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Human biomonitoring – limitations and opportunities

Diploma thesis

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Written Declaration

I declare that I completed the submitted work individually and only used the mentioned sources and literature. Concurrently, I give my permission for this diploma/bachelor thesis to be used for study purposes.

Prague 19.3.2010 Kristian Figenschou

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1. Summary

Human biomonitoring aims to measure the amount of certain substances in all aspects of the environment, how much of this that reach humans and in what way, and finally how this affects our health.

In all aspects of this process lays challenges that must be overcome. When measuring substances in the environment, one must make sure that one is measuring the biomarker which gives the most precise results according to what one seeks to find. Dependent on the biomarker in question, multiple factors can potentially affect the measurements.

When the most suitable biomarker has been found, one must make sure that all possible sources are located and taken into consideration, in order to provide a sufficient exposure assessment. The next challenge is to gather accurate epidemiologic data, and link this to the exposure in question, and make a reliable risk assessment.

As the examples in this paper highlights, within each step are challenges, and possible limitations. For most substances, there are data gaps and incomplete understanding. There is now much work done globally, on how to further improve the process. Based on today's experiences and knowledge, new guidelines are put down.

In Europe there was recently launched a program, that will co-ordinate the cooperation between the member states.

Though it is already a valuable tool in many cases, human biomonitoring is now being developed into a utility that yields great opportunities in the prevention of disease in the future.

2. Introduction

This paper seeks to describe the concept of human biomonitoring, and the opportunities and limitations to its use both contemporarily and in the future.

It is a part of the course in preventive medicine, which is being undertaken during the 6th year of medicine at the Charles University, 3rd faculty, in Prague.

The author has no practical experience in the field of human biomonitoring, and bases this text fully on the work of others. Hence the aim of the paper is to provide the reader with extractions from published articles about the field, and serve as both a useful and easily approachable summary on the topic, as well as a guide for where to find more information from the highlighted resources.

As a medical student, the author desires to have this paper leave the reader with and understanding of human biomonitoring and how it can be best used to improve the health of the population and individual patients. Further, the current work in Europe on the issue will be described, in order to give an idea of where the topic is moving in the near future.

It is not only in Europe that public and private demands for biomonitoring data are on the increase. In the United States, government-sponsored programs include the National Health and Nutrition Examination Survey (NHANES) conducted by the Centers for Disease Control and Prevention.

Epidemiology studies, which include a biomonitoring component, are also under way in numerous academic institutions, and The National Academy of Sciences/National Research

Council Committee on Human Biomonitoring for Environmental Toxicants has reviewed the current practices and made recommendations for improvement.

The large activity associated with biomonitoring data collection shows that better exposure data, especially in the context of population-based studies, is needed.

Today, risk assessors are given the difficult task of how best to interpret and apply biomonitoring data. Experience and guidance are needed to integrate the use of biomonitoring data into the risk assessment process (Albertini et al. 2006).

This paper aims to highlight some of the specific problems in the process of biomonitoring, by referring to certain examples. These topics are grouped into exposure biomarkers, exposure assessment, epidemiology, and risk assessment.

By presenting it in this way, the author wants the reader to get a sense of the complexity of the tasks facing the professionals in the field of biomonitoring.

This may create an understanding of the problems that have surrounded the human biomonitoring since its origin, and make it apparent why measures are taken both in a small and larger scale, to further improve this vast field in health care.

It is the author's opinion, that an appreciation of the problems approached by the researcher, and by the ones supposed to coordinate all the research being done, as well as interprets the results, forms the basic understanding of the limitations and opportunities of human biomonitoring. If one understands the limitations, the opportunities become obvious.

3. Methods

The literature reviewed in this paper was sampled by using the search engine Google to search for ‘Human Biomonitoring’. The search results were unsystematically assessed for quality and relevance. Articles that were found relevant where further investigated for useful resources amongst their references.

A search was also done for ‘Human Biomonitoring’ in amazon.com, to find online articles.

4. Definition of biomonitoring

Biomonitoring is the analytical measurement of biomarkers in specified units of tissues or body products (blood, urine, etc.). These biomarkers are any substances, structures, or processes so measured that indicate an exposure or susceptibility or that predict the incidence or outcome of disease (Toniolo et al. 1997).

