

Peer review and author responses for *Environmental Health* 2008, Volume 7, Supplement 1

Ethics and communication in human biomonitoring: European perspectives

Edited by Lisbeth E Knudsen, Franco Domenico Merlo and Ann Dryeborg Larsen

from the conference "Ethics and communication in human biomonitoring in Europe: results from preparation of pilot studies" , Copenhagen, Denmark, 11-13 March 2007

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Workshop on ethics and communication in Copenhagen 11-13.3.2007

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Environmental Health 2008, 7(Suppl 1):S1

Translating biomonitoring data into risk management and policy implementation options for a European Network on Human Biomonitoring

R Smolders, G Koppen and G Schoeters
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Conceptual framework for a Danish human biomonitoring program

Marianne Thomsen, Lisbeth E Knudsen, Katrin Vorkamp, Marie Frederiksen, Hanne Bach, Eva Cecilie Bonfeld-Jorgensen, Suresch Rastogi, Patrik Fauser, Teddy Krongaard and Peter Sorensen
Environmental Health 2008, 7(Suppl 1):S3

Bioethical committees and data protection issues in Poland

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Ethics issues experienced in HBM within Portuguese health surveillance and research projects

M Fátima Reis, Susana Segurado, Ana Brantes, Helena Teresinha Simões, J Maurício Melim, V Geraldés and J Pereira Miguel
Environmental Health 2008, 7(Suppl 1):S5

Communicating human biomonitoring results to ensure policy coherence with public health recommendations: analysing breastmilk whilst protecting, promoting and supporting breastfeeding

Maryse Arendt
Environmental Health 2008, 7(Suppl 1):S6

Research on ethics in two large Human Biomonitoring projects ECNIS and NewGeneris: a bottom up approach

Birgit Dumez, Karel Van Damme and Ludwine Casteleyn
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Applying bioethical principles to human biomonitoring

Myron Harrison

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Scientific integrity: critical issues in environmental health research

Domenico Franco Merlo, Kirsi Vahakangas and Lisbeth E Knudsen

Environmental Health 2008, **7**(Suppl 1):S9

Societal and ethical issues in human biomonitoring – a view from science studies

Susanne Bauer

Environmental Health 2008, **7**(Suppl 1):S10

Risk communication and human biomonitoring: which practical lessons from the Belgian experience are of use for the EU perspective?

Hans Keune, Bert Morrens and Ilse Loots

Environmental Health 2008, **7**(Suppl 1):S11

A proposed framework for the interpretation of biomonitoring data

Peter J Boogaard and Chris D Money

Environmental Health 2008, **7**(Suppl 1):S12

Human biomonitoring data interpretation and ethics; obstacles or surmountable challenges?

Ovnair Sepai, Clare Collier, Birgit Van Tongelen and Ludwine Casteleyn

Environmental Health 2008, **7**(Suppl 1):S13

Referee's comments to the authors

Title	Translating biomonitoring data into risk management and policy implementation options for a European Network on Human Biomonitoring
Author(s)	R. Smolders, G. Koppen, G. Schoeters
Referee's name	Peter Farmer

General comments:

With the rapidly increasing amount of human biomonitoring (HBM) data that is becoming available, there is a great need to develop a systematic approach for its interpretation. This manuscript describes a four stage approach which it is hoped will eventually lead to the formulation of risk reduction strategies based on HBM data. The procedure is logical, well thought out, and clearly described.

Minor essential revisions:

An abbreviation list would be valuable (e.g. NUTS, HBM, P₇₅ etc)

Line 100: 'completion' seems the wrong word

Line 108: 'pertain' seems the wrong word

Lines 135 and 164: 'a priori'

Lines 143, 379, 410, 514, 'cotinine'

Line 183: 'and' instead of 'an'

Line 209: Does this signify 120 participants in each state or in total? Please indicate.

Line 261: diphenyl'

Line 268: 'delete 'was'

Line 282: 'led'

Line 296: 'deducted' seems the wrong word. Should this be 'deduced'?

Line 300: delete 'a.o.'

Lines 396, 440, 450: 'advice'

Line 414: replace 'it' with 'which'

Line 436: delete 'of'

Line 443: 'outlined' seems the wrong word

Line 454: replace 'exist' with 'consist'

Line 553: it would be good to be more precise than 'early 21st century'

Line 558: insert 'of' between 'trends' and 'exposure'

Line 884: 'creatinine'

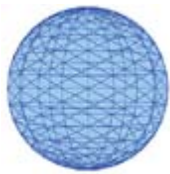
Discretionary revisions:

In step 1, 'Are there differences among biomarkers in time or space?', another important parameter is the analytical validation of the method, which is essential when data are aggregated. This includes both the collection and storage of the samples and the analytical process used for the determination. This was emphasised for example in the ECETOC publication on interpretation of biomonitoring data (reference 13).

In step 2, 'Are the observed differences reason for concern?' a variety of approaches are discussed. The use of biomonitoring equivalents as a screening approach for interpreting biomonitoring results from a public health risk perspective was also described by SM Hays et al, (2007) Reg Toxicol Pharmacol 47 (1): 96-109. Sharing of data is correctly mentioned as being important in order to get the optimal outcome from HBM data. The international exchange of data was also encouraged in the Research Agenda proposed in the publication on Human Biomonitoring for Environmental Chemicals from the National Research Council of the National Academy (reference 6).

The importance of knowing the dose-response relationship (especially at low doses) is also critical in this interpretation and this is correctly mentioned as an area for future research on page 27. Improved pharmacokinetic modeling is also important as a research area for the improvement of the interpretation of biomarkers. Finally (and probably outside the scope of this publication) is the question of susceptibility factors (e.g. genetic polymorphism) in the exposed population which should not be overlooked in the hazard/risk assessment process.

One of the current reasons for interest in this topic is the expected European Pilot Project on HBM, which is referred to in the abstract and elsewhere (pages 10, 40), and this document was developed in connection with the ESBIO project of HBM experts from several EU Member States which has acted as an EU Network in this area. If further details about the current plans for this Pilot project and its funding are available it would be informative to include these.

**Referee's comments to the authors**

Title	Translating biomonitoring data into risk management and policy implementation options for a European Network on Human Biomonitoring
Author(s)	R. Smolders, G. Koppen, G. Schoeters
Referee's name	Len Levy

General comments: A very well crafted and enjoyable paper that clearly represents the work of much detailed discussions. It sets out a case for the structured use of BM within a framework and, as the authors state, it might need some fine tuning with experience.

Discretionary revisions:

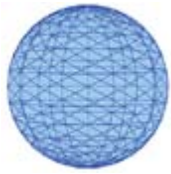
I have made some suggestions for small changes which are in tracking change on the MS for convenience.

Response to reviewers:

I have included the changes suggested by the authors in the document.

Kind regards,

Roel Smolders, Environment & Health



Referee's comments to the authors

Article ref no.	
Title	Conceptual framework for a national human biomonitoring program
Author(s)	Thomsen, M., Knudsen, L.E., Vorkamp, K., Frederiksen, M., Bach, H., Bonefeld-Jorgensen, E.C., Rastogi, S., Fauser, P., Krongaard, T. and Sorensen, P.B.
Referee's name	Ovnair Sepai

General comments: The paper is on the whole well written – but my only concern is its focus. If it is supposed to describe a National (Danish) Conceptual programme then the National needs need to be emphasised. The paper at present spends too much effort on describing the Potential Pilot for Europe as developed by ESBIO.

Major compulsory revisions: Please balance the paper – many comments and suggestions in the paper as tracked changes

Minor essential revisions: Indicated in the paper

Conceptual framework for a national human biomonitoring program

¹Thomsen, M., ²Knudsen, L.E., ³Vorkamp, K., ²Frederiksen, M., ¹Bach, H., ⁴Bonefeld-Jorgensen, E.C., ³Rastogi, S., ¹Fauser, P., ⁵Krongaard, T. and ⁶Sorensen, P.B.

Abstract

The aim of this paper is to present the conceptual framework for a **Danish national** human biomonitoring (HBM) program. The EU and national science-policy interface, that is fundamental for a realization of the national and European environment and human health strategies, is discussed, including the need for a structured and integrated environmental and human health surveillance program at national level. In Denmark, the initiative to implement such activities has been taken. The **??proposed??** framework of the national/ **Danish** monitoring program constitutes four scientific expert groups, i.e. i. Prioritization of the strategy for the monitoring program, ii. Collection of human samples, iii. Analysis and data management and iv. Dissemination of results produced within the program. This paper presents the overall framework for data requirements and information flow in the integrated environment and health surveillance program. The added value of an HBM program, and in this respect the objectives of national and European HBM programs supporting environmental health integrated policy-decisions and human health targeted policies, are discussed.

The abstract needs to be clarified.

Introduction

Sustainability and integrated protection of the environment and human health are closely linked [1]. Denmark has developed a national strategy for sustainable development for which the main goal is a constant decrease in pollutant levels in products, food, the working environment, traffic and the indoor environment [2-5]. The Danish vision of sustainable development is based on eight objectives and principles. According to objective 2, *'there must be a safe and healthy environment for everyone, and we must maintain a high level of protection'*[2]. This is further described in the section on the cross-cutting issue 'Environment and health' which states that: *'Denmark should be a country where pollution from products, food, working environment, traffic and physical indoor conditions affecting the population's quality of life and health is constantly falling. Harm to animals and plants from pollution should also be limited. The protection level must take account of especially sensitive groups of people - such as children, pregnant women, people who suffer from allergies or from chronic illness - and of particularly vulnerable ecosystems'* [2].

In 2003, the European Commission launched the European Environment and Health Strategy [6, 7]; a strategy to reduce diseases linked to environmental factors. The strategy, also known as SCALE, comprises the development of information systems as well as the compilation of

adequate political measures. Its themes are: Scientific evidence, focus on Children, raising of Awareness, improving the situation by use of Legal instruments and allowing Evaluation of the progress made.

In the same year, Denmark published a background report [8] for a strategy and action plan to protect public health against environmental factors [9]. The strategy addresses chemicals with respect to their harmful effects, which is also addressed in the overall Danish chemicals strategy

The European Environment and Health Action Plan 2004-2010 stresses clearly the need for closer coordination between the health and environment research areas [10, 11]. The action plan identifies 13 actions with a focus on: improving the information chain by developing integrated environment and health information (Action 1-4), filling the knowledge gap by strengthening research on environment and health and identifying emerging issues (Action 5-8) and reviewing and adjusting risk reducing policy and improve communication (Action 9-13) [12].

