Framework for the development and application of environmental biological monitoring guidance values (LRI-HBM1-UCRA-0712)

Final Project Report

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This document is a report by the BGV project team for Cefic-LRI and has been approved for general circulation.

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Executive Summary

Biomonitoring is widely recognised a useful tool to aid the assessment of exposure to many chemical substances but currently our ability to detect hazardous substances (or their metabolites and effects) in body fluids may often exceed our understanding of the biological relevance of these results to either individuals or populations. There are well-established frameworks for developing and using biological guidance values (BGVs) in the occupational health field but even these are limited in number, probably less than a hundred, and are only for data-rich substances that have been in use for some time. BGVs for new substances and those with undefined dose-response relationships are difficult to derive and the problems are compounded at environmental levels that are far below doses used in toxicity studies or those encountered in the occupational setting.

The focus of public health interventions, in the context of environmental chemical exposure, is to prevent and/or reduce exposure and limit adverse health effects through research aimed at development of recommendations (guidelines) that may, if appropriate, be incorporated into legislation and health policy. The development of such appropriate BGVs is of paramount importance for the effective use of HBM data, which are used in routine population exposure surveillance in some European countries (e.g. Germany) and the US.

An accepted framework is urgently needed to help scientists, regulators, and stakeholders to put available information in perspective, manage the expectations of its use and inform the need for additional data. Ideally, such a framework should be based on current scientific knowledge and best practice across Europe, the US and elsewhere, to help scientists, regulators, and stakeholders to design appropriate HBM studies, interpret HBM data (both for groups and individuals) and to take appropriate action when required. This appropriate action will comprise a range of risk management options, including risk communication to the public.

The study reported here describes the development of a scientifically-defensible practical framework for establishing different types of BGVs for the assessment of environmental exposures to a wide range of anthropogenic and naturally occurring environmental contaminants. Suggested uses of BGVs and their implications for public health are also addressed.

The initial design of the framework was developed by the research team based on their experiences and the existing literature, and was modified following critical comments from an expert advisory board, tested using a number of substances (data rich and data poor) and finally, fine-tuned following presentations and discussions at an expert Workshop.

The finalised framework provides robust criteria for interpreting HBM data in relation to environmental exposure. Levels 1 and 2 of the framework allow a non-health based BGV to be defined for compounds with only small amounts of HBM data (Level 1) or for which only a reference range has been established (Level 2). Levels 3 and 4, where toxicological and/or health data is available; additionally consider risk assessment data, providing health-based BGVs. It is hoped that the framework can now be further tested and modified over time through use within larger HBM projects such as the recently initiated EU COPHES project

It is envisaged that the framework, developed through this project, may be used as a tool to aid clear and transparent communication to a wide range of stakeholders, including the public, the study population, the scientific community, politicians, the media and other interested parties. Each of these audiences has a different goal, different needs and different perception of risk, but it important that the framework can give some confidence in the reliability of the science and logic underpinning the framework that can provide an agreed platform for meaningful dialogue and discussion.

Part A: Framework Development

1.0 Introduction

A comprehensive description of Human Biomonitoring (HBM) was proposed by Zielhuis (1984) as "*a systematic continuous or repetitive activity for collection of biological samples for analysis of concentrations of pollutants, metabolites or specific non-adverse biological effect parameters for immediate application, with the objective to assess exposure and health risk to exposed subjects, comparing the data observed with the reference level and, if necessary, leading to corrective actions*". Since that definition was put forward, HBM has evolved and today also encompasses the determination of hazardous substances or metabolites in human samples (dose monitoring) through quantitation of the reaction products of the substance with DNA, proteins and other biomolecules *(biochemical effect monitoring), through to the measurement of early biological effects caused by such reactions (biological effect monitoring).

The measurement of chemicals in biological samples has traditionally been used to assess occupational exposures in workers. Indeed, the monitoring of blood levels of lead and urinary levels of benzene metabolites in workers was described as far back as the 1930s (Kehoe *et al.,* 1933; Yant *et al*., 1936). Subsequent advances in analytical techniques in the 1960s, allowing measurement of very low levels of chemicals in complex biological samples, enabled environmental exposures to also be assessed. In the 1970s, application of biomonitoring to environmental exposures facilitated the discovery of harmful levels of lead in the environment. Immediate action to reduce lead levels was required, and facilitated the directive from the Commission of the European Communities (CEC) that necessitated member states to instigate a blood lead level screening programme for the general population (EC, 1977). Following this directive, several countries recognised the potential of HBM in monitoring environmental exposure of the general population to pollutants, and a number of biomonitoring programmes are currently running (discussed in a later section). Several national and international bodies (Academy of Sciences of the USA; Health and Environmental Science Institute of the International Life Science Institut; Deutsche Forschungsgemeinschaft), have assessed the potential of HBM which is proving to be an invaluable public health tool, giving a measure of the *total* internal dose following uptake by oral, dermal and inhalation routes. HBM is also often used to assess trends and changes in exposure of a population to environmental chemicals, and to help identify susceptible populations, such as children, who may be at higher risk from exposure. In addition, HBM data also supports and enhances that obtained through Ambient Monitoring (AM) which determines levels of chemicals in environmental matrices such as air, water, soil and food. It is clear that there are many

