Human biological monitoring – A versatile tool in the aftermath of a CBRN incident

Michael Müller,⁎, Katharina Schmiechen, Deike Heselmann, Lukas Schmidt, Thomas Göen

⁎ Department of Occupational, Social and Environmental Medicine, University Medical Center Göttingen, Waldweg 37 B, 37073 Göttingen, Germany

⁎ Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine, Friedrich-Alexander-University Erlangen-Nürnberg, Schillerstr. 25, 91054 Erlangen, Germany

HIGHLIGHTS

• Design of a compendium to define human biomonitoring sampling in a chemical incident.
• A single sampling approach (chemical, biological and radio-nuclear agents) is depicted.
• Human biomonitoring analysis methods are evaluated for 50 agents in civil protection.
• Holistic exposure data can be used to improve risk communication.

ARTICLE INFO

Article history:
Received 7 February 2014
Received in revised form 13 August 2014
Accepted 23 September 2014
Available online 26 September 2014

Keywords:
CBRN agents
Exposure
Civil protection
Compendium
Sampling

ABSTRACT

Human biological monitoring (HBM) is a well established tool in occupational and environmental medicine. It allows to determine the internal dose of a chemical absorbed by an individual after acute or chronic exposure. Biological reference and threshold values may be used to evaluate the internal dose and estimate its health impact(s).

HBM and its advantages have not been broadly recognized from a civil protection point of view in Germany, therefore we have designed a compendium to define state-of-the-art HBM sampling after a release of chemicals in a civil protection scenario. The compendium integrates the sampling of biological agents and the sampling of radio-nuclear target isotopes, to be analyzed by HBM, in a single sampling approach, thus limiting burden on the potentially exposed persons and facilitating comparison of their individual exposure to different CBRN agents. HBM analysis methods are evaluated and basic toxicity data (including biological reference and threshold values) are given for a list of 50 agents, previously identified as relevant in civil protection.

For on scene commanders and healthcare professionals the compendium may help to generate HBM and biological–radio-nuclear (BRN) exposure data after a CBRN incident which can be used to improve risk communication.

© 2014 The Authors. Published by Elsevier Ireland Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

1. Introduction

Human biological monitoring (HBM) has been used as a tool for prevention in occupational and environmental medicine for several decades. Starting 1890 with the detection of lead in the blood and urine of exposed workers, the application of HBM has ever since steadily increased in many countries around the world (Henschler, 2002; Göen, 2012).

1.1. Development of HBM in Germany

In Germany, the “Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area” of the Deutsche Forschungsgemeinschaft (German Research Council) has been and continues to be a constant driving-
force for the national and international development of HBM. In 1972 the “working-group on analyses of biological materials” for the development of standardized HBM methods was introduced in the commission, followed by the foundation of the “working group on the derivation of threshold values in biological materials” in 1979. In addition, members of the commission support the EU Commission’s Scientific Committee for Occupational Exposure Limits (SCOEL) (http://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/index.html).

In environmental medicine the “Human Biomonitoring Commission” of the German Federal Environment Agency evaluates different guidance values, e.g., “reference” and “HBM values”, since 1992. Briefly, “reference values” reflect the background of a chemical in representative biological specimens collected from the German population, “HBM values” are health effect based guidance values. Members of the commission support the EU HBM development in environmental and public health since 2005 in the projects ESBIOnet, COPHES and DEMOCOPHES (Smolders et al., 2008; Smolders et al., 2008)

Dose monitoring, biochemical effect monitoring and biological effect monitoring represent the three classical monitoring approaches in HBM (Angerer, 2002). Dose monitoring includes the detection and quantification of xenobiotics and their metabolites in German 1998. In human specimens. Biochemical effect monitoring analyses reaction products of chemicals and their intermediates with critical macromolecules like DNA or proteins. Biological effect monitoring observes first changes in somatic cells as reactions of xenobioc exposure through the determination of e.g., cytotogenic or immunological parameters. The predictive value of the different monitoring methods with respect to human health effects increases in the order from dose monitoring via biochemical effect monitoring to biological effect monitoring. In the last decade the three monitoring approaches were supplemented with a fourth approach: the determination of the individual disposition or susceptibility. At a fixed external exposure level the individual disposition or susceptibility of each exposed person modulates the internal dose, the biochemical and the biological effects. In an extreme case a susceptible person may show symptoms of intoxication while its non-susceptible counter-part is not affected. At present, HBM parameters of susceptibility focus on the description of human polymorphisms in enzyme activities, for example xenobiotic metabolizing enzymes, DNA repair enzyme systems and enzymes regulating oxidative stress (Müller and Hallier, 2012).

