

DRAFT - WORK IN PROGRESS

RECOMMENDATIONS from the Implementation Group¹ on Human Biomonitoring based on the first BiPRO report 10 October 2005

Members of the Implementation Group (IG) on Human Biomonitoring (HBM):
Botsivali Maria, Berglund Marika, Bloemen Louis, Boogaard Peter, Canna Michaelidou Stella, Cerna Milena, De Felip Elena, Fabianova Eleonora, Fréry Nadine, Fucic Aleksandra, Hirvonen Ari, Jakubowski Marek, Knudsen Lisbeth, Kyrtopoulos Soterius, Lehnert Maryse, Levy Len, Reis Fátima, Reisner-Oberlehner Martina, Sala Carlo, Schoeters Greet, Seifert Bernd, Kolossa-Gehring Marieke, Sepai Ovnair, Ten Tusscher Gavin, Van Wijnen Joop, Veidebaum Toomas, Joas Reinhard, Van Tongelen Birgit, Casteleyn Ludwine.

Background

A step-by-step procedure is adopted in the development of a EU coordinated approach to human biomonitoring in Europe² in order to allow an optimised dialogue between all partners involved and a co-decision procedure between Commission and Member States. Consequently several key elements related to a pilot project (such as: number of participating Member States, the budget available, the study design including sample size and distribution, the organisation and logistics) are to be developed.

The IG has prepared recommendations during their meeting on 29th-30th September. The group took into consideration the preliminary report produced by BiPRO³ which addressed (1) the elaboration of a tool to select biomarkers for a coordinated EU approach and, (2) possibilities of new technologies in toxicology. This report was a first step in the scientific support needed for the development of a coordinated approach for human biomonitoring in Europe.

The following recommendations are to be seen as a first draft for consultation reflecting the current discussion within the IG. Given the short timeframe it was not possible to collate comments on this first text from all IG members. Therefore these first recommendations should not yet be considered as a consensus document. At the next IG meeting - planned for November 7th - the group will finalise this first document taking into account the comments of the Member States and of the Consultative Forum.

Further scientific basis for the pilot project will also be provided by a specific Scientific Support for Policy contract (SSP)⁴ and complemented by results from other contracts actually running under the Sixth Framework Programme of the European Community for research (FP6)⁵ or planned within the Seventh Framework Programme of the European Community for research (FP7) (also e.g. preparing databases on biomarkers and their state of validation).

¹ Established in the framework of the European Environment and Health Action Plan 2004-2010 adopted by the Commission on June 9th 2004 (COM(2004)416 final)

² Implementation of Action 3 of the EU Environment and Health Action Plan 2004-2010

³ BiPRO project funded by the Commission, DG Environment.

⁴ ESBIO (Expert team to Support BIOmonitoring) project funded by the Commission, DG Research. ESBIO's mandate is to develop a coherent approach to HBM in Europe and in particular the preparation and follow-up of the Pilot Project.

⁵ Childrengenonetwork, ECNIS, NewGeneris, etc.

DRAFT - WORK IN PROGRESS

Recommendation

1. THE PILOT PROJECT AS A 'LEARNING BY DOING' TOOL

Last year's report of the Technical Working Group on human biomonitoring of children⁶ recommended the development of a coordinated approach to HBM in Europe and the launch of an EU Pilot Project. This Pilot Project was seen as a "learning by doing" tool that should:

- (i) facilitate the establishment of collaboration networks and the sharing of methodologies;
- (ii) help promote the idea of coordination/harmonisation in human biomonitoring;
- (iii) test methodological issues;
- (iv) give a first indication of the comparability of human biomonitoring data in Europe for the pollutant or pollutants that will become the object of the pilot project.

It was also suggested that - in view of not complicating the pilot project by major analytical problems - pollutants should be chosen on the basis of the availability of validated analytical methodology as well as many other factors including the health consequence of environmental exposure to the EU population.

The IG still underlines these considerations and builds further on them in the following.

2. OBJECTIVES OF THE COLLECTION OF BIOMARKER DATA IN THE EU PILOT PROJECT

The IG considers that biomarker data collected in the pilot project could be used:

- 1) to establish reference values and identify reference ranges that can be used by physicians and scientists to determine whether a person or group has an unusually high exposure;
- 2) to monitor geographical variations in exposure levels;
- 3) to determine the prevalence of people with levels above a certain toxicity level or level of concern;
- 4) to determine whether exposure levels are higher among specific subgroups;
- 5) to assess the effectiveness of intervention measures to reduce exposure of Europeans to specific pollutants (trend analysis);
- 6) to set priorities for research on human health effects.