5. Literature review

As Sexton and others (2004) point out, biomonitoring is not a new phenomenon. Occupational physicians and industrial hygienists have monitored worker populations for exposure to a variety of hazardous substances, for more than a century. 'Clinical medicine offers historical and contemporary lessons on the value of measuring human body fluids for indicators of adverse health risk' (Sexton et al. 2004).

Quality control, analytical standardization, availability of control groups, and other mechanisms for limiting uncertainty and variability, should optimally be supporting the biomonitoring data from environmental, occupational, and clinical settings (Albertini et al. 2006).

Biomonitoring is obviously not only about the measurements, as implied in its definition. In the same way that the measurements must be made in the most precise manner, so must the interpretation of the data and its implications on human health.

In 2004, and International Biomonitoring Workshop was set up, which explored the processes and information needed for placing biomonitoring data into perspective for risk assessment purposes, with special emphasis on integrating biomarker measurements of exposure, internal dose, and potential health outcome.

It was co-sponsered by , the Health and Environmental Sciences Institute, U.S. Environmental Protection Agency, Centers for Disease Control and Prevention, Agency for Toxic Substances and Disease Registry, and International Council of Chemical Associations.

In this particular workshop, scientists from international governments, academia, and industry recommended criteria for applying biomonitoring data for various uses. It was conducted through the examination of six case studies:

inorganic arsenic,

methyl eugenol,

organophosphorus pesticides,

perfluorooctanesulfonate (PFOS),

phthalates (occurrence measured through their metabolites di(2-ethylhexyl phthalate (DHEP) and diethyl phthalate (DEP),

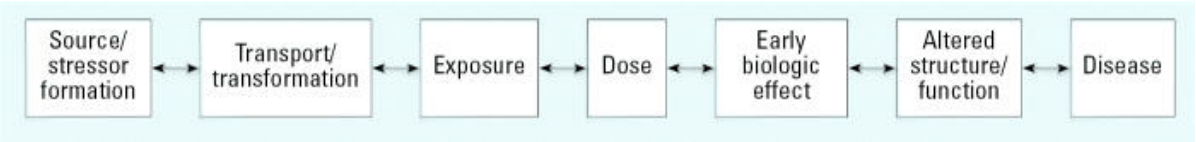
and polybrominated diphenyl ethers (PBDEs).

Albertini and others (2006), wrote an article which summarized lessons learned, identifies data gaps, outlines research needs, and offers guidance for designing and conducting biomonitoring studies, as well as interpreting biomonitoring data in the context of risk assessment and risk management. It was based on the workshop and the follow-up discussions.

Their work serves as the backbone of this paper, because it represents expert's view on human biomonitoring, its opportunities and limitations.

Examples from the mentioned case studies will be used to highlight the challenges of biomonitoring.

The starting point of the work for the workshop participants from governments, academia and industry, was The environmental public health continuum (EPHC).