With respect to legal and public communication issues the application of HBM in occupational and environmental medicine calls for a high quality standard for the entire procedure including specimen sampling, sample preparation, analytical determination, post-analytical evaluation and communication of the HBM results. Thus, the development of standard operating procedures (SOP) has been encouraged and pursued by the “working-group on analyses of biological materials” of the Deutsche Forschungsgemeinschaft (Goén et al., 2012b). The working group comprises of experts who possess the experience in developing, applying and validating biomonitoring procedures. The members are ready to examine those biomonitoring procedures in practice. Analytical procedures are adopted by the working group only after a thorough examination, which includes a reproduction of the method in at least one laboratory by an independent expert. Currently more than 200 of these SOP are available in English (DFG, 1985–2004DFG, 1985–2004; DFG, 2006–2013DFG, 2006–2013; Goén et al., 2012b). In addition, an external quality assessment scheme (German External Quality Assessment Scheme–G-EQUAS) with certification for occupational-medical and environmental-medical toxicological analyses in biological materials was founded in 1982. Today, up to 200 laboratories from more than 35 countries participate in this scheme on a regular basis (Goén et al., 2012a). Most participants of the programme are laboratories with extended experience in biomonitoring, which are interested to control reliability and quality of biomonitoring results.

1.2. Application of HBM in chemical incidents and CBRN scenarios

In the case of a CBRN incident in Germany there are two different populations at risk: the first group is the general population and the second group are the disaster relief forces, which include both professional and voluntary units. Healthcare for the general population is provided by the public healthcare authorities of the German states and the federal government, while healthcare for the professional and voluntary disaster relief forces is granted by the German social accident insurance (http://www.dguv.de/en/index.jsp) using the help of occupational physicians.

HBM has previously proven to be a versatile tool in the aftermath of an accidental chemical release with exposure of the public in the hands of the German public healthcare authorities in the 90’s of the past century (Heudorf and Peters, 1994, 1997; Heudorf et al., 1997; Heudorf, 1998). In 2002, HBM was again successfully used in the Bad Münster epichlorohydrin freight train accident for the assessment of long-term health effects of the potentially exposed persons (Wollin et al., 2008; Wollin et al., 2013, this issue). As a consequence of the incident the “Human Biomonitoring Commission” of the German Federal Environment Agency issued a “recommendation for the usage of HBM for chemical release related to accidents or non-normal conditions of operation with exposure of the public”. The recommendation “includes the informed consent of the affected individuals and the data security, the selection of applicable parameters and materials for sampling, the collection of samples including documentation and the logistics regarding shipping and handling of the samples” (Empfehlungen des Umweltbundesamtes, 2006). A list of substances/parameters which can be determined successfully by HBM is also provided (for example metals, organic solvents, aromatic amines, nitro compounds and some metabolites of the substance groups). Most important, the recommendation describes what may be called the “public interest–legal liability approach for the application of chemical incident HBM”, e.g., the obligation and immediate collection of human specimens after the accidental release of a chemical. The request for the ultimate safe-guarding of samples to be analysed by HBM allows the generation of exposure data on an individual and group basis to assure appropriate risk communication and respond to legal liability cases. The approach involves two pathways: if the substance is known and a HBM method is available “targeted HBM” may be applied and the appropriate human specimens (for example urine, blood, plasma, erythrocytes) will be collected. If the substance is unknown or a HBM method for a known substance is not available only urine will be collected for “validated HBM” after the development of a new HBM analysis method. Spontaneous urine samples can be easily collected from adults and from children (with the informed consent of their parents) and may be stored deep-frozen until analysis. In addition, ethical considerations ask for the appropriate use of a sample collected in an invasive manner, while there is no ethical problem to discard urine sample collected in a non-invasive manner, in those cases in which no adequate HBM analysis method can be developed.