Although the EU Environment and Health Strategy initially focussed on children, the current Action Plan broadened the scope to include parental exposure as well. At this moment the group recommends to address the general population with an emphasis on children.

Children are a vulnerable⁷ sub-group of the general population. Childhood exposure and subsequent health impact is of particular concern; adverse health effects associated with

⁶ Established in the framework of the European Environment and Health Strategy (COM(2003)338 final)

⁷ Children are more exposed to toxins since they drink more water, eat more food, breath more air than adults relative to their body volume. Furthermore their neurologic, respiratory and reproductive system are not fully developed yet, which makes them more vulnerable. They are often less able than adults to metabolize, detoxify, and excrete toxins. They face potentially longer exposure to toxicants and they cannot protect themselves. The enhanced rate of cell division and the longer life span during which cancers initiated in childhood can develop, can significantly affect cancer development. Due to their different and unique exposures and behavior patterns, metabolism, and special vulnerabilities determined also by the so called "critical windows of development",

DRAFT - WORK IN PROGRESS

childhood exposures to environmental pollutants are still not well understood. Biomonitoring in children will increase such knowledge⁸ and allow the development of national and EU environmental health programmes and policies for reducing environmentally relevant childhood diseases.

However, we should also take into account that sampling children may raise more difficult logistical issues and ethical questions⁹ than monitoring adults and therefore may result in a lower response to the pilot project. Also metabolism of children is different (growth, important activities) and the significance of the biomarkers can be different than those observed in adults. Non-invasive sampling of body fluids and tissues (urine, saliva) or requesting a minimal amount of blood may be a key issue in a childrens' human biomonitoring programme.

Considering that the assessment of maternal body-burden is, for some pollutants (e.g. some persistent organic pollutants which have high transfer ratios through placenta and milk) highly predictive of children exposure, monitoring of mothers (or women of childbearing age) was also suggested as a suitable alternative to monitoring of children.

Sampling plans and recruitment strategies are critical for obtaining reliable and comparable results and may largely differ depending on the age of the population to be addressed. Therefore it would be helpful for the work of the IG if the Member States could indicate their concerns/preferences in this respect.

3. NECESSARY CLOSE LINK WITH RESEARCH

The IG stresses the strong research aspect in the development of a coordinated EU approach for human biomonitoring as required by Action 3 of the EU Health and Environment Action Plan. HBM cannot be seen separately from research efforts in order to guarantee scientific sound results in a field that is evolving rapidly.

First of all specific research activities are needed to allow e.g. (i) defining harmonised procedures; (ii) defining best (harmonised) ways of providing information to and obtaining consent from study persons; (iii) the interpretation of measurements with biomarkers; (iv) the integration with other data (environmental and health); (v) the translation into policy.

Moreover, a larger scale HBM programme for surveillance offers a unique opportunity to develop hypothesis driven research programmes. Given the complexity of the link between health and the environment, science may profit from larger population groups with better exposure data to enable testing further hypotheses on e.g. cause–effect relationships¹⁰, mechanism, expected trends, combined exposures to low concentrations or cumulative effects, dose–effect and dose-response relationships.

A close link between surveillance and research activities therefore will allow (i) adding specific research projects on the surveillance framework; (ii) integration of information by bringing together available knowledge and actively promoting exchange of experiences between teams and countries (capacity building); (iii) incorporation of new developments in

children, from the prenatal period through adolescence often react differently to chemicals than do their adult counterparts (see also IFCS/FORUM-IV/14w, 2003). Of particular concern are the potential effects of Endocrine and Cell Signaling disrupters especially when exposure occurs during “critical windows of development”.

⁸ Biomonitoring data of children with complex environmental exposures shall be put in the context of age specific capacity of metabolism and detoxification. Interpretation of results performed by international and interdisciplinary experts will give new quality of collected data.

⁹ E.g. urine in children under 3 years old, blood in important quantities, etc.

¹⁰ Providing a health basis for environmental and biological standards

DRAFT - WORK IN PROGRESS

the emerging field of toxicology technologies such as genomics, transcriptomics, proteomics, metabonomics/metabolomics for filling the knowledge gaps in the relation between environment and health and developing better environment and health policy; (iv) taking advantage of the larger EU scale to have more meaningful results.

4. CRITERIA FOR THE SELECTION OF POLLUTANTS OF INTEREST

The group discussed several criteria for selecting the pollutants of interest for the pilot project. These criteria were considered as valuable elements in the selection process but should not necessarily all be fulfilled. In order to support and facilitate the decision making process these criteria will be included in a tool under construction by the BIPRO project.