The ultimate goal of the European and the national strategies is to develop an environment and health 'cause-effect framework' that will provide the necessary information for the development of policies dealing with sources and impact pathways of health stressors.

Action 1 (Develop environmental health indicators) and Action 2 (Develop integrated monitoring of the environment, including food, to allow the determination of relevant human exposure) of the European Environment and Health Action Plan 2004-2010, concerns the health of the environment and integrated monitoring of environmental contamination leading to human exposure, i.e. external human exposure. Action 3, currently underway, focuses on internal human exposure or human biomonitoring. In the third action, the European Commission commits itself '*to develop in close cooperation with the Member States a coherent approach to Human Biomonitoring in Europe and to launch an EU Pilot Project to test out the feasibility of such a coordinated approach*'. For this reason, an Expert team to Support BIOmonitoring (ESBIO) together with the Implementation Group (IG) of the European HBM has been preparing implementation of an EU pilot project, which was launched in the spring 2007. The background and rationale for the EU Pilot Project and the Danish proposal of a conceptual framework for a national HBM program, are presented in this paper. The **proposed** framework builds on the principles and experience gained from scientific work at national and EU level in aggregated as well as environment and human health indicator reporting within the area of cumulative risk from exposure [7, 13-19].

Conceptual framework for a national HBM program

A HBM program should be a central part of any national integrated environmental and human health surveillance program, and there is a need to develop an interface between the science and the policy decision support systems – in SCALE denoted a 'response system'. To make this interface as transparent as possible, we suggest risk scenario descriptions and selections (prioritization) to form the basis for human health oriented biomonitoring surveys. The scenario selections will be based on hypothesis-driven risk scenario descriptions focusing on children as the most vulnerable sub-population. The scenario descriptions deliver input to the prioritization of the exposure modelling of high-risk chemicals with respect to the national and European priority diseases as well as the biomonitoring and monitoring

activities. The modelling of outdoor exposure is already included in the national monitoring program of the environment [29], whereas the indoor exposure needs to be monitored in addition to internal exposure, i.e. biomarkers of exposure. This could be formulated as a minimum requirement for the output from the basic scenario, as defined in the second recommendation from the Implementation Group.

Referee's comments to the authors

Title	Conceptual framework for a national human biomonitoring program
Author(s)	Thomsen, M., Knudsen, L.E., Vorkamp, K., Frederiksen, M., Bach, H., Bonefeld-Jorgensen, E.C., Rastogi, S., Fauser, P., Krongaard, T. and Sorensen, P.B.
Referee's name	Roel Smolders

General comments:

The paper describes the recent actions that have been taken by the European Environment & Health Action plans, and how this is translated to the specific Danish situation. The focus is on human biomonitoring, and the development of biomarkers to measure exposure and effects of contaminants. The paper is generally well written, provides a good overview of Danish HBM developments, and is generally of a very good quality.

Major compulsory revisions:

- Although the paper describes in detail all the different actions that are going on in Denmark with regard to HBM, it is not clear how these actions are coordinated, who sets up the research agenda and priorities, and who decides on the way forward (is it scientists, policy makers, a multi-professional panel,...?). It would be interesting to know which stakeholders are involved in the decision making, and how decisions are made.
- The same comment goes for the DPSEEA process. While this of course is a very useful and well-documented approach, how is this translated into the particular Danish situation, with which stakeholders involved and decision structures set up? (e.g. page 11: "...by prioritizing of the human biomonitoring strategy and design of monitoring activities..." Who sets the priorities and designs the activities?)
- How does the Danish HBM network compare to the European Network. Will the Danish program only follow the protocol, sample numbers, contaminants,... outlined in the Third Recommendation of the IG and the European Pilot Project, or will it include more age groups, participants, pollutants,...
- Figure 2 is difficult to interpret, with different shades and line colors being discussed. However, it is rather confusing and a different approach or revision of the figure is advisable

Minor essential revisions:

- Page 5: there is also a Third Recommendation from the IG available. Please refer to the latest version of the IG recommendation
- Page 5-6: The difference between the "basic scenario" and the "extended scenario" is not very clear from the text. I would like to see a more careful and precise wording to describe the similarities and specificities of both scenarios and how this reflects on the Danish program
- Page 9: An HBM program will naturally for a central part...
- Figure 1 mentions a "black inner part of the figure" which I seem to miss
- Figure 2: Helth status

Revisions according to recommendations of reviewers:

Revisions according to reviewer 1

In reply to bullet 1 to 3 under Major revisions has been addressed by several of the specific changes listed below; e.g. point 5, 8, 11, 12 and 13. According to the comments in bullet 4, a wrong version of figure 2 has been replaced by a corrected version.

In reply to the bullets under Minor essential revisions, the mistake addressed by bullet 1 has been corrected in point 16 below. In respond to bullet 2, no changed has been inserted as the basic and extended scenario the terminology used in the IG recommendation and further specification are not relevant at the stage of proposal which the paper represents. The sentence on page 9 has been corrected as explained in point 15 below. Line 1 of the figure text to Figure 1 ‘... black inner part of the figure’ has been changed to ‘...black box in the middle of the figure’. Figure 2 has been corrected

Revisions according to reviewer 2

1. The title has been changed from ‘Conceptual framework for a national human biomonitoring program’ to ‘Conceptual framework for a Danish human biomonitoring program’.
2. Line 1 of the abstract ‘...to present the conceptual framework for a Danish national human...’ has been changed to ‘to present the conceptual framework for a Danish human...’
3. Line 6 of the abstract has been clarified according to the question marks (The ?? framework of the national ?? monitoring) of reviewer 2: ‘...The proposed framework of the Danish monitoring...’
4. The addition the clarification mentioned in point 2 and 3, the situation in Denmark regarding the bias surveillance towards parts of the environment and scattered HBM has been added by adding the paragraph: ‘In Denmark environmental monitoring has been prioritized by extensive surveillance systems of pollution in oceans, lakes and soil as well as ground and drinking water; the latest year also including air. Human biomonitoring has only taken place in research programs and few incidences of e.g. lead contamination. However an arctic program for HBM has been in force for decades and from the preparations of the EU-pilot project on HBM increasing political interest in a Danish program has developed.’
5. Line 5 of the introduction and the remaining of the first paragraph: ‘...principles. According to objective 2, *‘there must be a safe and healthy environment for everyone, and we must maintain a high level of protection’*[2]. This is further...’ has been changed to:

‘...principles [2]:

1. *The welfare society must be developed and economic growth must be decoupled from environmental impacts.*
2. *There must be a safe and healthy environment for everyone, and we must maintain a high level of protection.*
3. *We must secure a high degree of bio-diversity and protect ecosystems.*
4. *Resources must be used more efficiently.*
5. *We must take action at an international level.*
6. *Environmental considerations must be taken into account in all sectors.*
7. *The market must support sustainable development.*
8. *Sustainable development is a shared responsibility and we must measure progress.*

Objective 2 is further...’

6. Paragraph 3 of the Introduction: The following text has been added:

The action plan includes a ten-point plan:

1. *Negative impacts from chemicals are to be reduced, and the substitution of hazardous substances by less hazardous ones must be accelerated*
2. *The incidence of allergy and respiratory disorders is to be reduced*
3. *Measures directed at endocrine-disrupting substances are to be intensified*
4. *Noise nuisance is to be reduced*
5. *The negative impacts on health from air pollution and from the indoor climate are to be reduced*
6. *Food is to be safe and free from pollution*
7. *Groundwater and drinking water must be protected*
8. *Research into the significance of environmental factors on health is to be enhanced*
9. *Cooperation between the authorities must be strengthened*
10. *Increased attention must be accorded to environmental factors and health in international cooperation*

Human biomonitoring is only addressed indirectly by the need for 'health monitoring'. Enhancement of the cooperation at administrative level is however highlighted as the 'National Board of Health has primary responsibility for general health monitoring, while the responsibilities of other ministries are more linked to preventive initiatives such as setting limit values and detailed requirements for the different sources of environmental factors'. Enhanced cooperation between ministries is to ensure coordinated and cohesive action against environmental factors that can affect health, and in particular within areas of common interest are need for the realisation of the strategy and action plan [9].

7. Paragraph 5 of the Introduction has been changes to emphasize a citation from the European E&H strategy : *'develop an environment and health cause-effect framework'*
8. The last three lines of the Introduction: 'The framework builds on the principles and experience gained from scientific work at national and EU level in aggregated as well as environment and human health indicator reporting within the area of cumulative risk from exposure [7, 13-19].' has been changes to 'The proposed framework builds on the principles and experience gained from scientific work at national and EU level, e.g. NoMiracle, as well as environment and human health indicator reporting within the area of cumulative risk from exposure [7, 13-19]. Furthermore, ideas and discussion within the Danish interest group for a national HBM program constituted by the authors of this paper.'
9. Line 3-6 in the first paragraph of the Background 'The basic scenario includes mainly heavy metals and cotinine, whereas the extended scenario includes contaminants, for example brominated flame retardants (BFRs), for which complex analytical methodologies are required.' has been changes to 'The basic scenario includes mainly heavy metals (lead, mercury and cadmium) and the metabolite cotinine from nicotine in tobacco smoke, whereas the extended scenario includes contaminants, for example brominated flame retardants (BFRs), for which complex analytical methodologies are required.'
10. The section titled 'Danish initiatives and projects', first paragraph..... the sentence ' Focussing on BFRs, existing knowledge of external and internal exposure was reviewed recently, with emphasis on identification of exposure routes [25]' has been extended by '; the study concluded that unintentional ingestion of dust is at least of similar importance as food.'
11. The section titled 'Danish initiatives and projects', second paragraph 'Analogous to e.g. the WHO's integrated information system (http://www.who.dk/EHindicators/indicators/20040311_1); a national pilot project on the integration of environmental data bases and population health registers has been performed at the national level, in Denmark [26].' has been extended by 'The project proposes that the geographically based health database of the National Board of Health, is utilised as the basis for linkage of health and environmental registers [26] '