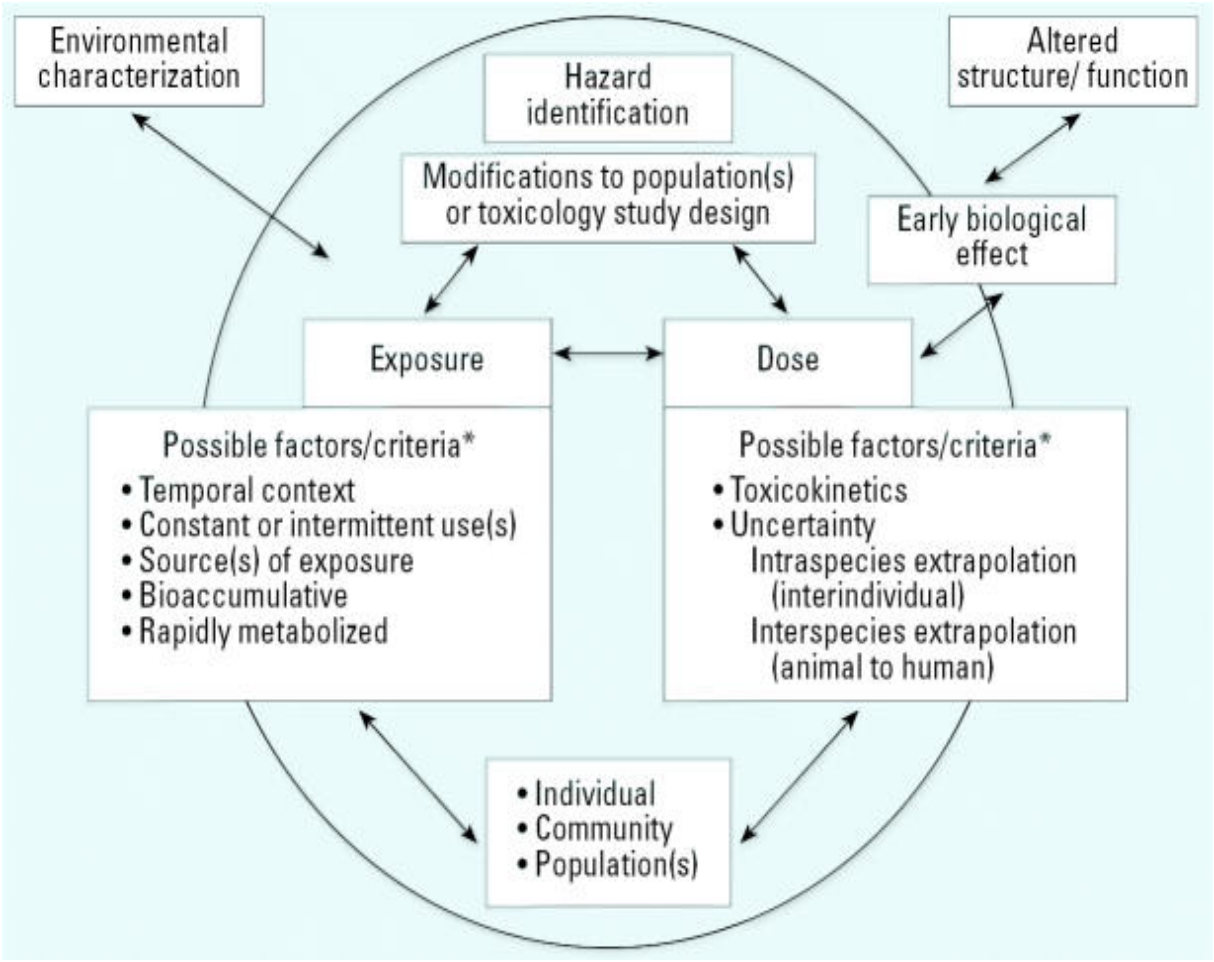
The unique usefulness of EPHC as a tool (Albertini et al. 2006), is:

> that one may start at any point on the continuum and work forward or backward through the links. Because the links work both ways, it is possible to examine what is not known and which data gaps need to be filled. Careful definition of the link being assessed, as well as the question being asked, is critical.

The EPHC highlights the important components of biomonitoring. The exposure, what its sources are and how it is transported. As well as the dose of a substance which an individual or population is exposed to, and how this can alter structure and function in the human body.

Hence, it is useful to discuss the opportunities and limitations of biomonitoring, according to the different components of the EPHC. By improving each step to the outermost excellence, the highest quality of the overall result can be achieved.

In order to fully capture the workshop focus area, some modifications were made to the EPHC, seen in the figure on the next page.



It recognizes the main goal of hazard identification, and includes factors that may affect dose and exposure.

In coherence with the EPHC, aspects of biomonitoring will be discussed under the sub-categories

- Markers of exposure
- Exposure assessment
- Epdemiology
- Risk assessment

The first two obviously serves to assess the left side of the EPHC, whereas latter two concerns the right side.

5.1 Biomarkers of exposure

Biomonitoring programs for assessing exposure to environmental chemicals generally require the measurement of the relevant analytes at much lower concentrations than needed in human clinical or animal toxicology studies, thus posing considerable challenges. Therefore, biomonitoring approaches for assessing exposures to environmental chemicals must employ state-of-the-art analytical methods, which often include isotope-dilution mass spectrometry, to limit the uncertainty for measuring low-level concentrations. Improved analytical capabilities make possible the accurate and precise measurement of many environmental chemicals at very low levels in the tissues of the general population, thus demonstrating human exposure to and absorption of chemicals, and often their distribution, metabolism, storage, and elimination (Albertini et al. 2006).