A methodology based on a four step approach¹¹ has been suggested:

- Ø Step 1: Compilation of a broad list of pollutants
- Ø Step 2: Assessment using Exclusion criteria
- Ø Step 3: Assessment using Selection criteria
- Ø Step 4: Evaluation and ranking

The 4 steps will result in a well-justified short list of suitable pollutants, related biomarkers and human tissues/fluids and possible packages as a basis for decision making.

Selection criteria suggested are:

- **Health relevance:** it was proposed to focus on the four priority diseases as mentioned in the EU Environment and Health Strategy: (1) Childhood respiratory diseases, asthma, allergies, (2) Neurodevelopmental disorders, (3) Childhood cancer, (4) endocrine disrupting effects.
- **Environmental relevance:** pollutants with known broad exposure or currently under great concern with undocumented exposure.
- **Integration with the EU Integrated Environment and Health Information System** currently under development by the European Commission.
- **Availability of a biomarker with established analytical methods and well-validated** with, in an ideal situation, predictive value towards health effect. Low cost of the analysis and non-invasive aspect of the sampling were also considered, but not deemed as a priority to all of the members of the group.
- **Existing¹² or envisaged¹³ programmes in several MS.**
- **Innovative aspect:** this issue will further be addressed at the next meeting of the IG where a more extensive report will be presented.
- **Recommendations by other SCALE Technical Working Groups:**
 - o The *TWG on Heavy Metals* proposed a HBM programme for the exposure of children to toxic metals. The adverse effects on health from toxic metals in EU

¹¹ See document "Summary of first BIPRO report"

¹² See for current programmes the inventory on:

http://www.brussels-conference.org/Download/baseline_report/BR_Biomonitoring_final.pdf

¹³ E.g. France has an obligation to start a HBM programme related to lead exposure in children by 2006. The Public Health Law of August 9th 2004 requires the measurement of the prevalence of blood lead level > 100 µg/L in children aged 1 to 6 as an indicator of prevention policy. Recent publications (Canfield 2003, Lanphear 2005) show that neurodevelopmental disorders are observed at blood lead levels lower than this threshold: the scientific consensus is now that there is no threshold.

DRAFT - WORK IN PROGRESS

children would be estimated using existing data on dose-response relationships collected during the programme¹⁴.

- The *TWG on Endocrine Disruptors* recommended the integration of existing national monitoring activities with a focus on *Bio-banks/Human Bio-monitoring* putting emphasis on the development, harmonisation and integration of biomonitoring activities and biobanks, in order to pinpoint possible risk factors for populations/groups with high incidence of certain health effects¹⁵.
- The *TWG on neurodevelopmental disorders* recommended that representative biomonitoring surveys should be performed including or prompting monitoring of eventual risk groups. Regarding Neurodevelopmental Disorders (NDD) the approach has to be focused on substances known or supposed to correlate to NDD and on women of child-bearing age and children with a special stress on perinatal monitoring¹⁶.
- **The POPs Convention¹⁷ in its Article 11** announces that the Parties shall, within their capabilities, at the national and international levels, encourage and/or undertake appropriate research, development, monitoring and cooperation pertaining to persistent organic pollutants and, where relevant, to their alternatives and to candidate persistent organic pollutants, including on their presence, levels and trends in humans;
- **WHO:** keeping in mind the Fourth WHO-coordinated survey of POPs in Human Milk to be launched soon and the outcome of the 2003 workshop organised by UNEP Chemicals to develop a global POPs monitoring programme (GMP) to support the effectiveness evaluation of the Stockholm Convention¹⁸. Four matrices were proposed for POPs GMP, among them human milk.¹⁹

¹⁴ The *TWG on Heavy Metals* proposed an expert group to recommend and interpret a biomonitoring programme for the exposure of children to toxic metals. The adverse effects on health from toxic metals in EU children would be estimated using existing data on dose-response relationships collected during the programme. The expert groups would review current national biomonitoring programmes, assess priorities and recommend common activities. An associated pilot study would explore, at the practical level, the possibility of implementing the biomonitoring procedures, and integrating existing databases for application to this programme.

¹⁵ The *TWG on Endocrine Disruptors* highlighted the need to take into account three types of data sources, collected for different purposes, *i.e.*: environmental monitoring, biomonitoring, and monitoring of health effects that may have a plausible association with exposure to ED during early life stages (*e.g.* hypospadias; testicular cancer). The TWG recommended the integration of existing national monitoring activities with a focus on *Bio-banks/Human Bio-monitoring* putting emphasis on the development, harmonisation and integration of biomonitoring activities and biobanks, in order to pinpoint possible risk factors for populations/groups with high incidence of certain health effects.