12. The section titled ‘Danish initiatives and projects’, third paragraph ‘Several research projects are addressing chemicals and biomarkers focusing on the priority diseases included in the NEHAP [9], e.g. COPSAC (www.copsac.dk) and AIPOLIFE (www.airpolife.dk).’ have been changed to ‘Several research projects are addressing chemicals and biomarkers focusing on the national priority diseases respiratory disorders and allergy included in the NEHAP [9]; e.g. COPSAC (www.copsac.dk) and AIPOLIFE (www.airpolife.dk).’
13. The section titled ‘Danish initiatives and projects’, fourth paragraph ‘...Denmark [28]. The ideas of this report have been presented to the Danish Interministerial Group for Environmental Factors and Health, which was established in relation to the National Environment and Health Action Plan (NEHAP).’ has been extended by the sentence ‘One of the ideas of the report are to establish a systematic surveillance and risk assessment of chemicals with negative effects on health in consumer products, food and tap water and to clarify the relation between environment and food contaminants and related health effects on male reproductive organs [28].’
14. The chapter title ‘Conceptual framework for a national HBM program’ has been changed to ‘Conceptual framework for a Danish HBM program’
15. The first sentence of the chapter (point 14) ‘An HBM program will naturally form central part of a national integrated environmental and human health surveillance program, and therefore there is a need to develop an interface between the science and the policy decision support systems – in SCALE denoted a ‘response system’ has been changed to ‘A HBM program should be a central part of any national integrated environmental and human health surveillance program, and there is a need to develop an interface between the science and the policy decision support systems – in SCALE denoted a ‘response system’
16. Line 13 of the first paragraph in the chapter (point 14) ‘...as defined in the second recommendation from the Implementation Group.’ has been corrected to ‘as defined in the third recommendation from the Implementation Group.’
17. Line 5-6 of the second paragraph of the section titled ‘Dataflow within integrated environment and health monitoring’: ‘Additional chemical-specific properties may be taken into account addressing critical exposure routes, as has for example been carried out for BRFs [25].’ has been extended: ‘Additional chemical-specific properties may be taken into account addressing critical exposure routes, as has for example been carried out for BRFs in which case unintentional ingestion of dust is suggested at least of similar importance to food intake [25].’
18. There is no relevant text to include in the suggested section titled ‘Competing interests’ and the suggested section have therefore not been included.
19. The section on Authors’ contributions has been added. The text inserted presented here: ‘The authors of the paper are all members of a Danish working group that has made an effort to gather all national main actors within human biomonitoring research in Denmark. The group prepared an expression of interest for a Danish human biomonitoring programme to the relevant authorities and suggested a Danish human biomonitoring programme at the same scale as the existing National Monitoring and Assessment Programme for the Aquatic and Terrestrial Environment (NOVANA). Marianne Thomsen has taken the initiative to write this paper based on the experiences from the working group and scientific projects such as e.g. NoMiracle. Hanne Bach, Peter B. Sørensen and Patrik Fauser have been involved in the same projects and contributed mainly in the early phase of this paper, with input on the structure of the paper and, more specifically, a cause-effect framework. Lisbeth Knudsen contributed to the manuscript with her insights into human biomonitoring activities on the national and European level, among others from participation in the EU network “Expert team to support biomonitoring in Europe (ESBIO)”. Lisbeth Knudsen, Katrin Vorkamp, Marie Frederiksen and Marianne Thomsen have been involved in related human biomonitoring activities with focus on brominated flame retardants. Katrin Vorkamp has also contributed with experience from NOVANA and the Arctic Monitoring and Assessment Programme (AMAP). Suresh Rastogi has long term experience with near-field exposure from consumer products. Eva Bonefeld-Jørgensen has likewise been active within human biomonitoring for many years, among others within the Human Health Programme under AMAP. Teddy

Krongaard coordinated the Danish expression of interest. All authors have contributed to the manuscript with discussion and comments.'

20. A section titled Acknowledgement has been added, the text included in the section as follows: 'The authors acknowledge the support of the project ESBIO (Contract No: 022580) funded by the European Commission (Directorate-General Research) under the 6th Framework Programme for Research and Technological Development in close cooperation with Directorate-General Environment .'
21. The reference list has been updated according marked changes in the document titled 'Thomsen M et al_track changes revisions.doc'



Referee's comments to the authors– this sheet WILL be seen by the author(s)

Title	Activity of Biomedical Ethics Committees and Data Protection issues in Poland
Author(s)	Danuta Ligocka
Referee's name	Lisbeth E. Knudsen

General comments:

The paper describes the Polish situation related to ethics approval of biomonitoring programs and data protection and especially activities at the Nofer Institute in Lodz which are engaged in human biomonitoring. The paper will benefit from more examples e.g. as titles of projects evaluated and table 1 need some update. Figure 1 need some text.

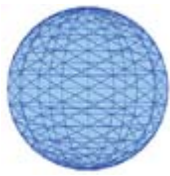
A language edit is necessary but can be done in Copenhagen.

I strongly encourage the author to include and update the two tables on REC and data protection developed by ESBIO in the publication, as appendixes. These are enclosed.

Major compulsory revisions:

Minor essential revisions:

Discretionary revisions:

Referee's comments to the authors– this sheet **WILL** be seen by the author(s)

Title	Activity of Biomedical Ethics Committees and Data Protection issues in Poland
Author(s)	Danuta Ligocka
Referee's name	Leslaw Niebroj

General comments:

The paper by Danuta Ligocka, entitled "Activity of Biomedical Ethics Committees and Data Protection issues in Poland", is undoubtedly, interesting article covering a very important, both from theoretical and practical points of view, topic. Although, since the early 1990s', the Iron Curtin which previously divided Europe (or even entire World) has not existed any more, and since 2004 Poland, with other Central and East European countries has become the EU member, it is an everyday experience that these countries (maybe excluding the Czech Republic) are still considered as "terra incognita". It should be emphasized that what is unknown is very often perceives as dangerous. In consequence, there are many obstacles which impede the potential collaboration of Polish scientists with renowned universities and research institutes of Western Europe. From this, practical perspective, the article written by Ligocka is of particular importance, especially when taking into account that there are relatively few articles, at least in English, which deal with the problems of standards in research ethics in Poland. The topic covered by this article is interesting and important – as it was said - also from theoretical point of view. Moral pluralism and justifications of the ethical principles and rules in the world which does not share the same ethical vision should be listed among the most of the debates in bioethics. Ligocka's article can provide some interesting insights into these debates, especially by indicating the specific (or rather the lack of this specificity) character of Polish deontological guidelines of medical research.

Major compulsory revisions:

I have serious doubts as to whether "Conclusions" accurately reflecting the finding of the paper. In fact the Author in the text of the article pays little attention to providing sufficiently precise information concerning the "EU and international rules with respect to ethical issues". Although, in the main body of the article's text (e.g. p. 6) there is a statement that "This Act fulfils the Directive 95/46/EC", I has been unable to find the justification for this, very 'strong' opinion. I suggest limiting the purpose of the article to describe Polish norms without deciding whether they are / are not fulfils EU or other international standards. Maybe it would be enough to indicate that, at least, some of Polish regulations make direct references to these internationally recognized documents.

Minor essential revisions:

Taking into account that the "target readers" of this article would be persons who are not accustomed to the structure of Polish Institutional Review Boards (IRBs), I strongly advise the Author of this paper to translate the Polish name of IRBs [Komitety bioetyczne] into English using always these same words. Danuta Ligocka wrote about "Regional Ethical Commissions", "Bioethical Commissions" "Biomedical Ethics Committee". The use of different terms could – at least in my opinion – misleadingly suggest that there are substantially different institutions. In order to avoid misunderstandings I think it is a good practice to write in square brackets the name of institutions or titles of official documents in the original language (both in the text and in the list of references).

Discretionary revisions:

I will appreciate if Danuta Ligocka would explain her methodological decision to use as an example of Polish IRBs just the committee at the Nofer Institute in Lodz. The Author wrote: "In the frame of Human Biomonitoring Programme, the application for biomedical evaluation will be submitted to Biomedical Ethics Committee at the Nofer Institute" (p. 4). Is it the only reason?

Thank you for the opportunity to review this interesting manuscript.

Follow letter:

ENVIRONMENTAL Health - "Activity of Biomedical Ethics Committees and Data Protection issues in Poland" Danuta Ligocka

Responding to Reviewer Lisbeth E. Knudsen

Thank you very much for reviewing my paper and your comments.

According to your suggestions I updated and add some comments to table 1.

Updated table developed by ESBIO are now included as Appendix 1 – REC in Poland and Appendix 2 – Data Protection in Poland.

With best regards,

Danuta Ligocka

Responding to Reviewer Leslaw Niebroj

Thank you very much for reviewing my paper and your constructive comments.

I agree with reviewer concerning “Conclusions” – this part has been changed.

English versions of official websites of different institutions (including some ministries) use different terms which is confusing. Nevertheless, I follow your suggestion unifying terms to avoid misunderstanding.

According to your suggestions titles of official documents are now also in original language, but only in the reference list. All bilingual names and documents titles in the text could make it less clear.

Polish Minister of Health and Welfare supports the European Human Biomonitoring Programme and Prof. Marek Jakubowski, the Nofer Institute of Occupational Medicine as the national work package leader. That is the reason why within the frame of, that pilot project the application for bioethical evaluation will be submitted to the Biomedical Ethics Committee at the Nofer Institute of Occupational Medicine in Lodz.

Additional information is now included as two Appendixes - tables developed by ESBIO Appendix 1 (REC in Poland) and Appendix 2 (Data Protection in Poland).

Thank you for your kind words.