In contrast to the German recommendation Dutch public health researchers have designed a HBM application strategy which may be called the “pre-defined transparent procedure for early decision-making concerning application of HBM following chemical incidents” (Scheepers et al., 2011; Scheepers et al., 2014, this issue). They propose a stepwise procedure to rapidly decide about
the usefulness and feasibility of applying HBM. Starting with ambient measurements and dispersion modeling, ambient exposure in a chemical incident is estimated. If the ambient exposure exceeds intervention values for emergency response (IVERS), e.g., the exposure is sufficiently high to induce adverse health effects, the application of HBM may be considered. IVERS that perfectly fit the demand to describe the onset of adverse health effects after the release of a chemical are the US EPA acute exposure guideline levels (AEGL) [http://www.epa.gov/oppt/aegl/]. Within the system the AEGL-2 value is of special importance as it marks the transition level for health-threatening exposure. If adverse health effects can be anticipated the decision process advances by considering the key parameters availability and persistence of biomarkers in biological tissues, mechanism of toxicity, and sensitivity of the analysis of a biomarker. At any step (except one) along the proposed decision tree the answer “No” prompts the person in charge to stop the application of HBM. The decision whether to apply HBM (or not) needs to be motivated to the potentially exposed population and information gathered within the procedure may help to make the decision-making process transparent and convince the public of its accuracy. Scheepers et al. (2011) present comprehensive datasheets for a preliminary selection of 15 substances based on the Dutch “Register Risk Situations Hazardous Substances” to which their decision making procedure can be applied. Advantages and disadvantages of both approaches will be considered in detail in Section 4.

While public health authorities in Germany and the Netherlands are well aware of the added value of HBM for the general population in a chemical incident, HBM and its advantages have not been broadly recognized from a civil protection point of view. As indicated above the healthcare of potentially exposed disaster relief forces in Germany differs from the healthcare of the general population. Although a few national guidelines, e.g., the occupational medical guideline for biomonitoring (AfaMed, 2013) and the manual for disaster relief forces in a CBRN incident (“SKK-DV 500”) [http://www.dgkm.org/files/downloads/cbrn/Einheiten_2006_jan_500.pdf], recommend the application of HBM for disaster relief forces, most on scene commanders and many healthcare professionals other than the public health authorities are not aware of HBM as a versatile tool in the aftermath of a chemical scenario.

Moreover, modern civil protection has to respond to scenarios, which may involve the additional release of biological agents and of radio-nuclear agents together with chemicals, resulting in CBRN incidents. As an example a terrorist attack may involve all three threats concomitantly. In this case, specific BRN measurement methods need to be applied, although HBM monitoring radio-nuclear target isotopes may also be used. Nevertheless, a single sampling approach for HBM and the other measurement procedures will be favorable. This may limit burden on the potentially exposed persons and facilitate comparison of their individual exposure to different CBRN agents.

Identifying these needs in civil protection prompted us to design a compendium to define state-of-the-art HBM sampling after a release of chemicals in a civil protection scenario together with a single sampling approach for the BRN measurement procedures. In addition, HBM analysis methods are evaluated and basic toxicity data (including biological reference and threshold values) are given for a list of 50 substances and substance groups, previously identified as relevant in civil protection (Table 1, Supplementary information 1). Thus, the compendium may help to generate HBM and BRN exposure data following a CBRN incident which can be used to improve risk communication.

2. Material and methods

2.1. Selection of chemical substances and substance groups in a civil protection scenario

During a project, initiated by the “commission on civil protection of the federal ministry of the interior” [http://www.schutzkommission.de/SubSites/DE/EN/Home/home_node.html] a list of 50 chemical substances and substance groups was prepared (Burbiel et al., 2009). Special emphasis was laid on a civil protection point of view by considering the abuse of chemicals for terrorist attacks. Initially, different lists of chemicals from military sources, for example from NATO (STANAG 2909, 2002), and civilian sources like the Centers for Disease Control and Prevention (http://www.bt.cdc.gov/agent/agentlistchem.asp) were compared and a consensus list was created. While most of the sources focused on the toxicity data to establish a ranking of importance Burbiel et al. designed a scoring system to evaluate the key parameters “availability”, “application” and “socio-economic impact” in addition.

2.2. Literature search for HBM analysis methods and toxicity data

A thorough literature research for the respective HBM analysis methods was conducted including inter alia the “The MAK Collection for Occupational Health and Safety” [http://

- Standard operating procedures (SOP) for HBM

This category comprised HBM analysis methods evaluated and published by scientific or governmental associations, institutions or agencies. The procedures are commonly accepted and used on a regular basis by the HBM analytics community. For several HBM parameters biological reference or threshold values, e.g., the “biologischer Arbeitsstoffreferenzwert” (BAR) (Göen et al., 2012c) or the biological tolerance value (BAT) were established, applying such methods. Due to the high degree of standardization measurement results of different laboratories will be comparable to each other if determined using the same SOP. Examples for this category are benzene and arsine.

- Non-standardized HBM analysis methods

This category comprised well described HBM analysis methods, published in peer-reviewed journals. These methods have not yet been evaluated by scientific or governmental associations, institutions or agencies. The procedures have to be established at an expert laboratory and measurement results need to be reviewed by independent experts. Moreover, biological reference or threshold values are often not available to evaluate the results. Examples for this category are boron (in boron trichloride, boron trifluoride, diborane) and furan.

