentations from the national coordinator training organized by WHO. It might be more efficient to organize the fieldworker training in the target hospitals.

The selection of interviewers is a task for the survey team. The interviewers should ideally possess the following basic skills: experience with and knowledge of the topic, good experience in dealing with people, no reservations about people of different social classes or ethnic origin, and a professional manner. In addition to these obligatory skills, the following would be desirable: local knowledge of the sampling areas, a communication style that suits local cultural norms and experience in interview conduct.

## 6. Questionnaire

The standard questionnaire form in English is offered to all participating countries. The first task for each country is to translate the questionnaire into the national language if necessary. It is recommended to have the questionnaire translated by two different translators, to compare the two versions and choose the final version according to an expert opinion.

To adjust the wording to the local culture and lifestyle, the questionnaire has to be tested. At least five test-interviews should be carried out during the pilot testing.

## 7. Quality control

To enable high-quality data collection, the survey coordinators in each country should develop detailed guidelines in the form of a fieldwork manual. The fieldwork manual describes all steps of the fieldwork and provides SOPs for all essential steps. Checklists for all important steps should also be compiled.

The fieldwork manual takes the form of a folder that is provided to all those who need to be informed about the fieldwork details or who are involved in fieldwork. This folder is divided into two main sections. In the first section, the basic modules of the survey are explained. The second, bigger section is the extensive annex, which includes all the information and documents needed for conducting the fieldwork: master copies of forms, written information needed for the participants, questionnaires and checklists.

The quality of the fieldwork is closely related to the ability of the interviewers to perform the interviews in an appropriate way. Thus, the training of the interviewers is an essential element of quality control. The scientists who are in charge of internal and/or external quality control should be involved in all stages of the training because they know all the pitfalls in the practice. This can help ensure good-quality fieldwork.

Everyone involved in fieldwork must keep a log-book. Positive and negative experiences should be written down and exchanged, not only with other team members but also with survey office staff, to facilitate learning from each other. It could be worthwhile communicating some experiences to WHO and other countries.

At the beginning of the survey, the criteria for quality targets have to be defined, as do procedures for how to deal with errors. Both aspects have to be part of the interviewer training.

Both internal and external quality control are necessary as it is in the interest of all partners to ensure that fieldwork is performed in a harmonized and correct way. It is recommended that checklists be used to facilitate internal and external quality control of the fieldwork. Internal quality control means that each step of the fieldwork is controlled by the staff member performing the work. Dealing with respective checklists should be part of the training. External quality control – or field visits – refers to quality control of the work of the field team members by researchers from the survey office or an auditing expert. This is also recommended.

## Annex 5. Community involvement strategy

Community involvement in the survey has the potential to positively influence the response rate and retention of participants, as well as implementation of possible risk-reduction measures, as the project follow-up. The community needs to be involved in all stages: prior to the survey, during its implementation and in survey follow-up, especially if risk-reduction measures are to be implemented.

Community involvement will be beneficial and is necessary:

- to enable planning of the survey to take into account community needs;
- to ensure support for project implementation from the local authorities and population, and get a higher response rate for the survey; this will positively influence the reliability of survey results;
- to create a sense of participation and co-ownership, and to build trust towards the survey and the survey field staff;
- to increase acceptance of the survey results;
- to strengthen community knowledge and skills to understand the problem and implement risk-reduction measures;
- to ensure implementation of risk-reduction measures if they are needed.

Development of a comprehensive community involvement strategy will add value to both the professionals involved in the survey matter and to society. The main guiding principles to be followed in this process include:

- align the strategy with stakeholders needs
- establish the goals and expected outcomes of the strategy
- explore best practices for community involvement.

The next steps involve creation and execution of a community involvement plan, following the main principles:

- establish an evaluation plan, including measuring, assessing and reporting
- build effective communication skills and strategies to advance community involvement
- advance community relationships into shared value partnerships
- institutionalize community involvement within your organization.

Several steps are recommended for the development and implementation of the strategy and action plan for community involvement.

### **1. Learn more about the community**

It would be useful to collect information about the community: community profile and organization, main problems and needs; environmental conditions; general health status of the population; results of previous investigations, if any; and opportunities, potential risks and threats to the survey.

### **2. Develop a communication package about the survey**

Information about the project should be adapted to the target audience; development of a different set of information for the local authorities and community members should be considered.

Information on the survey should be easily understandable and based on scientific knowledge. The information package should explain: the rationale for the survey and its objectives; who will be

involved; how the survey will be implemented; what risks it could pose to the community and its members, if any; what the benefits for the community are; how the survey results will be communicated; what the follow-up is, in particular, if high levels of exposure to mercury are detected.

### **3. Ensure support from influential people**

Information about the planned survey should be first communicated to people with authority (formal and informal) within the community. This could be community leaders or people held in respect by community members (e.g. health-care professionals serving the community, older members of the community, trade union members, representatives of women's organizations, spiritual leaders, etc.). Engagement and support from those people will allow better understanding of the community's needs, and help to gain trust of the community in the planned survey.

### **4. Communicate information about the survey to community members**

Information about the survey can be communicated to community members in several ways, including through:

- developing and disseminating an information leaflet about the planned survey; this allows outreach to a wider audience but does not allow immediate answering of questions and providing clarifications;
- reaching out directly to potential survey participants (pregnant women) and their families; this is one of the most effective ways of communication, also giving the opportunity to provide any necessary clarification; recruitment can start from these visits, however, it is time- and resource consuming; identification of the target population might also be a challenging task;
- agreeing joint antenatal visits with gynaecologists and obstetricians serving the community;
- organizing dedicated meetings with the target population; this could be, for example, meetings of pregnant women with health-care workers; this approach requires organizational support from the local authorities, arranging the meeting venue, dissemination of information about the meeting, etc.

In practice, a combination of different approaches to communicating information about the survey should be considered.

### **5. Keep contact open during the survey implementation**

Communication channels need to be maintained during the implementation of the survey in order to respond quickly and effectively to any problems which the survey field staff might face, but also to answer any questions and to provide further clarification to the community and its members, if requested.

### **6. Communicate the survey results**

The survey results should be communicated irrespective of the measured concentrations of mercury. In cases where high levels of exposure to mercury are detected, the communication of the project results should include a proposal for risk-reduction measures (see Section 9 Communication). Furthermore, it is recommended that information about possible future (longer-term) actions be provided, for example, plans for a follow-up survey in 3–5 years.

***7. Follow up with community members who need specific attention and support in implementation of risk-reduction measures, if necessary***

In cases of high level concentrations of mercury in biological samples, the participants will receive additional information on how to interpret the results and recommendations on individual preventive measures to reduce exposure. In the unlikely case of very high mercury concentrations, recommendations for individual medical consultations with health-care workers will be communicated directly to the affected participants. Further to providing information at individual level, risk-reduction measures need to be implemented at the community level. This requires active interaction and full engagement of the local authorities in the development and implementation those measures.