With best regards,

Danuta Ligocka



Editors-in-Chief
Philippe Grandjean and David Ozonoff

Referee's comments to the authors– this sheet WILL be seen by the author(s)

Title	Ethics issues experienced in HBM within Portuguese health surveillance and research projects
Author(s)	Fátima M Reis, Susanne Segurado, Ana Brantes, Teresinha Helena Simões, Maurício Melim, V Geraldes, J Pereira Miguel
Referee's name	Lisbeth E. Knudsen

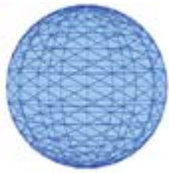
General comments:

This paper discusses the ethics in biomonitoring in several Portuguese studies. The paper is not complying with the introduction, methods and materials, results and discussion standard and the abstract exceed the allowed number of words. The authors are recommended to restructure the paper and to put more emphasis on the description of the studies mentioned as well as results from these studies. The authors are recommended to include the tables related to ethics and to data protection as developed within the ESBIO project

Major compulsory revisions:

Minor essential revisions:

Discretionary revisions:

**Referee's comments to the authors– this sheet WILL be seen by the author(s)**

Title	Ethics issues experienced in HBM within Portuguese health surveillance and research projects
Author(s)	Fátima M Reis, Susanne Segurado, Ana Brantes, Teresinha Helena Simões, Maurício Melim, V Geraldés, J Pereira Miguel
Referee's name	Helena Moniz (assistant professor at the Faculty of Law, University of Coimbra, Portugal; researcher in Biomedical Law Centre, Faculty of Law, University of Coimbra, Portugal)

General comments:

Knowing that the article has been written by scientific researchers (not lawyers) it is a good article. But it is necessary to add some information.

Major compulsory revisions:

1) The duty to document all the acts in medical practice is not only necessary "in order to be able to refute accusations of improper conduct", but also a disciplinary duty according to the Deontological Code of the Portuguese Medical Association (Ordem dos Médicos). The article does not refer how they collected data, and if they used clinical files of the patients for research purposes. If so, they must mention:

a. If they have got patient's consent to use health information and clinical files for researcher purposes;

b. If they have got authorization to use the clinical files to research purposes from the National Commission for Data Protection (Comissão Nacional de Protecção de Dados), and if they have notified CNPD about this collections, the purposes of the collection, the period of time of the collection, and the person responsible for the collection.

c. Throughout the article there is no reference to the National Data Protection Law (Law n.º 67/98, 26th October); and there is no reference to the Access to the Public Documentation (Lei de Acesso aos Documentos Administrativos – Law n.º 46/2007, 24th August, or the old Law n.º 65/93, 26th August, with modifications). It is important to be aware of it, because this Law regulates the access to clinical files when in public hospitals.

2) The European Convention on Human Rights and Biomedicine is a very important law, but there are also rules in Portuguese Constitution (article 26, 1) and Civil Code (article 1878, 2) which impose the respect to the minor's opinion according with is age and mental maturity.

Minor essential revisions:

1) The European Convention on Human Rights and Biomedicine is a convention promoted by the Council of Europe, and it is not by the European Union, so it is not correct writing "European Community Convention" (page 4).

2) "The responsibility for the protection of their rights is shifted to their guardians and to the researchers" (page 4) – I don't think that we could say that the researchers have a responsibility for the protection of the children rights, a responsibility different from the one that they have to all patients.

3) It would be well advised to mention the special rules for clinical trials involving minors.

4) "All projects store sensitive data in health so participants' names are coded prior to data processing and analysis and database access is protected by user passwords, conforming to legislation on information storage" (page 11) – authors only mention Law n.º 12/2005, 26th January. But this is not enough – they have to mention Data Protection Law. Otherwise, if they were using health information for scientific investigation according to the Law n.º 12/2005 they have to anonymize all information before working with it.

5) If body samples have been stored, the biobank should be authorized according to the article 19, Law n.º 12/2005, and the samples must have to be kept anonymized or must be kept separately from the identity data. The authors should mention that they work according to these rules.

Discretionary revisions:

1) The consent form should have mentioned two different consents:

- a. Consent for using body samples for scientific research and
- b. Consent for data collection for scientific research.

Follow letter:

By Fátima Reis et al: "Ethics issues experienced in HBM within Portuguese health surveillance and research projects"

Response to revisors:

Following the suggestions of the revisor Lisbeth Knudsen, the article was completely restructured. However, this restructuring did not sacrifice the corrections/clarifications made in reply to the recommendations/suggestions of the revisor Helena Moniz.

Response to Helena Moniz:

Major revisions

1. The Deontologic Code of the Portuguese Medical Association has been referred to. No clinical files are accessed - all health information required is provided by questionnaire by the participant, with their informed consent. We have added a paragraph to clarify this point.
2. Both these documents have now been referred to in the text.

Minor revisions

1. This has been corrected.
2. This has been clarified.
3. No clinical trials take place in HBM.
4. This law has now been referred to.

Anonymization is incompatible with the work that is performed, and with the very principles governing HBM e.g. the right to know.

Article 19 refers to the collection of biological samples for research and contemplates the possibility of coding as opposed to irreversible anonymization.

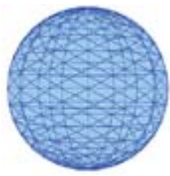
5. The suggestions concerning the storage of biological samples have been incorporated. The issue of authorization has been considered, especially in the Conclusions, and will be reassessed within the projects and measures taken to conform to regulations.

Discretionary revisions

1. The final paragraph under the subheading "Data protection" mentions both forms of consent. They are also now mentioned under "Information practices".

Response to Lisbeth Knudsen:

1. The article was restructured as suggested in order to comply with the recommended structure for a Research article, which includes Abstract, Background, Methods, Results and Discussion and Conclusions. The items Competing interests, Authors' contributions, Acknowledgements and References are also included.
2. The Abstract was reformulated in order to comply with the maximum word allowance of 350.
3. As suggested, greater emphasis was placed on the description of the studies conducted, as well as on the results, which are presented in the section entitled Results and discussion.
4. The tables which the revisor suggests be included were not compiled by these authors. As such, the document "Ethics and data protection in a number of European countries", available for download, in which these tables are included is referenced.



Referee's comments to the authors– this sheet **WILL** be seen by the author(s)

Title	Communicating human biomonitoring results Interference with public health recommendations Analysing breastmilk - promoting, protecting and supporting breastfeeding
Author(s)	Maryse Arendt-Lehners
Referee's name	Lisette van Vliet

1. The author is not an English native speaker, so I suggest some revisions to the language, for improved clarity and grammatical correctness. (I have included these suggestions via 'track changes' to the article – and believe these keep as close to the author's intended meaning as possible).

2. I found many of the points extremely important and valid – for instance, I particularly liked the comment on page 4 that providing breastmilk samples may not be easy for some women. This shows the author's experience with the challenges of expressing breastmilk, and illustrates merely one, albeit not the most important aspect of the depth of the undertaking in biomonitoring breastmilk. Regarding the more important aspects: it may be worth adding a sentence or two that expresses recognition of why NGOs and the media choose to focus on breastmilk, beneath its immediate resonance with the public - because of the 'sense of the sacred' – the social/cultural norms vested in the 'inviolability' of a mother and baby's breastfeeding relationship, and the notions of 'purity' of this food.

I believe this essentially normative aspect, perhaps counter intuitively, strengthens the subsequent points about the enormous need to ensure awareness of the 'counteracting' benefits that breastfeeding provides to chemical exposures, and the manifest importance of political action to regulate and eliminate the sources of chemical exposures.

3. The only other significant improvement that I might wish to see in this article would be more substantiation of the points concerning the negative effects on the confidence in breastfeeding which arise from biomonitoring showing chemical presence. Such substantiation could follow such sentences as those below:

Information on chemicals in breastmilk may affect the mother and her social network in a way that undermines their confidence in the continuation of breastfeeding. (p.4)

Sensational messages about contaminants in breastmilk undermine the value of breastfeeding and the confidence of parents and health care professionals in breastfeeding and long term breastfeeding. (p.8)

While I absolutely agree with the author, there are others that may not, and I believe it would help the argument to provide some forms of evidence. Even discussion of direct experience and observation from the Initiative Liewensunfank could assist here.

Referee's comments to the authors– this sheet **WILL** be seen by the author(s)

Title	Communicating human biomonitoring results Interference with public health recommendations Analysing breastmilk - promoting, protecting and supporting breastfeeding
Author(s)	Maryse Arendt-Lehners
Referee's name	Alison Linnecar

General comments:

This well-evidenced article addresses the problem of policy coherence in communicating public health recommendations in the fields of environmental and of child health. This is a recent problem caused by use of biomonitoring of breastmilk as an indicator of environmental contamination, reflecting the burden of chemicals in all human bodies. Evidence of man-made chemical residues in breastmilk can provide a shock tactic to push for stronger laws to protect the environment. When there is adequate legislation to address the problem of pollution, there is a documented decrease in levels of chemicals residues in humans. However, alarmist messages about chemicals detected in breastmilk can cause a backlash against breastfeeding, thus running counter to the consistent public health messages used by the World Health Organization to improve child survival. The article proposes key messages from WHO's Fourth Coordinated survey of human milk as an example of balanced communication of biomonitoring results.

Minor Essential Revisions:

1. The Title needs careful consideration. There may be three titles or sub-titles but the second, "Interference with public health recommendations" is perhaps too strongly worded. I would prefer: 1. Main title: "Analysing breastmilk whilst protecting, promoting and supporting breastfeeding" and 2. Sub-title: "Communicating human biomonitoring results to ensure policy coherence with public health recommendations".

2. The Abstract needs to be reworked to reflect better the argumentation in the article. The first sentence (lines 2-4) does not flow well and is difficult to understand.

It might be preferable to change the sequence of the arguments in the Abstract, and to start with the breastfeeding recommendation, for example:

* This article addresses the problem of ensuring consistent messages in communicating public health recommendations on environmental health and on child health.

See suggested grammatical improvements in Track Changes mode in the text.

Discretionary revisions:

* The World Health Organization states that the protection, promotion and support of breastfeeding rank among the most effective interventions to improve child survival.

* International public health policy recommends exclusive breastfeeding for six months, followed by continued breastfeeding with the addition of safe and adequate complementary foods for two years and beyond. There should be unequivocal support for this global public health recommendation.

* The detection of chemical residues in breastmilk is thus not only a sad and shocking reality: it also creates a dilemma to ensure consistency in communicating policy messages.

* Biomonitoring of breastmilk is used as an indicator of environmental contamination and of the consequent burden of chemicals in all human bodies.

* Evidence of man-made chemical residues in breastmilk can provide a shock tactic to push for stronger laws to protect the environment. If the problem of pollution is adequately addressed by legislation, there is a consequent decrease in levels of chemicals residues in humans.

* However, messages about chemicals detected in breastmilk can become dramatized by the media and cause a backlash against breastfeeding, thus contradicting the public health messages issued by the World Health Organization.

*The article proposes messages from WHO's Fourth Coordinated Survey of Human Milk as an example to be followed to contribute to policy coherence:

"Given that breastfeeding reduces child mortality and has health benefits that extend into adulthood, every effort has been made to protect, promote and support breastfeeding in the context of these studies."