- HBM method not available

This category contains chemical substances for which HBM analysis methods are not yet available. A default sampling protocol is recommended and calls for the collection of urine spot samples of the potentially exposed persons and deep-frozen storage of the specimens (preferred temperature: −80°C). Meanwhile HBM experts can evaluate, whether a new analysis method can be designed and evaluated to measure the stored samples in due time. Examples for this category are chloropirine and perfluorooisobutene.

2.3. List of HBM laboratories and German poison information centres

To create a list of high quality standard HBM laboratories interested to support physicians in the collection and analysis of human specimens after a chemical incident the G-EQUAS was used as an information exchange platform. Accompanying the official invitation of the 44th G-EQUAS (fall 2009) a questionnaire in German was sent out to regional HBM laboratories. In addition, the members of the “working-group on analyses of biological materials” of the Deutsche Forschungsgemeinschaft were addressed. The registration form to be returned to the authors involved a declaration of consent, full address of the HBM laboratory (postal address, phone and fax number), contact person(s), office hours/availability, and analytical focus (organic chemicals/inorganic chemicals/both). The efforts resulted in a list of 13 HBM laboratories.

Poison information centres may help on scene commanders and healthcare professionals to gain toxicological information on chemicals, to coordinate HBM campaigns and to get access to high quality standard HBM laboratories. Thus, a list of the poison information centres is included in the compendium (https://www.klinitox.de/index.php?id=3).

3. Results

In Germany a compendium was designed to introduce and facilitate the use of HBM and BRN measurement methods in a single approach following CBRN incidents. The compendium was published in 2012 as a guideline in the publication series “Forschung im Bevölkerungsschutz” of the German Federal Office of Civil Protection and Disaster Assistance (BBK) (Müller and Schmiechen, 2012). This paper briefly describes the main results of the research project.

3.1. Concept of the compendium

The concept of the compendium serves two major aims. First aim is to provide information to on scene commanders and healthcare professionals for state-of-the-art HBM sampling after a release of chemicals in a civil protection scenario together with a single sampling approach for the BRN measurement procedures. The expected benefits of the unified sampling strategy in the case of a concomitant release of several CBRN agents is to limit burden on the potentially exposed persons and facilitate comparison of their individual exposure to different CBRN agents. The second aim is to evaluate HBM analysis methods and to provide basic toxicity data (including biological reference and threshold values) for a list of 50 agents.

As a consequence the compendium consists of two parts. After giving general information part 1 focuses on sampling of human specimens for HBM and BRN measurement procedures. Part 2 contains short profiles of 50 substances and substance groups, previously identified as relevant in civil protection.

3.2. Compendium part 1

3.2.1. State-of-the-art HBM

The compendium part 1 introduces the reader to the three stages of an HBM procedure: the pre-analytical stage, the analytical stage and the post-analytical stage. A clear focus is laid on the pre-analytical stage, which involves sampling preparations, ethics, communication and sample collection (Fig. 1).

3.2.2. Sampling preparations for HBM

In the pre-analytical stage advise is given to the acting physician with respect to analyte/parameter selection, sample matrices and time points for sample collection. Considering the average metabolic half life times of chemicals, time windows for the collection of samples after exposure are predefined: urine metabolites 1–2 days, albumin adducts 1–10 days, DNA adducts 1–20 days, hemoglobin adducts 1–60 days (maximum 120 days). Specimen cups for the matrices urine, blood, feces and saliva are depicted in detail and sources of supply are mentioned. With respect to the transport of the human specimens the threefold containment of the biological samples is described: for example a
Sequence of stages in human biomonitoring

- Pre-analytical stage
  - Sampling preparations
  - Ethics:
    - Informed consent
    - Communication:
      - Medical interview
      - Self-reported exposure
      - Sample collection
- Analytical stage
  - Sample preparation
  - Analytical determination
  - Data collection
  - Quality management
- Post-analytical stage
  - Evaluation of the analytical results
  - Medical evidence
  - Evaluation of the results by experts

Fig. 1. Sequence of stages in human biomonitoring.

liquid-tight specimen cup or tube, a liquid-tight jar with screw cap and a rigid cardboard box. Furthermore, a brief overview of the most relevant parts of the national and international transport guidelines for human specimens is given. The interaction with the HBM laboratory involves a first estimate of the number of collected samples, the allocation of appropriate capacities by the laboratory and specialities in sampling and transport. A decision has to be made, whether the samples are stored prior to transport or not. In addition, proper financial support and how to organize sample collection of human specimens by authorized physicians in line with the public health system for the general population and the insurance system for the disaster relief forces in Germany are considered.