The performance of the laboratory cannot be overstated, according to Albertini and others (2004). The selection of the proper metabolites for the biomonitoring program is important, and every biomonitoring laboratory should participate in inspections such as those conducted in the United States according to the Clinical Laboratory Improvement Amendments (CLIA 1988). In addition, interlaboratory studies should be available.

Hughes (2006) described one example of such need of interlaboratory studies, apparent from the case study of inorganic arsenic in the mentioned workshop.

Reference standards and human urine samples were introduced with different amounts of the same species of arsenic and provided to different laboratories for analyzing. At arsenic levels in the urine at concentrations that are relevant to research on the metabolism of arsenic in humans (> 5 μg/L), there was little difference between the laboratories.

The differences did however become obvious at lower levels, with much larger variances in levels ranging from 1-5 μL/L.

Clearly, this indicates poor interlaboratory comparison at lower concentrations that is, in large part, due to differences in analytical methods (Albertini et al. 2006).

Careful consideration must be put into developing the strategies for collecting samples for biomonitoring. Using the inorganic arsenic study case as an example, sampling strategy was considered, but historical experience indicates that there is relatively little intraindividual variability in urinary arsenic levels (Hughes 2006). Thus, sampling time may be less of a consideration for an individual. However, because of potential problems with arsenic in seafood, which can confound exposure results based only on total arsenic urinary analysis, subjects should refrain from consuming seafood for a few days before urine collection.

In addition, as Concha and others highlighted (1998), there may be differences in the metabolism and excretion of inorganic arsenic between children and adults. The consequence of this being that consideration of age of the population studied may be important for arsenic exposure analysis.

It is different with methyl eugenol, which is rapidly absorbed from the gastrointestinal tract and metabolized to multiple species. These include hydroxy acids, *O*-demethylation, and hydroxylation of the benzene ring (Robison and Barr 2006). For this substance, the sampling time has a great impact on the result.

In one study, the participants ingested cookies containing methyl eugenol and sampling was done at fixed time points afterwards to evaluate the human uptake (Schecter et al. 2004).

The studies showed that serum levels of methyl eugenol reach its highest levels about 1 hour after and acute exposure, and about 2 hours after the ingestion the levels are close to the pre-exposure or background levels.

In the case of the human uptake study, fasted subjects were used, which greatly reduced the potential variability caused from concurrent exposures to methyl eugenol through the normal diet. This was of obvious importance, because methyl eugenol a chemical that is to be found naturally in spices and herbs, for example basil.

The consequence clearly being, that any biomonitoring study should also include consideration of dietary habits.

Nevertheless, Albertini and others (2004) concludes, based on the reports by Schecter and others, and Robison and Barr, that existing background levels, even though they are low, suggest that some portion of the methyl eugenol remains in a third compartment, which may be adipose tissue, and this residing quantitative is in equilibrium with the concentration in the blood.

Thus, the case of methyl eugenol highlights the challenges when it comes to the affects of acute changes to samples made by recent dietary intake, the differences in results according to sampling time, and storage of the substance in a third compartment in the body.

The phthalates case study brings to light an additional consideration for sampling strategy, that is, knowledge about possible different sources of sample contamination (Calafat and McKee 2006). Because DEP and DEHP are relatively ubiquitous materials that can be found in plastics (DEHP) and soaps/cleaning solutions (DEP), laboratory containers and cleaning solutions that contain fragrances are potential sources of contamination. In the case mentioned here, the solution they went for was to measure phthalate metabolites in urine rather than the parent compounds.

According to Albertini and others (2006), given the lessons learned from the case studies, several key questions regarding analytical approaches for biomonitoring should be considered. These questions are as follows:

> Were standard reference materials used that were prepared in the biologic matrix of interest (matrix based)?
> What are the specificity and sensitivity of the analytical method?
> Is the biomarker of exposure valid for the intended use (i.e., Does it accurately reflect the intended use?) [Validity is defined as the (relative) lack of systematic measurement error when comparing the actual observation with a standard. Validity differs from reliability in that reliability is the extent to which an experiment or measurement procedure yields the same results (tendency toward consistency) on repeated trials.]
> Have there been intra- or interlaboratory comparisons of methods?
> Did the sampling strategy include consideration of toxicokinetics?
> Did the sampling strategy include consideration of potential sources of error or sample contamination?
> Did the sampling strategy include consideration of the stability of the compound in question with respect to the appropriateness of sample collection and storage methods?