3. Discretionary Revisions: the letters refer to relevant pages in the text, where suggested improvements are inserted in Track Changes mode.

a. The author uses the term "healthy nutrition" and "food", whereas other properties of breastmilk are comprehensively described later in the text. It would be preferable to use more comprehensive wording such as "live protective factors", as suggested. It can be stated that breastmilk provides not only the first food, but also the first medicine and the first vaccine to confer immunity.

b. Throughout the text, the author uses the word "communication" with its French connotation. In English it would be preferable to use more specific terms: "messages directed to mothers", or "publication of results", as used by WHO.

c. The second reviewer could advise whether the author should qualify the term "chemicals" by "*man-made chemicals*".

d. There appears to be one step missing in the argument – see suggestions above for the revised Abstract:

- The results of biomonitoring of breastmilk provide the evidence base for adopting strengthened legislation to reduce environmental contaminants.
- In turn, such legislation is effective in reducing the accumulation of man-made chemical substances in the human body.

4. Additional considerations:

a. Reference could be made to the ratification and entry into force of the Stockholm Convention on Persistent Organic Pollutants.

b. Reference could also be made to the fact that breastfeeding is a renewable natural resource that does not generate pollutants from transportation, nor waste products that contaminate the environment.

Note: The spelling of breastmilk and breastfeeding always presents variations, ranging from "breast milk" to "breast-milk" etc. For reasons of correct quotation of published work, it appears impossible to avoid these variations in spelling.

Maryse Arendt 21 av GD Charlotte L 3441 Dudelange

Dudelange, le 14 décembre 2007

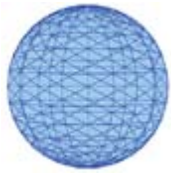
Concerning the review

I have applied all the changes proposed related to the language. They are not all highlighted as I was only told this after I had accepted the changes.

I have rephrased the abstract based on the suggestion of Alison Linnecar and added a sentence on opurity and another on NGOs to reflect the changes proposed by Lisette van Vliet.

I have send the revised article once again to the reviewers too check if I have understood and well integrated their comments, they agreed upon them.

Maryse Arendt

**Referee's comments to the authors– this sheet WILL be seen by the author(s)**

Title	Research on ethics of Human Biomonitoring studies in ECNIS and NewGeneris: a bottom up approach
Author(s)	Birgit Dumez, Karel Van Damme and Ludwine Casteleyn
Referee's name	Ulf Görman

General comments:

The article brings up several interesting conflicts when it comes to the application of current ethical and legal framework for doing research on humans.

However, the structure of the article itself is still unfinished and raises a number of crucial questions that need to be handled before the article can be ready for publication.

Major compulsory revisions:

The Oviedo Convention, the Privacy Directive, and a number of other documents aim at establishing a common European value system when it comes to the protection of individuals that are made subjects for research. They point out the primacy of the protection of the integrity of the individual and set out a framework for how to find a balance between this protection and the common interest to increase knowledge through research.

It is not clear whether the questions raised in the article (“Profound rethinking of current ethical and legal framework is desired since the notion of public interest moves more to the forefront,”) aim at pointing out difficulties in implementing these basic values in a number of specific situations, or whether they aim at questioning these basic values themselves.

Neither is the relevance of the comment “the notion of public interest moves more to the forefront, leading to substantial differences as compared to clinical settings” made clear, as the Privacy Directive, as well as the ongoing work on a regulation of biobanks, clearly includes large scale registers.

The claim that a bottom-up approach is “based on a firmly rooted methodology for comparative analysis of determinants in ethical reasoning” lacks justifying arguments.

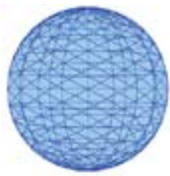
It is not made clear why discussions with stakeholders should be a crucial instrument for “rethinking of current ethical and legal framework”. It may be evident that such a discussion will cast light on conflicts of interests, but that is not enough to answer any of the main questions mentioned above.

The main part of the article (the section “Results and discussion”) presents a number of cases, followed by questions. When it comes to the use of these real and imagined cases, it is unclear whether the article aims at

- 1) presenting a strategy to be used or that is currently being used in order to discuss questions raised by the cases (i.e. discussions with relevant stakeholders), or
- 2) reporting results from such discussions with stakeholders.

A number of results and conclusions are presented. However, in the first case, no conclusions can currently be drawn, although ongoing discussions may indicate interesting problems and raise hypotheses. In the second case the article would need a careful presentation of the empirical investigations in question, and how the line of argument is carried through in order to reach the conclusions. Do the authors want to say that the “bottlenecks” are those questions that have received the greatest attention in the discussions with stakeholders?

A third understanding of the section “Results and discussion” may be that it consists of a number of general reflections from the authors on the issues in question, partly inspired by earlier discussions. I suggest that the relation should be made clear between 1/ reflections that are used as presuppositions, 2/ empirical investigations, 3/ confirmed conclusions from such investigations, 4/ further speculations.

Referee's comments to the authors– this sheet WILL be seen by the author(s)

Title	Research on ethics of Human Biomonitoring studies in ECNIS and NewGeneris: a bottom up approach
Author(s)	Birgit Dumez, Karel Van Damme and Ludwine Casteleyn
Referee's name	Marja Sorsa

General comments: This is a very important discussion document for human biomonitoring studies in general, even if the experiences derive from two specific collaborative projects.

Very rightly the authors give example cases, point to the ethical problems and give some solutions, pointing to the need of open discussion in each specific project case - maintaining the legal background and the common ethical framework.

Several linguistic - wording remarks have been made into the manuscript. Some erroneous wordings and suggested additions are included in the referee report.

This is a valuable discussion paper to tackle the ethical dilemmas and research interests within large collaborative human biomonitoring projects, using ECNIS and NewGeneris as examples. Some minor comments and clarifications below:

1. Title

for clarification ...since the acronyms may not be known to all readers

RESEARCH ON ETHICS IN TWO LARGE HUMAN BIOMONITORING PROJECTS ECNIS AND NEWGENERIS. A BOTTOM UP APPROACH

2. Abstract, last para

...of the rights of European citizens and establish...ethical values within the EU legislative framework.

3. p.3, last para

...in respect to ethical values generally considered as....This methodology has been developed...

4. p. 4, first para

(3) analysis of the national decision making process

2nd para: ...scenarios developed. ...virtual case scenarios,

3rd para: In human biomonitoring research, ethics...

, Council of Europe's Convention...

5. p.5, 1st para : ...may even overlook the main objective.

3rd para: The World Wildlife Fund (WWF) for instance.....According to the protocol to the Convention on Human Rights and Biomedicine (9), every.....approval of an ethics committee has to be required before...since its purpose is not primarily to produce...Furthermore, only very few samples were collected in a large number of countries. The key question is whether ethical approvals were requested in each country; there is no documentation about this. Analogously, no documentation has been released, whether the national privacy authority in each country was consulted before onset of the study.

4th para: .According to the EU Privacy legislation, ...However, further processing of personal data for scientific purposes (so called secondary use of data) is generally not considered... suitable safeguards. If a new purpose is found incompatible, the research proposal is considered as a new project and consequently new informed consents must be requested. There may be exceptions: if the provision of...Divergent interpretations on the "compatibility of a purpose" and on what is "impossible or disproportionate effort" reflect uncertainties about the best interpretation of the Directive and may cause confusion, if not properly clarified before the project onset.

6. p.6 2nd para: In this kind of situation, how will the (affected) population perceive an eventual (financial) involvement (of industry) in a human biomonitoring study? Will the people have trust in a transparent and fair interpretation and communication of data? How will their potential economic losses, together with future health effects, be compensated?

3rd para:, last sentences: ...after a positive tumor marker test may cause unnecessary side effects...Furthermore, the test may detect insignificant tumors that would never become clinically life threatening. From a medical point of view, it is not yet known which tests actually save lives and it is...

7. p.7, 1st para...it is not necessarily accepted nor validated that a specific correlation exists.

...Questions related to the role of local ethics committees are relevant, since...

3rd para...under auspices of the parents until the children reach the age of 18. (not parents!)

8. p.8 , 1st para...dignity of the mother guaranteed without hampering...

3rd para...The first one would be never to communicate... ...Thirdly, the possibility would also be to communicate the individual results, unless specified otherwise...

9. p.9. 1st para: ...the wish of the participant not to know has to be established.

4th pararegulation with respect to regional or local ethics committees is carried out.

5th para....burden of ethical constraints both for the study subjects and the researchers.

Second review by Marja Sorsa of "Research on ethics in ECNIS and NewGeneris: a bottom up approach" by Birgit Dumez et al.

I have today read the revised manuscript - I think it as an important discussion paper; its readability could still be improved and more example cases could be added...but this is probably a later effort - after the projects are over. A few clarifications:

In abstract, p.2, 5. row : Introduce the abbreviation HBM when first mentioned.

p. 3, 2. para. Difficult to grasp...My suggestion would be. The two key questions at stake are (1) how research subjects.....the whole of Europe, and (2) how scientific research in the field of environmental health would not be prevented for wrong reasons.

later on row 9: ...from ethically correct research,

last sentence of the para...is it intermediate or immediate solutions???

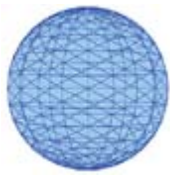
p. 4 2. para, last sentence:..As an example, can the validation of DNA repair phenotyping be performed with an informed consent on samples for genotyping?

The referencing is accurate and OK!

Best regards, Marja

Please find attached the revised paper.
We have included the changes suggested by the reviewers in the document.

Best regards,
Birgit



Referee's comments to the authors– this sheet WILL be seen by the author(s)

Title	Applying Bioethical Principles to Human Biomonitoring
Author(s)	Myron Harrison
Referee's name	Franco Merlo

General comments:

The declared scope of the paper as declared in the introduction is “to contribute to a dialogue on concerns surrounding biomarkers of exposure for industrial chemicals.” This is done by a series of subheadings reporting about too many specific aspects of biomonitoring, biomarkers of exposure, risk, individual risk, group risk, interpretation of data, public health decision, surveillance, medical practice, etc. The paper is lacking focus on any specific issue discussing a little bit of everything and providing a rather general conclusion, without a practical usefulness.