3.2.3. Ethics, communication and HBM sample collection

Ethics is always an important issue in the context of HBM. Several experts have dealt with this subject with regard to scientific HBM studies (Casteleyn et al., 2010; Moodie and Evans, 2011; Quigley, 2012). However, the principle task of the application of HBM in the aftermath of chemical incidents is not scientific evaluation but the supply of additional specific diagnostics, which proves the extent of the individual exposure to a single chemical or a chemical mixture. Thus, the ethical criteria, which have to be considered for the application of HBM in CBRN scenarios, are comparable with the general ethical issues of medical diagnostics (Engelhardt 1980; Decker et al., 2013).

Communication is another crucial issue in the whole process. It comprises crisis communication with the exposed groups and the public and individual communication with trained crisis intervention personnel and physicians. In line with the ethical guidelines of medical diagnostics for HBM the acting physician needs to inform the patient on the tasks and risks of the planned examination and request an informed consent of the patient prior to the sampling of the specimens. Therefore a ready-to-copy informed consent form is part of the compendium. Ideally the physician can give the patient information on the medical follow-up while collecting the sample. If this is not the case a contact point, e.g., the local public health authorities, needs to be assigned by the on scene commander to coordinate crisis/risk communication and communication of HBM results in the aftermath.

Prior to sample collection exposed persons have to be decontaminated to avoid exposure of the medical personal. Basic rules of hygiene and personal protection have to be obeyed during the sampling process. In a medical interview the physician may ask for personal data and general HBM influencing factors like smoking, medication and food consumption, e.g., eating fish and seafood modulates levels of arsenic in blood and urine. In addition self-reported exposure data shall be gathered. This comprises time-point and duration of exposure, status (person of the general population/member of the disaster relief forces), proximity to the source of exposure, personal or technical protection equipment (yes/no), signs of intoxication and medical treatment so far. For self-reported exposure data a ready-to-copy form is included in the compendium, the human specimens collected can be documented on the same data sheet. The generated documents and the collected specimen(s) need to be assigned to the exposed individual without doubt anytime during the HBM process. Ideally a unique code number or barcode label(s) supplied by the HBM laboratory are used for this purpose.

As already indicated in the introduction the ultimate safeguarding of samples in line with the “public interest–legal liability approach for the application of chemical incident HBM” is the preferred way to implement HBM in a CBRN incident in Germany. Therefore, if the substance is unknown or a HBM method for a known substance is not available urine sampling is requested for “validated HBM” after the development of a new HBM analysis method. Spontaneous urine samples can be easily collected from adults and children (with an informed consent of their parents) and may be stored deep-frozen until analysis. For the assessment of the spontaneous urine samples (concentrated/diluted urine) the determination of creatinine is recommended prior to analysis.

3.2.4. Sampling of biological agents

Among others bacteria, fungi and viruses are prominent examples for biological agents relevant in civil protection scenarios. Moreover, biotoxins need to be considered. While many of the other biological agents give rise to infectious diseases, biotoxins may cause intoxications. Therefore, three biotoxins, namely botulinum toxin, ricin and saxitoxin were included in the list of the 50 agents of the compendium.

Although the health impact of a biological agent is generally delayed, potential exposure in a CBRN scenario is of great concern to the persons affected. In Germany the public healthcare authorities of the German states and the Robert Koch Institute
of the Federal Government (http://www.rki.de/DE/Home/home-page_node.html) organize human specimen sampling and laboratory diagnostics. Microbiological detection methods of biological agents involve microscopy, cultivation of pathogens, polymerase chain reaction (PCR) analysis and antigen and antibody detection. In addition to the sampling methods described for HBM, which can be used for biological agents as well, the compendium briefly describes special specimen sampling techniques for biological agents to allow a single sampling approach, thus limiting burden on the potentially exposed persons and facilitating comparison of their individual exposure to different CBRN agents.

3.2.5. Exposure monitoring to radio-nuclear agents and HBM of RN target isotopes

Individuals may be exposed to radioactivity in three ways: ionizing radiation directly from a source, contamination due to direct contact with radioactive agents and uptake of radioactive agents in the body. Exposure of persons to radiation can be stopped by shielding or safe removal of the source and radioactive agents may be decontaminated. In contrast, incorporation involves absorption of the radioactive agents in the body, metabolism and excretion. Radioactive agents can exert classical chemical toxicity and radio-toxicity resulting in somatic and genetic damage, either acute or delayed. Radioactive exposure can be detected using biological dosimetry, e.g., determination of radionuclide activity in the body or in the organs, determination of radionuclide activity concentration in excretions or measurement of chromosome aberrations. The determination of radionuclide activity concentration in excretions calls for a 24h urine collection (pre-cleaned specimen cups are supplied by the analyzing laboratory, urine needs to be acidified (10 mL HNO3 (65%) / L urine)). The Federal Office for Radiation protection (http://www.bfs.de/en/bfs) supports and coordinates radioactive exposure monitoring. A network of “Approved Laboratories for Incorporation Monitoring (ALIM)” is available in Germany.