¹⁶ The *TWG on neurodevelopmental disorders*: existing data on biomonitoring in Europe must be collected in a database. Representative biomonitoring surveys (*e.g.* Umweltsurvey Germany) should be performed including or prompting monitoring of eventual risk groups. Regarding Neurodevelopmental Disorders (NDD) the approach has to be focused on substances known or supposed to correlate to NDD and on women of child-bearing age and children with a special stress on perinatal monitoring. Such a biomonitoring program must closely liaise to the monitoring of NDD recommended elsewhere. Correlations between the two outcomes have to prompt further research or in some cases even to give cause for action.

¹⁷ Stockholm Convention: <http://www.pops.int/>

¹⁸ United Nations Environmental Programme (UNEP) Chemicals, Proceedings: UNEP Workshop to develop a global POPs monitoring programme to support the effectiveness evaluation of the Stockholm Convention, Geneva, Switzerland, 24-27-March 2003

¹⁹ Fourth WHO-Coordinated Survey of Human Milk for Persistent Organic Pollutants
A Protocol for Collection, Handling and Analysis of Samples at the Country Level

DRAFT - WORK IN PROGRESS

5. POLLUTANTS OF INTEREST

Based on the criteria mentioned above, on the comments of the Member States and the Consultative forum dd 18th and 19th October, and on the work to be done within work package 2 of the ES BIO contract, pro's and con's of the pollutants of interest and the correlated biomarkers will be elaborated together with ideas on expected costs, relevant population groups to be studied, and possibilities for a recruitment strategy.

Candidates suggested are e.g.: lead, methylmercury, cadmium, arsenic, selected persistent halogenated organic compounds, selected pesticides with endocrine activities, phthalates, indoor radon, PAH, non-dioxin like PCBs, dioxin, cotinin.

6. SCENARIO'S

As indicated above, several key elements (such as: the number of participating Member States, the budget available, the study design) are currently still under discussion. This hampers the elaboration of a fully fledged protocol. Therefore the group proposes the concept of different scenario's for a EU wide pilot project. This allows discussion of the scope of the pilot project in more concrete terms.

- A '**BASIC**' scenario: were only a few "well-known" pollutants and biomarkers are assessed. These have to comply with basic selection criteria such as (1) well-established analytical methods, (2) ongoing programmes in most Member States, (3) clear health relevance. E.g.: lead, methylmercury, cadmium, selected persistent organic pollutants, PAHs and cotinine. As much research is already available on these markers, the public environment and health aspect predominates, the research needs focus mainly on developmental aspects of defining the best approach. The choice of such biomarkers will lead to harmonisation of biomonitoring in 'simplest' conditions, focussing on logistics and quality control and assurance elements of already well established methods.
- "**MORE EXTENSIVE**" scenario's adding to the Basic scenario:
 1. Addition of less well-defined human biomarkers e.g. related to some pesticides, brominated flame retardants, endocrine disruptors, with a less-defined toxicological profile and/or involving a higher research aspect e.g; in validation of the markers or developing methodology.
and/or
 2. specific research on the potential application of new technologies (e.g. toxicogenomics, proteomics, metabonomics) in HBM research, using the structure developed for the coordinated surveillance programme to perform coordinated (*hypothesis testing*) research activities (see also under point 3 above). For instance, at the last IG meeting in Ispra, the possibility was presented to the members of the group to add a research project further exploring the potential of metabonomics in the field of environment and health to the surveillance programme.

The Implementation Group recommends the implementation of at least a basic scenario with one or a few pollutants in as many Member States as possible, in order to fulfil the requirements related to the establishment of collaboration networks and sharing of methodologies, promotion of the idea of coordination/harmonisation in biomonitoring, testing methodological issues, obtaining a first impression of the comparability of biomonitoring data in Europe.

DRAFT - WORK IN PROGRESS

If the more extensive scenarios would not be possible in all Member States, but feasible in some of them, a list could be established, proposing several options with their pro's and con's. By choosing out of the list, several groups of Member States could take advantage of the efforts within Action 3 of the EU Health and Environment Action Plan in their preparation for a HBM programme and, in addition to the basic scenario, seek for further coordination. This would lead to a multi-layer model; a core basic level with more advanced levels which will incorporate plasticity giving the opportunity for each Member State to include specific interests. It is envisaged that this will produce a very powerful means of not only establishing a network but also for the development of synergistic links between Member States feeding on each others current knowledge.