Major compulsory revisions:

My suggestion is to reorganize the paper according to a logically fluent subheadings such as, for example:
human biomonitoring ability of measuring environmental exposure to hazardous agents;
human biomonitoring ability of measuring environmental health risks;
human biomonitoring data and risk assessment.
Human biomonitoring scientific evidence and public health debate
Normative and non normative arguments

The paper should define what is meant by human biomonitoring and when and how it can be used (e.g., environmental health studies, health surveillance). The section on Human Research should address when human biomonitoring is scientifically justified and what are the main ethics principles for being accepted: biomarkers must be studied in humans (with no harm) in order to be validated. This is a fundamental issue to address.



Editors-in-Chief
Philippe Grandjean and David Ozonoff

Referee's comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	
Title	Applying Bioethical Principles to Human Biomonitoring
Author(s)	Myron Harrison
Referee's name	Ludwine Casteleyn

General comments: The article contributes to the dialogue on concerns surrounding biomarkers of exposure for industrial chemicals by approaching many of the important issues in the ongoing discussion in a systematic and well-documented manner.

Major compulsory revisions: NA

Minor essential revisions: NA

Discretionary revisions: It refers mainly to the US context and this might be more clearly indicated (e.g. it does not take into account the EU context in which the implementation of the EU Privacy Directive has - in many EU Member States - an important impact on the communication with the study subject by strongly stressing the right to know, including the right to know study results, if wished.

PS: typing error in ref 2 (ESBIO instead of EBSIO)

Response to reviewers:

One of the reviewers accepted the article as written (and, by the way I am comfortable if it is a "commentary"). The other asked me to do things about which I know nothing. It is an article on ethics. I can't give simple guidance on what is or is not "ethical." Ethics is a fluid, on-going process that does not provide universal, necessary and consistent answers -- the kind to which science aspires. That was, in part, the point. There are no clearly right and wrong answers. It may well be that this is in the wrong journal. All I can say is that while I can tinker around the edges, I cannot reorganize and fundamentally rewrite the ideas I presented at the ESBIO meeting.

Myron Harrison



Referee's comments to the authors– this sheet **WILL** be seen by the author(s)

Title	Scientific Integrity: a critical issue in environmental health research
Author(s)	Domenico Franko Merlo, Kirsi Vahakangas, Lisbeth E. Knudsen
Referee's name	Alberto Mantovani

General comments: Accurate, well-planned, informative and comprehensive paper; the Authors may consider some recommendations to further improve the manuscript (see below)

Discretionary revisions: a) under 3.4 “Conflicts of Interest” the authors may give emphasis on how this issue may be critical for environmental health field. In such field, epidemiological research and biomonitoring often consider agents (e.g., industrial chemicals, pesticides) that are also target for important economic interests. The same economic interests can also make research funds available (sometimes important ones).; granting may be, and often actually is, accompanied. This is, in principle, fully legitimate; however, in practice is often accompanied by claims over ownership of results. In practice, this a really critical issue for the “trust or mistrust of science”, where full transparency must be enforced with determination by all actors involved, scientists and funding bodies.

b) the authors mention in several points the privacy-related issues of biobanks. Since biomonitoring can involve also genotyping for potential biomarkers of susceptibility, the authors could discuss in more detail whether genetic data, as several authors claim, deserve specific attention from the privacy standpoint as they are connected with personal identity: in particular, they could discuss genetic data in comparison with other biomarkers that might predict long-term effects (e.g., cancer).

Response to reviewers:

Attached is the revised manuscript with some addition lines 332-347 (discretionary revision required by reviewer).

If you feel to add something concerning the second suggestion (see below) feel free of doing it:

b) the authors mention in several points the privacy-related issues of biobanks. Since biomonitoring can involve also genotyping for potential biomarkers of susceptibility, the authors could discuss in more detail whether genetic data, as several authors claim, deserve specific attention from the privacy standpoint as they are connected with personal identity: in particular, **they could discuss genetic data in comparison with other biomarkers that might predict long-term effects (e.g., cancer).**

I think as it is the paper is ready to be published.

Franco

Referee's comments to the authors– this sheet **WILL** be seen by the author(s)

Title	Societal issues in human biomonitoring – a view from science studies
Author(s)	Susanne Bauer
Referee's name	Uffe Lind

General comments: The manuscript discusses ethical, societal, epistemological as well as political issues regarding human biomonitoring. The manuscript gives a good overview of the recent rise of human biomonitoring as a new research platform. Without being ethical in a moral philosophical sense of the term the manuscript provides a critical discussion of ethical problems in relation to the different research practices making up human biomonitoring. Being a “view from science studies” the manuscript also provides the reader with a novel and refreshing set of concepts such as “biological citizenship”, “biopolitics” and “biomedicalization” in the comprehension of the broader societal and political effects of human biomonitoring

Major compulsory revisions: none

Minor essential revisions:

Continued: The manuscript uses a number of concepts from the social sciences and humanities that without further definition or explanation may be difficult for readers without such a background to understand. These include:
Epistemological: Throughout the manuscript. A short definition of this when used first time in the abstract would be very helpful.

Civic epistemologies: p. 6

Epistemic cultures: Throughout the manuscript.

Biopolitics

Biological citizenship: p. 1 and 15

Biosociality

Platform sociology: p. 1 and p. 5

Discursive: p. 6

Historiographic and microsociologic: p. 4

Argument about “biological dosimeters” that may “qualitatively indicate increased risk of cancer” should be explained more thoroughly (p. 7).

Argument about “error ranges and uncertainties in the interpretation of biomarkers are substantial” should be explained more thoroughly (p. 11).

Argument about “epistemology is a matter of politics” should be explained more thoroughly (p. 13).

It is not clear what “RfD/RfC” stands for on p. 14.

Points about “biomedicalization” and “biological citizenship” need to be elaborated p. 15.

The sentence “HBM is currently at a stage of development and exploration; for many biomarkers of exposure no reference values that would constitute the “normal” are available” should be supported by a reference (p. 7).

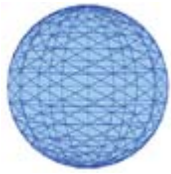
Discretionary revisions:

The reviewer suggests the title of the manuscript changed to “Societal and ethical issues in human biomonitoring – a view from science studies”.

Answering points to consider

1. The research question/purpose of paper is well defined: “This paper explores HBM in the light of established research frameworks and practices in both environmental field sciences and environmental epidemiology, by using science studies tools to map out selected epistemological and societal aspects” (p. 5).

2. Methods should be better described by defining or explaining central concepts more thoroughly (see minor essential revisions). Strengths of methods are that they provide a novel and needed social scientific perspective on human biomonitoring. Weakness of methods is that they may seem difficult to comprehend for readers outside the social sciences and humanities. As mentioned, better explanation of central concepts is needed.
3. Data are sound and well controlled.
4. Does the manuscript adhere to relevant standards for reporting and data deposition: Of no relevance for this manuscript.
5. Discussion is well balanced and adequately supported by the data
6. The reviewer suggests the title of the manuscript changed to "Societal and ethical issues in human biomonitoring – a view from science studies" (see discretionary revisions).
7. No need for improvement of writing, organization, tables and figures
 - Interpretation should be more elaborated at central passages (see minor essential revisions).
 - There are no ethical or competing interests issues.



Referee’s comments to the authors– this sheet WILL be seen by the author(s)

Title	Societal and ethical issues in human biomonitoring – a view from science studies
Author(s)	Susanne Bauer
Referee’s name	Christine Holmberg

The paper “Societal issues in human biomonitoring – a view from science studies” by Susanne Bauer is very rare in its approach to bioethical themes from an epistemological perspective. This specific angle highlights issues that otherwise remain hidden and may well be missed in discussing research developments in environmental health. I therefore highly recommend its publication.

As the author argues the themes discussed in the paper are particularly prominent at this time were policy decisions are at stake towards the future direction of the new research tradition of human biomonitoring. The paper convincingly discusses all relevant themes that have emerged out of an analysis informed by science studies. It is an excellent paper that shows how supposedly minor shifts in the approach to a problem intended as improvement of the research may lead to different questions and entirely different outcomes (a shift towards risk factor epidemiology) that have significance way beyond the research approach.

While the overall topic and analysis is excellent, I suggest that the paper be further refined and reorganized. First some comments regarding the entire paper. These will be followed by specific remarks

1. the method section has parts of the research question and results included. I suggest a rework of the methods section in the following way: use the second paragraph under the method heading as beginning then describe what types of texts were searched for the analysis, discuss in more detail the analysis and finally discuss the concepts being used in more detail (E.g. research platform, biosociality and biocitizenship).

2. Overall, the paper has some redundancies. In each section there are two to three sentences that have been stated in every previous section.

In this light the results section may need to be reorganized – or more precisely the subheadings should lead the reader through discussion/results section and identify the key issues addressed in each subsection. It may be helpful to return to the concepts introduced in the methods section and highlight how the results refer to the different STS concepts through which analysis took place.

The results/discussion section is very dense. It may be worthwhile to think about focusing on fewer aspects and to discuss those aspects in more detail. (I suggest some in the detailed comments)

It may be worthwhile to think through if it may be beneficial to discuss the texts of the analysis in more detail so that the entire results/discussion section becomes more specific?

The detailed comments are as follows:

p.4 (Background), sentence after reference 13,14 doesn’t make sense: why does an overlap between environmental science and public health suggest that microsociological and historiographic studies should have been conducted on the field?

p.5 (Background) last sentence before the methods sections. “to map out SELECTED epistemological and societal aspects” – these are? Introduce briefly!

Methods section
See general comment

p. 8 (though styles and epistemic cultures)
be more specific about the thought styles in the following paragraphs – while all themes are present they are hidden in the text and difficult for the reader to follow.

There seems to be a difference between environmental health science and environmental science – This difference is neglected which is to the disadvantage of the analysis.

p.8./9 last sentence prior to (Epidemiology) – is somewhat detached. This is explained before – needs a different last resuming sentence.

p. 9 (epidemiology) sentence after reference 31, delete “in practice”.