In addition, HBM of radio-nuclear (RN) target isotopes may support the data supplied by the other RN measurement procedures. Generally, radioactive agents released by accidents, military or criminal activities are seldom single pure nuclides, but they consist more likely of mixtures of isotopes of several chemical moieties. Most of these mixtures contain uranium, which may be used as target isotope for initial appraisal of RN exposure. A HBM standard operating procedure of the “working-group on analyses of biological materials” of the Deutsche Forschungsgemeinschaft is capable of detecting and quantifying 232Th thorium and 238U uranium in blood and urine (http://onlinelibrary.wiley.com/book/10.1002/3527600418/topics). This procedure can be used to detect background levels of 238U uranium in human specimens of the general population. Since some mineral waters in Germany contain uranium, thorough investigation of HM8 influencing factors by the acting physician prior to HBM analysis is advised.

With respect to the transport of potentially radioactive human specimens, radioactive monitoring of the samples has to be conducted and an official clearance has to be issued by the appropriate authorities. After the clearance the transport of the human specimens has to be conducted in line with the recommendations outlined above.

3.3. Compendium part 2

3.3.1. Profiles of chemical substances and substance groups

In the compendium part 2 HBM analysis methods are evaluated. Basic toxicity data, including biological reference and threshold values are given for a list of 50 agents, previously identified as relevant in civil protection (Burbiel et al., 2009). The list comprises of 37 substances and substance groups classified as “Toxic Industrial Chemicals” (TIC), 9 substances and 1 substance group classified as warfare agents and 3 biotoxins (Table 1). The profiles include the following items, if applicable, for each chemical substance or substance group:

- Name(s) (German, English), UN- and CAS number(s)
- IVERs (German “Einsatztolleranzwerte”, US EPA AEGL-2 (4h)); German occupational air threshold values, German biological reference and threshold values
- Basic toxicity data: toxicokinetics, acute and chronic toxic effects
- HBM sampling: biological matrix, sampling, pretreatment, conditions of storage
- HBM method: brief evaluation and classification of the method (s) (standard operating procedure for HBM/non-standardized HBM analysis method/HBM method not available)
- Brief introduction to literature: references of HBM method(s) and basic toxicity data

Supplementary information 1 presents a list of the 50 agents with condensed profiles including name(s), CAS-number(s), HBM method(s); parameter, LOD, reference(s).

In addition, the HBM data base of the German Federal Institute for Occupational Safety and Health (http://www.baua.de/de/The-men-von-A-Z/Gefahrstoffe/Blutmonitoring/Auskunftsystem.html) can be used to identify HBM methods of chemical substances and substance groups not included in the compendium.

3.3.2. List of HBM laboratories and poison information centres

A list of high quality standard HBM laboratories interested to support physicians in the collection and analysis of human specimens after a chemical incident was created in cooperation with the G-EQUAS and the “working-group on analyses of biological materials” of the Deutsche Forschungsgemeinschaft. Currently this network comprises of 13 HBM laboratories; anybody interested to be included in the planned update of the list is encouraged to contact the authors of this article. Supplementary information 2 presents the list of HBM laboratories, each with full address (postal address, phone and fax number), contact person(s), office hours/availability, and analytical focus (organic chemicals/inorganic chemicals/both).

Since poison information centres can support on scene commanders and healthcare professionals with toxicological information on chemicals, coordinate HBM campaigns and facilitate access to high quality standard HBM laboratories a list of the German poison information centres is included in the compendium (https://www.klinitox.de/index.php?id=3).

4. Discussion

Chemical incidents warrant a rapid decision whether HBM shall be applied and clear strategies for collection of biological samples, HBM analysis and communication on the outcomes of a HBM study to an individual or group in the aftermath. From a European perspective two alternative approaches are offered: the German “public interest–legal liability approach for the application of chemical incident HBM” (Empfehlungen des Umweltbundesamtes, 2006; this article) and the Dutch “pre-defined transparent procedure for early decision-making concerning application of HBM following chemical incidents” (Scheepers et al., 2011; Scheepers et al., 2014, this issue). Both procedures share important features, nevertheless there are also obvious differences.