It is clearly beyond the scope of this paper to answer these questions in relation to each specific case, substance and research. But the examples given, and the raised questions, shows the limitations and opportunities regarding this part of the biomonitoring. It clearly shows that within this part of the process lies the possibility of numerous mistakes that may affect the overall quality and credibility of the results of any human biomonitoring.

5.2 Exposure assessment

'Biomonitoring data represent an integration of exposure from all sources and routes, which provides an important perspective on overall exposure. Collection of serial biomonitoring samples over an extended period of time can provide information regarding variability and trends in exposure' (Albertini et al. 2004).

When such information is collected, it can also be very useful to assess whether environmental remediation programs has had an impact, and to see if removal or reduction in the use of a chemical has changed the exposure data (e.g. in the case of lead).

In biomonitoring analytic methods are used that permit the accurate measurement of low levels of environmental chemicals in human tissues. Depending on the intended use, it is with biomonitoring as it is with other exposure tools, that it cannot be the only measurement made for some of its environmental public health uses. It is a fact, that biomonitoring data demonstrate that many environmental chemicals are absorbed in human tissues. Even so, one cannot know for sure if, and at what concentrations, many of these chemicals cause damage to the health.

It is important to know in addition the exposure pathway, in order to relate biomonitoring results to sources and routes of exposure and create effective strategies on how to solve the problem and ensure better outcomes. (Albertini et al. 2006)

It is with the case studies referred to in this paper, as it is with many cases of biomonitoring. The primary sources of exposure are not fully understood.

'For example, in the case of DEP, it is known that fragranced cosmetic and other consumer products may contain DEP; however, the use of DEP in the cosmetic and fragrance industry accounts for < 20% of all DEP production' (Api 2001). Thus, there are many sources that surely affect the exposure to DEP, and when only a limited number of them are fully known and mapped, it may cause limitations to the biomonitoring data.

The same goes for DEHP, which can be found in a vast number of sources, including medical plastics like tubing and syringes, household materials like floor or wall coverings, and plastic toys (Calafat and McKee 2006).

The cases of PBDEs and PFOS represent yet another possible limitation to biomonitoring. These are chemicals, of which the presence in different products is well known. They are ubiquitous in the environment and have been found in many different human biologic samples.

PBDEs are found in hard plastics, electronics, textiles, and polyurethane foam products.

Past or current commercial uses of PFOS predominantly include surface treatments for soil- and stain-resistant coating on fabrics, carpets, and leather; coatings on paper and packaging products for grease and oil resistance, including food contact papers; and performance chemical uses, such as fire-extinguishing foam concentrates, mining and oil surfactants, electroplating and etching bath surfactants, household additives, chemical intermediates, coatings and coating additives, carpet spot cleaners, and insecticide raw materials.

Although both PBDEs and PFOS have been used in various consumer products, neither of these classes of chemicals was expected to be found in measurable levels in human tissues, given their specific chemical properties and uses (Albertini et al. 2006).

But although the uses of PBDEs and PFOS have been identified, there is not much knowledge about the sources of exposure. Neither is much known on how PBDEs and PFOS enter the environment (Birnbaum and Cohen Hubal 2006; Butenhoff et al. 2006).

Hence, considering this in the light of the EPHC, this example highlights a limitation on the left side of the continuum, between the source and exposure. One has knowledge about the possible sources, but one does not know how the substances reach the environment, and thus it is difficult to accurately predict how the population is exposed to the chemicals, and to what degree.

In the case of arsenic, this is an example of a chemical that you both find naturally in the environment, and which also is introduced to the environment by human activity. Such chemicals illustrate how detailed understanding of potential sources is needed, and how these sources contribute to the overall exposure.

There are many species of arsenic that can be potential biomarkers of exposure. One of these is arsenobetaine, a relatively nontoxic organic form of arsenic, which can be found in seafood like shrimps. Arsenic can also be found in drinking water. The diet is the major source of nonoccupational exposure to arsenic, but it is also found in the soil and air; thus, inhalation and dermal absorption are additional routes of exposure. Inhalation can be a significant route of occupational exposure to inorganic arsenic (Hughes 2006).