P. 10 last sentences prior to (Evidence hierarchies and im/perceptibility) the points you raise are more generally true (and important!) – what is specific to HBM? (this also goes for the following subheading section)

p.11 the middle of the second paragraph explains why the highest mode of evidence cannot be met by environmental health studies? – it the issue indeed the focus per se on the individual?

p. 13 first paragraph – I would focus on this in more detail! Especially “What are the terms of proof asked for and the trade-offs in risk enacted, when environmental policy and the distribution of resources is decided upon?” – this is a crucial result/discussion – more detail, more discussion, be more precise.

In the next sentence the author refers to the ethical debate on resource allocation and what constitutes best treatment – there is an ethical debate in this field – reference it.

p. 13 next paragraph (what kind of evidence is considered sufficient for action, or, in epidemiological terms, under what conditions can the null hypothesis be rejected?) again a crucial point which warrants further discussion.

Same is true for last sentence p. 13.

p.17 third last sentence before conclusions a “be” is missing. “would no longer BE available and locally meaningful research may be precluded”.

p. 17 (conclusions) Second sentence should read: “Science studies can help understand”

Food for thought (this point doesn't need to be addressed but it's an interesting question to pursue):

p. 15 why may it be that the risk factor epidemiology paradigm will be successful and it will lead to a focus on individual behavior change? (The question refers to the epistemological question of how a paradigm becomes prominent)

Response to reviewers:

First, I would like to thank both Christine Holmberg and Uffe Lind for valuable comments and helpful suggestions to this paper. The referees' comments have been highly valuable in revising the manuscript.

I have followed almost all of the reviewers' suggestions. In the following, I will address comment by comment:

Review by Christine Holmberg:

General comments:

Both the general and specific comments have been extremely helpful in thinking through and rewriting the manuscript:

1. I have reworked the methods section, as advised in the referee's report, added the information on types of texts searched for and then described the analysis and the concepts used in more detail (s. pp. 5-7, new manuscript).

2. I have minimised redundancies and reorganised the subheadings, hoping that they work better now in providing guidance through the results/discussion section. In the results/discussion section I have also returned to the STS concepts introduced before (s. new p. 9, 10-12, 13, 19, 20, 21, 22).

I have worked on making the results/discussion section less dense and more readable, by focussing the discussion and by omitting unnecessary detail, while still keeping the different key aspects. I have decided not to cut down much as to the topics covered, because of the specific goal and context of the paper as part of a special issue on ethical questions in HBM: The goal in this paper was to open up and broaden the aspects already discussed in the ethical debate on HBM. However, I could clearly see that this makes it very dense; I have therefore made an effort to skip unnecessary detail and to be more specific when it comes to HBM, in particular when it comes to the key points suggested in the referee report (detailed comments).

I have thought through how the analysis is presented and considered whether and how to provide more detail and context with respect to the analysed texts. I have related the more general points to HBM in more explicit ways in order to make the arguments more specific throughout the manuscript.

Detailed comments:

Old p. 4, new p. 4:

I have changed this sentence. (The point here was that while there are a number of science studies accounts either relating to the environmental field or to the health/medical field, the intersection – very recent history of environmental health and environmental epidemiology – are still understudied.)

Old p.5, new p. 5:

I have specified these epistemological and societal aspects I look into, "such as the recent shift to biomarkers in exposure assessment and related conceptual changes in what is known on environmental health." (I have revised the whole sentence).

Methods section (s. above)

I have revised the entire methods section as advised, added the information on types of texts searched for and then described the analysis and the concepts used in more detail (s. pp. 5-7, new manuscript).

Old p. 8, new p. 10-12:

I have rewritten parts of the paragraphs on environmental sciences and epidemiology – to be more explicit on thought styles (pp. 11-12).

Difference between environmental science and environmental health sciences:

When analysing thought styles, I have decided to restrict the analyses to "environmental science" and "epidemiology" as two, epistemologically different types of approaches to "environmental health". I have now reserved the term "environmental health" precisely for the research area at this intersection.

Old p. 8/9, new p. 11.

As suggested, I have replaced the former detached sentence by a resuming sentence.

Old p. 9, new p. 12.

I have deleted: "in practice".

Old p. 10, new pp. 13-14:

I have added a paragraph that is more specific to HBM. I tried to elaborate why the issues dealt with are relevant for HBM, without neglecting the more general points that hold broadly for the health sciences.

Old p. 11, new pp. 14-16:

I agree that the issue here is less the focus on the individual (although I am not quite sure if I understood the comment and the sentence it refers to correctly here) than the methodological requirement of individual-level data and the random allocation into groups with different degrees of exposure/intervention. I have tried to avoid misunderstandings by revising the wording of the respective paragraphs. (e.g. p. 16)

Old p. 13, new pp. 17-18:

- I have provided more detail in the revised version (p. 18).
- I have included references for both arguments – EBM and resource allocation as well as best treatment and equipoise debate. (p. 17)

Old p. 13, new pp. 18-19:

I have added further specification and discussion on these points (p. 18-19).

Old p. 17, new pp. 22/23:

These language errors have been corrected. (Thanks!)

Old p. 15, new p. 21:

The success epidemiology paradigm is an interesting question that indeed warrants explanation. This could be approached on different levels – in the history of science but also socially, economically. Aronowitz [57] has an interesting discussion on this for the US context, where he traces it to some extent to its openness as an explanatory concept that can integrate the biomedical and social concepts of disease causation; as a robust tool, the individual risk factor approach provides stability. On the other hand it was in line with the decreasing role of the state in the health care system in western capitalist societies; it fitted with the self-determination and individual autonomy shift in medicine. Environmental health becomes something to act individually about.

These comments have been extremely helpful and stimulating and have helped to rearrange and focus the paper. Thanks very much again!

Review by Uffe Lind

Minor essential revisions:

Thank you very much for specifying the terms and concepts that require explanation; this has been very helpful:

I have provided an explanation of "epistemological" on the abstract, as suggested. The terms listed have been explained where they are first mentioned in the full text; I have either described the concepts in more detail and/or provided examples. However, I do not use the terms biopolitical and discursive in the new version, as they are less central to the arguments in this paper.

- civic epistemologies, old p. 6, new p. 7.
- epistemic cultures, explained new p. 6
- biological citizenship, old p. 1, 15, explained on (new) p. 7
- biosociality, s. new p. 7.
- platform sociology, old p. 1 and 5, new p.6.
- historiographic and microsociologic, old p. 4, new p. 4.

Old p. 7, new p. 9/10:

I have added 1 sentence to explain the term "biological dosimeter" from this quote.

Old p. 11, new p. 16:

I have added details (non persistent character of many biomarkers, error ranges) and references for this argument.

Old p. 13, new p. 18-19:

I have elaborated on this – epistemology as a matter of politics – in more detail.

Old p. 14, new p. 20:

I have added the terms these abbreviation stand for in brackets [..].

Old p. 15, new p. 20:

I have introduced and elaborated on biomedicalisation (earlier in the paper – (new) p.13 and on (new) p.20) and biological citizenship (p. 21).

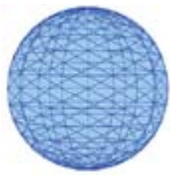
Old p. 7, new p.9:

As this sentence seemed confusing, I have revised it and added some references.

Discretionary revisions:

I have followed the suggestion to change the title, as it is true that ethical issues are the topics I deal with (just not from a moral ethics or bioethics perspective, but with the aim of broadening this to an epistemological and societal perspective).

I have attempted to provide better explanation of the concepts from science studies and on how they were applied – both in the methods section as well as throughout the paper, in order to make it more accessible for readers not yet familiar with these concepts. In doing so, the comments have been very helpful and helped me a lot to determine what concepts and terms need further exemplification. Thanks very much for indeed!



Referee's comments to the authors– this sheet **WILL** be seen by the author(s)

Title	Risk communication and human biomonitoring: which practical lessons from the Belgian experience are of use for the EU-perspective?
Author(s)	Hans Keune, Bert Morrens, Ilse Loots
Referee's name	Christina Benighaus

General comments:

The question of the authors: "practical lessons from Belgian experience and the use for the EU-perspective" is very well defined. The methods and the results are good and detailed described to replicate the work. The manuscript uses the relevant standard for reporting. The discussion and conclusions are well balanced. The title and abstract convey all important contents which are described in the manuscript. The writing is understandable and in a precise way.

Major compulsory revisions:

none

Minor essential revisions:

none

Discretionary revisions:

None

The manuscript is very well structured and gives a detailed description of the work experience of the Centre of Expertise for Environment and Health.

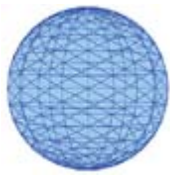
The short chapter of risk communication shows the evolution of the different approaches of traditional and modern risk communication. It discusses the effect, benefit and restrictions of the different strategies in the European context. From the discussion the authors convey guideline or practical principals for the involvement of stakeholders.

The next chapter explains traceable the methods, the procedure and results of the stakeholder involvement of the Centre.

Finally the results are discussed with regard to human biomonitoring in the EU. The discussion could be more comprehensive particularly with regard to use in the EU context and would give the whole manuscripts a better closing.

For Example answering the following questions in more detail: Where can the results used and under which conditions? What should be done on the EU and national perspective?

The Conclusion shows the main results in a logical and understandable way.

**Referee's comments to the authors– this sheet WILL be seen by the author(s)**

Title	Risk communication and human biomonitoring: which practical lessons from the Belgian experience are of use for the EU-perspective?
Author(s)	Hans Keune, Bert Morrens, Ilse Loots
Referee's name	Silvio Funtowicz

General comments:

The subject and the case-study of the paper are of interest and relevant to the journal but the current draft does not realize its potential.

The paper is divided in two parts: a history of risk communication and a description of the human biomonitoring case-study.

The history is well done and written but unfortunately it is not (in my opinion) the most interesting part of the paper.

Major compulsory revisions:

The original part (justifying publication) is the case-study which is, I have to say, poorly written.

See, for example, sections "limitations" and "from experiment to integral part of human biomonitoring research" (page 22) or the following paragraph:

"About 25% of the persons we invited responded cooperatively. Except for the environmental organisations, from all different groups representatives cooperated, in total 35, of which 13 local residents" (page 23)

Another problem is the presence of loose ends, aspects which are not explained in the text. For example, second generation human biomonitoring.

It seems to me that the case-study is very interesting and that a lot of good work went into this research. Considering that the paper is already too long, I suggest rewriting as follows:

1. To shorten the risk communication history by concentrating on the most relevant aspects for the case-study.
2. To rewrite the case-study; avoiding loose ends and improving considerably the language.