With respect to the selection of agents the first approach covers a list of 50 chemical substances and substance groups (Burbiel et al., 2009). In creating this compilation special emphasis was laid on a civil protection point of view through considering the abuse of
chemicals for terrorist attacks. In addition to the toxicity data Burbiel et al. designed a scoring system to evaluate the key parameters “availability”, “application” and “socio-economic impact” to establish a ranking of importance. The second approach comprises of 15 chemical substances and substance groups from a public health point of view. The selection is partially based on practical toxicological experiences and considerations, e.g., substances being important constituents of process emissions and fires or identification as acute exposure threshold level case study substances. Moreover, the key parameter “availability” plays an important role as the relevance of the chemical substances and substance groups was assessed based on the Dutch “Register Risk Situations Hazardous Substances”. The registry highlights nationwide the frequency of occurrence of chemical substances using the format of risk maps (http://www.risicokaart.nl). The use of the identical criterion “availability” in both procedures results in 47% match (7/15 of the Dutch list) of identified hazardous substances, namely acrylonitrile, arsine, benzene, dioxine, ethylene oxide, hydrogen cyanide and hydrogen fluoride. This may form a nucleus for a future European consensus list.

The two approaches supply for each chemical substance or substance group CAS-number(s), basic toxicity data, IVERs (especially US EPA AEGL-2 values), occupational air and biological threshold values and HBM procedure data. Following their individual aims, the German compendium emphasizes the obligate HBM sampling process and facilitates the introduction of its users to the interpretation of the HBM results, while the Dutch procedure focuses on the decision making process whether or not HBM should be applied. A unique feature of the German approach is the integration of the sampling of BRN agents in biological matrices together with HBM specimens in a single sampling approach to limit burden on the potentially exposed persons and to facilitate comparison of their individual exposure to different CBRN agents.

Prior to a detailed comparison of both procedures the basis of the “pre-defined transparent procedure for early decision-making concerning application of HBM following chemical incidents” has to be considered. As already indicated in the introduction, the US EPA Acute Exposure Guideline Levels (AEGL) (http://www.epa.gov/oppt/aegl/) are the IVERs of choice to describe the onset of adverse health effects after the release of a chemical. Within the system the AEGL-2 value is of special importance as it marks the transition level for health-threatening exposure. Ambient monitoring combined with simple dispersion modeling like ALOHA result in a uniform AEGL-2 contour on which the further decision-making process may rely as exemplified by Scheepers et al. (2011). Recent advances in dispersion modeling indicate a non-uniform dispersion of chemicals from a given chemical incident source depending on several factors, inter alia meteorological conditions and existing development, resulting in “hot spots” of high concentrations of a chemical (e.g., >AEGL-2 level) and areas of low concentrations (e.g., <:AEGL-2 level) (Schatzmann and Leitl, 2009; Harms et al., 2011).

Thus, the application of simple dispersion modeling in a chemical incident scenario is of limited value, while current in situ ambient monitoring data shall be preferred for the decision making process. AEGL values clearly reflect inhalative exposure. Consequently, Scheepers et al. emphasize the relationships of ambient exposure levels and biomarker levels for their toxicokinetic considerations (Scheepers et al., 2011). This is a pragmatic approach for most chemical incidents. Nevertheless, dermal exposure should not be underestimated, e.g., in scenarios when chemicals soak the clothes of exposed persons or personal protection equipment of disaster relief forces gets damaged or is not functioning properly.

The major difference between both approaches is the decision on usefulness of HBM. All other issues to be discussed are consequences of this Table 2. The “public interest–legal liability approach for the application of chemical incident HBM” warrants the obligate immediate collection of human specimens after the accidental release of a chemical. This is in line with recommendations of the WHO to obtain blood and urine samples from the exposed workers and members of the affected population if possible in the given scenario (WHO, 1997; WHO, 2009). The safeguarding of HBM samples raises hopes of the exposed persons to determine their individual exposure and to describe their personal health impacts based on their internal doses in the future. These hopes may be fulfilled if a well-established HBM method exists, which is conducted by a qualified laboratory, but if efforts fail to develop an adequate HBM analysis appointment at least in parts of the affected population will be on hand. Although the delay of the decision on usefulness of HBM opens the option to develop a HBM method for the safe-guarded urine samples, it may not lead to the intended positive results in all cases. In contrast, the “pre-defined transparent procedure for early decision-making concerning application of HBM following chemical incidents”