Thus, the case of arsenic shows how complicated it can be to assess potential sources of exposure and their contribution, and when precise assessment cannot be made, it limits the biomonitoring.

Methyl eugenol, is another example of where dietary intake, sampling and analysis strategies can affect biomonitoring of this chemical.

Lifestyle differences, such as wine consumption (De Simon et al. 2003) and occupational setting (agricultural use), can contribute to exposure (Vargas et al. 2000). Methyl eugenol is found in air, water, and some foods, spices, and oils (Barr et al. 2000; Smith et al. 2002). Thus, the intake of any of these sources can significantly affect the measured blood levels.

'Importantly, the biomonitoring data for methyl eugenol do provide information on total exposure to this chemical, which can be compared with dietary estimates to provide some perspective on the fraction of exposure from food consumption' (Albertini et al. 2006).

Based on the experiences from the fore-mentioned workshop, Albertini and others (2006) concluded that the following questions must be considered when designing, conducting, or interpreting exposure studies in the context of biomonitoring:

> Have the primary sources of exposure been identified?
> Are the pathways/routes of exposure understood?
> Can human exposure be related to animal toxicology studies?
> Is there some understanding of the exposure–dose relationship?
> What is understood about temporality and duration of exposure?

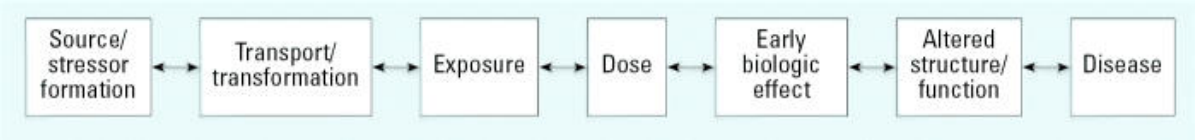
New technologies in molecular biology, including genomics/proteomics and nano-technology, offers greater insights into environment-gene interactions and can be used together with traditional biomonitoring data to better interpret issues like differences between individuals and populations (Schwartz et al. 2005).

Metabolomics will give the opportunity of rapid identification of metabolic differences in populations. And according to Balshaw and others (2005), development of nanosensor technologies will greatly facilitate real-time exposure biomonitoring.

With the emerging technologies, discussions regarding the use of these may be warranted.

5.3 Epidemiology

Staying with the continuum described in the EPHC, the importance of precise collection of exposure data discussed so far, concerns the left side of the process.



If this is not done at a necessary level of precision, it obviously limits the opportunities of biomonitoring to perform its supposed task. This, according to its definition as mentioned earlier, is to demonstrate the exposure to a substance, which at a certain dose is likely to result in certain health consequences.

In order to make this clear connection between exposure and health outcomes, it is apparent that the collection of data regarding the health effects must be gathered precisely as well. The epidemiology is the key on the right side of the continuum.

One outcome of the international biomonitoring workshop in 2006 (Albertini, et al.) was 'the development of guidance on the application of biomonitoring data in the context of risk assessment, risk management, and disease prevention'

In accordance with the different purposes, different criteria are recommended for applying and interpreting biomonitoring information. As Doerrer and Holsapple summarizes it (2004):

> For instance, epidemiology/human effects data would not be needed to address the question of whether there is a trend for a substance or an increase (or decrease) in the environment over time; however, epidemiology/human effects data (and or animal toxicology data) would be necessary if the question being asked is whether there is a potential human health risk from exposure to the substance.

The general ideas outlined in this paper are the summarized experiences from experts in the field of biomonitoring. The aim is to serve as a starting point for how to perform this part of the biomonitoring in the best possible way.

If one is able to do this part precisely, here within lays the great opportunity of biomonitoring. Data from epidemiology studies can provide the critical information needed to support the link between human exposure and human health effects.

'At the September 2004 International Biomonitoring Workshop, the inorganic arsenic case study was used as an example of epidemiology data that provide the initial evidence and link to health effects in humans' (Hughes 2006). Through epidemiologic studies, it has been shown that inorganic arsenic elevates the risk of certain cancer types, including bladder, skin, and lung.

When seeking to define associations between specific exposures and specific human health effects (or their absence), several factors should be considered when designing, conducting, or interpreting such epidemiologic studies.

Careful definition of the link being assessed, as well as the question being asked, is critical (Albertini et al. 2006).