Cover letter corrections made based on review remarks
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Title	Risk communication and human biomonitoring: which practical lessons from the Belgian experience are of use for the EU-perspective?
Author(s)	Hans Keune, Bert Morrens, Ilse Loots

We concentrated on the remarks of Silvio Funtowicz, since Christina Benighaus did not have any major compulsory remarks.

Main adaptations (in general):

- *The English has been reviewed by a (academic) native speaker; all recommendations implemented*
- *The theoretical part on risk communication was cut by one page*
- *An academic not familiar with the topic has read the paper on clarity; recommendations were implemented*
- *Loose ends were clarified*
- *The text has been edited to make things more clear for readers*

All parts changed are highlighted (yellow) in the original text (attached). Also the text based on all adaptations is attached.

Specific adaptations:

Major compulsory revisions (Funtowicz):

The original part (justifying publication) is the case-study which is, I have to say, poorly written.

The English was both reviewed by a (academic) native speaker and an academic not familiar with the topic in order to improve both the language and the clarity.

See, for example, sections "limitations" and "from experiment to integral part of human biomonitoring research" (page 22) or the following paragraph:

"About 25% of the persons we invited responded cooperatively. Except for the environmental organisations, from all different groups representatives cooperated, in total 35, of which 13 local residents" (page 23) *Clarified and rewritten*

Another problem is the presence of loose ends, aspects which are not explained in the text. For example, second generation human biomonitoring. *Loose ends (such as the ones mentioned) were adapted, deleted and/or clarified.*

It seems to me that the case-study is very interesting and that a lot of good work went into this research. Considering that the paper is already to long, I suggest rewriting as follows:

1. To shorten the risk communication history by concentrating on the most relevant aspects for the case-study. *Shortened by one page*
2. To rewrite the case-study; avoiding loose ends and improving considerably the language. *Rewritten based on comments of a (academic) native speaker and an academic not familiar with the topic, loose ends a (academic) native speaker and an academic not familiar with the topic*



Editors-in-Chief
Philippe Grandjean and David Ozonoff

Referee's comments to the authors– this sheet **WILL** be seen by the author(s)

Title	A proposed framework for the interpretation of biomonitoring data
Author(s)	Peter J. Boogaard, Chris D. Money
Referee's name	Frans Jongeneelen

General comments:

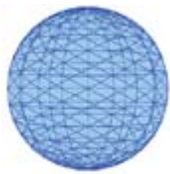
The paper is not a scientific data-driven paper, but more an editorial type of paper in which a viewpoint is explained on how human biomonitoring can be and should be applied in human health risk monitoring and assessment.

Major compulsory revisions:

Framework point 1: 'analytical integrity' does not include external quality control to warrant the comparability of result of different labs. Several European institutions are performing EQA programs. I would ask for a more prominent position for such external quality assurance programs.

Framework point 2: 'ability to describe dose' seems not to hold the variability of toxicokinetics. Biological variability can not only be explained by toxicodynamic factors, but also by toxicokinetic factors. I would urge to give more attention to an integral view on how to deal with biological variability within the framework. (See for example Manini et al, Toxicology Letters 166 (2007) 210-218).

Framework point 4: 'overall evaluation and weight of evidence' is unclear and vague. Explanation is too short. I would like to see a clear description of what the authors mean. Who, what, when, why and how is weighted?



Referee's comments to the authors– this sheet **WILL** be seen by the author(s)

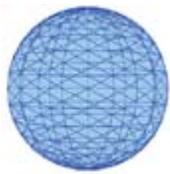
Title	A proposed framework for the interpretation of biomonitoring data
Author(s)	Peter J. Boogaard, Chris D. Money
Referee's name	Len Levy

General comments: Very readable and succinct paper that introduces faithfully the key concepts set out in ECETOC Doc No. 44. My understanding is that this paper should encourage the reader to go and look at the full ECETOC doc. so it might be helpful if the authors said so directly and gave the web-link in the text.

Major compulsory revisions: None

Minor essential revisions: None

Discretionary revisions: I have suggested some minor language changes and asked the authors to consider adding a few extra explanatory sentences. I have attached the MS with suggested changes in tracking mode for convenience.



Referee's comments to the authors– this sheet **WILL** be seen by the author(s)

Title	A proposed framework for the interpretation of biomonitoring data
Author(s)	Peter J Boogaard and Chris D Money
Referee's name	Ovnair Sepai

General comments:

The paper is a well written and thought out proposed framework for the interpretation of human biomonitoring data.

My only reservation is that the paper is based on the ECTOC Doc No. 44 and I can not see any additional content. As long as this is acceptable then the paper should be published.

Major compulsory revisions:

No revisions.

Minor essential revisions:

I noticed that Frans Jongeneelen, not surprisingly considering his background, has reviewed the paper mainly from an occupational viewpoint whilst the paper primarily focuses at environmental HBM.

Specific responds to his comments/suggestions:

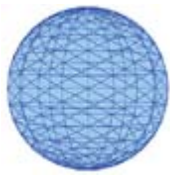
1. In my view, analytical integrity also comprises external quality control. However, I have included a statement to specify this in the text. Indeed, several EQA programmes are available for HBM at the occupational level but, at present, to the best of our knowledge there is only a single EQA for HBM at the environmental level (the Erlangen scheme) which includes a very limited number of substances. I think it would be too detailed for a short paper like this to get into much detail and with the added specification I hope to have addressed the limited availability.
2. I agree that biological variability is explained by both toxicokinetic and toxicodynamic factors and this has been specified in the text. After ample considerations, I have decided to include a reference to the paper by Paola Manini and co-workers (assuming this is the paper Frans meant, the reference given in the review is incorrect) as well - despite the fact that it only deals with occupational exposure and I strongly disagree with several of the statements in the paper - since it explains nicely how biological variability can influence HBM results.
3. As indicated in the text, the evaluation of causal criteria that link an exposure to a specific effect is usually highly complex as it requires integration of data from many studies that differ in terms of experimental conditions and the parameters examined. This makes it practically impossible to describe the "who, what, when, why and how" as they will be different from case to case. Nevertheless, I have added in the text that expert judgment is usually required to highlight the complexity.

Specific responds to Len Levy's comments/suggestions:

- I have accepted all editorial changes suggested
 - Len had also put 5 comments in the text:
1. This remark is unclear: I don't mean uptake per se, but the fact that BM integrates all routes of exposure as stated in the text. I have added the word 'integrated' to emphasise this
 2. As suggested, a paragraph has been added to explain.
 3. Indeed confounding factor need not be systematic, the text has been adapted.
 4. A few sentences to explain the relevance of this approach have been added as suggested.
 5. A few explanatory sentences were added as suggested.
- I trust that with these revisions the manuscript now meets the standards of Environmental Health and look forward to the publication of the paper.

According to the review report of Ovnair Sepai, there are only one remark. This single remark is along the lines of Frans' remark that the paper is not an investigative science paper, which we, of course, fully acknowledge.

The remark about the paper mainly pointing at the actual ECETOC report is very much along the line of Len's last remark. In response to that remark we have already made a more clear reference (including a link where the full report can be downloaded) in the paper.



Referee's comments to the authors– this sheet WILL be seen by the author(s)

Title	Stakeholder Opinion: Human biomonitoring data interpretation and ethics, obstacles or surmountable challenges?
Author(s)	Ovnair Sepai, Clare Collier, Birgit Van Tongelen, and Ludwine Casteleyn
Referee's name	Peter Farmer

General comments:

This is a descriptive report of a workshop at which I was present. It quite accurately reports the proceedings and is very informative. The two main areas covered are Data Interpretation and Ethical issues, and the reported recommendations from the workshop are highly appropriate for future human biomonitoring studies. The proposal to develop European Guidelines (and hopefully standardized procedures) for ethical consideration should be highly supported, as the varying approaches within Europe are currently causing delays or difficulties in international studies.

Major compulsory revisions:

None

Minor essential revisions:

Page 1: Address author 3, spelling of 'Brussels'

Page 2: Recommendation 6 'disseminated'

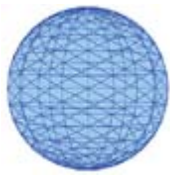
Page 5: Communication line 5. 'buy in'

Page 6: Ethical issues line 12. 'in line'.

Page 7: third paragraph. Meaning of the sentence concerning 'right to service' needs to be clarified.

Discretionary revisions:

Page 3 refers to an EU Pilot Study to be launched by the end of 2007, i.e. close to the present date. The current situation regarding this should be given if available.

**Referee's comments to the authors– this sheet WILL be seen by the author(s)**

Title	Stakeholder Opinion: Human biomonitoring data interpretation and ethics, obstacles or surmountable challenges?
Author(s)	Ovnair Sepai, Clare Collier, Birgit Van Tongelen, and Ludwine Casteleyn
Referee's name	Soterios Kyrtopulos

General comments:

I attach the manuscript with some comments and suggested minor editorial corrections noted. Here are some additional comments:

1. As I understand it, the m/s is meant to present the conference conclusions as regards data interpretation and ethics. As such it is generally fine. On the other hand, the words "Stakeholder Opinon" in the title are slightly confusing, as they give the impression that this is a commentary from the side of stakeholders. Maybe a title such as "Human biomonitoring data interpretation and ethics: obstacles or surmountable challenges?" would be more appropriate. Whether this is a presentation of the conference conclusions or a commentary should also be made clearer in the early part of the text.

2. An ethics issue that is not mentioned relates to the harmonisation needed in ethical approvals in connection with the conduct of international biomonitoring projects. It seems that currently multiple approvals, in different countries, may be needed in order even to blindly analyse a biological sample received from another country. I don't know if such an issue was discussed but it would be useful if it were mentioned if possible.

In regards to:

Regarding submission of a paper to the Journal of Environmental Health

Title: Stakeholder Opinion: Human Biomonitoring data interpretation and ethics, obstacles or surmountable challenges?

Authors Ovnair Sepai, Clare Collier, Birgit Van Tongelen, and Ludwine Casteleyn

Dear Editor ,

Subject: Response to Reviewers Comments

The reviewers made valid and constructive comments and therefore, I have taken into account all the comments and attach a suitably revised manuscript with tracked changes.

Yours faithfully,

Ovnair Sepai