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Comparison of the proposed German and Dutch approaches to HBM following chemical incidents.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspect</td>
<td>Public interest–legal liability approach (this article)</td>
</tr>
<tr>
<td>Field of application Principle</td>
<td>CBRN incidents</td>
</tr>
<tr>
<td>Decision on usefulness of HBM</td>
<td>Obligate and immediate collection of human specimen</td>
</tr>
<tr>
<td>HBM method development for safeguarded samples</td>
<td>Possible</td>
</tr>
<tr>
<td>Coverage of internal exposure and legal liability data</td>
<td>Not and likely affected persons</td>
</tr>
<tr>
<td>Public and media demand for action</td>
<td>Fully satisfied</td>
</tr>
<tr>
<td>Level of preparedness</td>
<td>Moderate</td>
</tr>
<tr>
<td>Training of HBM executing personnel</td>
<td>Healthcare professionals can receive an on-site introduction to HBM sample collection in addition to their basic skills</td>
</tr>
<tr>
<td>Availability and allocation of resources</td>
<td>High level</td>
</tr>
<tr>
<td>Moderate level</td>
<td></td>
</tr>
</tbody>
</table>
results in an immediate decision on the usefulness of HBM supported by scientific data. Consequently, the option to develop a HBM method for obligate collected specimens is not provided and the raise of false hopes of the exposed persons is avoided.

There is another difference between both procedures, if HBM is applied. Due to its set-up the Dutch approach will only cover the internal exposure data and if necessary produce legal liability data for likely affected persons. The German approach supplies internal exposure data and if applicable legal liability data for not affected and likely affected individuals. By presenting HBM results which rule out enhanced exposure, this strategy may have an additional positive societal impact as it helps to reassure not affected persons that they have not been exposed to the chemical(s). With respect to the psychological burden of the disaster relief forces resulting from a potential exposure, its exclusion will generate relief and help them to better cope with similar incidents in the future. HBM results indicating enhanced exposure may be used for legal liability issues in both approaches.

For both procedures the public and media demand for action has to be considered. While the “public interest–legal liability approach for the application of chemical incident HBM” can offer a high extent of satisfaction very early in the aftermath of a chemical incident, the “pre-defined transparent procedure for early decision-making concerning application of HBM following chemical incidents” requires an appropriate and convincing communication on a societal level, if the decision is made not to start a HBM campaign. In the worst case speculations about possible exposure to toxic substances may last for decades after the chemical incident.

With respect to the preparedness, both procedures ask for a moderate level of material and personnel. In line with their aims the first approach lays emphasis on the preparation of logistics, e.g., materials for sample collection, documentation and a laboratory network, while the second approach focuses an information gathering, e.g., data bases and computer modeling, to support the decision making process. In addition, the training of the HBM executing personnel differs: The German procedure can be conducted by common healthcare professionals, an on-site introduction to HBM sampling using the compendium deems possible, in contrast the Dutch procedure relies on experts trained on the method in advance. Moreover, if HBM will be executed additional healthcare personnel will be required.

Finally, availability and allocation of resources may be compared. The first approach asks for a high level of availability and allocation of resources. An HBM campaign with a high number of samples can only be conducted successfully with an appropriate number of trained persons, well organized logistics and a competent laboratory network. The second approach can already avoid the waste of resources by a science-based decision process not to apply HBM. In the case of HBM application, the approach can help to identify the likely affected persons and to restrict HBM sample collection to these individuals.

5. Conclusions

The compendium described in this article and the procedure of Scheepers et al., 2011; Scheepers et al., 2014, this issue) form a good starting point for the routine application of HBM in the case of a chemical incident from a European perspective. Additional initiatives are on the way in Flanders (Smolders et al., 2014, this issue) and in the UK (http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/ HPAweb_C/1287146816461). Recently, a first paper describing the framework for HBM of emergency responders following disasters in the U.S.A. has been published (Decker et al., 2013).

As discussed both approaches have advantages and limitations which need to be further explored in the future. Therefore, the dissemination of the methods among disaster relief forces and healthcare professionals and their training on the procedures need to be promoted. Thus, experiences may be generated, which can be evaluated to optimize the approaches and ultimately harmonize them in a single guideline. In addition, recent technical developments, e.g., the determination of the cholinesterase status (http://www.securetec.net), allowing “field”-HBM on the disaster site and enabling subsequent therapeutic treatment if necessary, may be incorporated.

Conflict of interest

The authors declare no conflict of interest.

Transparency document

The Transparency document associated with this article can be found in the online version.

Acknowledgements

This research project was funded by the Federal Office of Civil Protection and Disaster Assistance (BBK) (Förderkennzeichen: III. 1-623-10-350), Germany. The authors thank Dr. Paul Scheepers for reading an early version of the manuscript and for his very helpful comments on it.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.toxlet.2014.09.017.

References