The Bradford Hill criteria (Federal Focus 1996), has been used with success to establish causality in many epidemiologic studies, and could be as useful in biomonitoring studies.

The following basic characteristics are included in these criteria:

- the strength, specificity, and consistency of the association
- the temporality and duration of exposure
- the biologic gradient or the relationship between the dose and the response
- the effects of the removal of the suggested cause
- the biologic plausibility of the association; and the coherence between the association and other findings.

Again, Albertini and others (2006), concluded the lessons learned from the International Biomonitoring workshop with the following questions that must be taken into consideration:

> Has an adverse health effect been demonstrated in humans?
> Is there information regarding the mode of action for the agent producing this health effect?
> Are there health effects observed in populations exposed to the agent of concern? (Note that some characterization of the health effects observed in populations exposed to the agent of concern is needed to design a new epidemiologic study that is focused on disease end points. Furthermore, these health effects must be known before biomarkers are used to identify population exposures and assess risk.)
> Are any toxicokinetic and/or toxicodynamic genetic polymorphisms known to modify risk and define susceptible populations?

5.4 Risk assessment

When exposure data is collected in a way that ensures reliable results, and so is the epidemiological data, the biomonitoring has the opportunity of assessing the risk that a certain exposure yields to the human health.

Biomonitoring data can however be used in other ways, e.g. to analyze trends in regards to the level of a substance in the environment. In such cases, the same supporting data as needed for risk assessment purposes, is not always necessary. When biomonitoring data are used for these non-risk assessment purposes, the uncertainty associated with their intended use(s) should be acknowledged and communicated.

In terms of risk assessment and risk management biomonitoring data have the potential to be a valuable tool (Albertini et al. 2006).

As Albertini and others state (2006):

‘Given the increased sensitivity of analytical methods, simple detection of a chemical in biologic samples such as blood, urine, breast milk, or body fat should not be confused with or equated to increased risk. Exposure information must be carefully evaluated against all

relevant toxicology data and any human epidemiology data. In addition, the relevance of the toxicology data to humans should be considered'.

Considering the case examples discussed in the International workshop, and referred to in this paper, causation between exposure and health effects for inorganic arsenic and organophosphorus pesticides has been found. This is based on epidemiological data, biological statistical associations, and animal and other toxicologic data.

Regarding DEP, DEHP, methyl eugenol and PFOS, there are statistical associations, but the evidence is limited.

Based on the workshop discussions, the following questions should be considered in the process of risk assessment (Albertini et al. 2006)

> Are there sufficient and relevant toxicology data?
> Is there a relationship between the biomarker of exposure and a known human health effect?
> Are there pharmacokinetic data that can be useful in the risk assessment?
> If applicable, is there evidence that remediation efforts are working?

5.5 Contemporary development in Europe

With the international co-operation in Europe, made possible through the expanding European Union (EU), more and more focus is put on biomonitoring.

The European Commission (EC) has developed background materials for environmental health, named SCALE (Scientific evidence, focused on Children, meant to raise Awareness, improve the situation by use of Legal instruments, and ensure a continual Evaluation of the progress made).

Shortly after this the EU launched its environmental health action plan, “Action 3” focusing on biomonitoring. And over the last years the EU has financed several research programs that focus on development and validation of biomarkers.

A review of the purpose and uses of biomonitoring data, with guidance on interpretation, and suggestions for a framework for placing biomarker data into context, was published in

2005 by the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) under the title “Guidance for the Interpretation of Biomonitoring Data”.

As a symbol on how important the biomonitoring now is considered, several prominent European Union officials in 2004 gave blood as part of a World Wildlife Fund (WWF) survey to demonstrate the presence of environmental chemicals in the human body. ‘Although examples are by no means a complete inventory of existing or planned biomonitoring activities, they provide the reader with a snapshot of the magnitude of global interest in biomonitoring (Albertini et al. 2006).

EU’s Action Plan 3, already mentioned, announced to develop a coherent approach to Human Biomonitoring in Europe in close cooperation with the Member States.

On 1 December 2009 a consortium comprising 35 institutes from 24 Member States as well as Switzerland, Croatia and Norway launched the COPHES project which is funded by the European Commission DG Research under the 7th Framework programme (European Human Biomonitoring, [Online]).

The work of the European Commission and European Union, offers to see the greater picture of human biomonitoring, and to consider the limitations and opportunities at this level.

In 2007, The European Commission published a brochure (Do you want to know more, [Online]) that summarizes well these issues and puts them into some perspective. The slogan on the front page was ‘Human Biomonitoring (HBM), breaking the divide between environment and health’.

It states that ‘current fragmentation of HMB activities in the Member States leads to efficacy loss and waste of resources’. The many member states are running their own programs, but when they do this, they are using different methodological approaches. The inevitable result of this is that it is impossible to compare the data and draw conclusions for the whole EU population. EU is in need of a uniform approach.

Further addressing the limitations of HMB today, it says that ‘HBM is a promising tool, but many obstacles must be overcome before it reaches its full potential’. Lack of toxicological and medical information makes it impossible to precisely interpret the health significance of many pollutants. One needs also to research more on human biomarkers, as internal levels cannot be directly linked to the external exposure source.

Since HMB concerns people, ethical frameworks must also be developed.

The European commission proposed in 2007, ‘to develop a coherent approach to HBM in Europe in close cooperation with the member states’. Their main arguments for doing so highlight some of the main opportunities of HBM in the future, when looking at the great picture (EC, Do you want to know more, [Online] 2007):

> EU coordination of HBM activities will make for a more targeted and cost-efficient European environment and health policy. It will provide policymakers with more comparable and accessible information both within and between countries. It will assemble all available knowledge and stimulate exchange of experience between teams and countries. This in turn may enable a more effective use of resources and the development of a common European set of tools and strategies. Finally, it will make it possible to detect population groups with high levels of environmental exposure and lead to health strategies on better environmental equity.

6. Conclusion

Biomonitoring data can offer information on exposure to a variety of environmental chemicals, which is of need and great value to the society. In order to be able to make meaningful interpretations of existing and future biomonitoring data, it will take rigorous, scientific approaches to data collection, analysis, interpretation, and application.

Investigators must define and clearly state the question to be addressed in any given biomonitoring study. The data required for the assessment and interpretation of exposure trends may be different from those necessary for the assessment of health risk.

The fact that critical pieces of data in some cases are lacking, does not mean that the biomonitoring data is unusable. Rather, these gaps need to be filled to reduce the uncertainty. 'Filling these critical data gaps is essential to reduce these uncertainties in interpretation, thus providing the most reliable data for public health decisions' (Albertini et al. 2006).

The author if this paper can only support and communicate the findings of the International Workshop in 2006, because there within lays the essentials of the topic of this thesis.

According to Albertini and others (2006), they highlighted the issues that need to be addressed in order to improve the utility of biomonitoring. These issues represent the limitations of biomonitoring if an adequate level of quality is not present and the opportunities once data gaps are filled. The highlighted issues are as follows;

- Improve the understanding of the predictive relationships/linkages between measures of exposure, dose, and effect. Such insight would allow the development of an interpretation strategy and specific criteria for moving from any point on the EPHC toward either the “exposure” or “effects” sides.
- Emphasize biomarker validation and precision. For analytical measurements, conduct interlaboratory comparison trials.
- Characterize a baseline for biomarkers, and apply statistical methods to assess temporal departures from the baseline.
- Improve understanding of the origin of the biomarker and its relationship to the disease process and/or individual, multiple, and exogenous or endogenous exposure. Establish a database of biomarker disease associations, including null and negative studies.

- Improve study design to better assess intra-and interindividual variability related to measures of exposure, dose, metabolism, and effects that would influence the likelihood of observing predictive relationships between these variables and aid in identifying subpopulations that might be at greater risk. Such data would also clarify the relevance of biomarkers for the target tissues of certain organs.

- Apply new technologies such as gene expression, proteomics, and protein activity profiling, both in terms of development of potential new biomarkers and as screening tools for identifying candidates for biomonitoring.

Based on the biomonitoring workshop of 2006, it is recommended that future studies be designed with some or all of these considerations in mind to achieve optimal application and interpretation of biomonitoring data for human health risk assessment, though acknowledging that no individual study can address every question.

With the contemporary work in Europe, on better co-operation in the work on human biomonitoring, the development will go faster. Research processes will be improved and data gaps filled, giving greater understanding and knowledge.

The opportunities look great.

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