areas in which HBM can make a major contribution, including exposure and risk assessment, risk management, health prevention and policy making.

1.1 Human Biomonitoring

The terms 'biomonitoring' and 'biomarkers' are often applied in a wide range of circumstances, from occupational to environmental monitoring and from genotyping to clinical measurements; this inevitably can lead to confusion in meaning. Biomonitoring is a general term that encompasses (i) biological monitoring (ii) biochemical effect monitoring (iii) biological effect monitoring and (iv) abnormal clinical parameters. It is also a term used in environmental monitoring and ecotoxicology where the above measurements can be made in fish, crustacae and many other animals. This can add a further layer of potential confusion. In this report, comments are restricted to human biomonitoring.

The degree of exposure of an individual undergoing biomonitoring is assessed through measurement of specific biomarkers, which have been defined as "*any substances, structures or processes that are measured to indicate an exposure or susceptibility or, that predict the incidence or outcome of disease*" (Toniolo *et al*., 1997), as depicted in Figure 1.

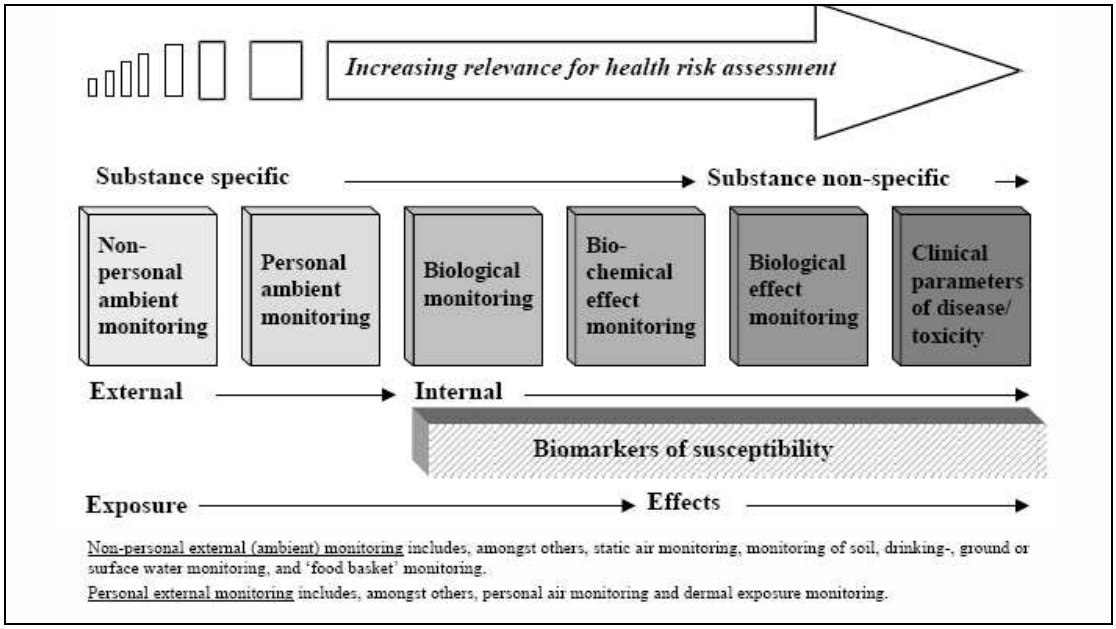

Figure 1: Monitoring techniques as part of the exposure-disease continuum (ECETOC, 2005. Permission for reproduction of figure received from ECETOC, however it should be noted that this does not constitute endorsement of this report by ECETOC).

Biological monitoring and biochemical effect monitoring

Biological monitoring and biochemical effect monitoring are biomonitoring techniques used to assess links between external and internal dose and potential health effects that may result from that

exposure. This is achieved through measurement of specific biomarkers of exposure, and of effective dose respectively. Both of these techniques measure the total dose to an individual and are not exposure-route specific. Biochemical effect monitoring has been described as 'early biochemical change, preceding structural or functional damage, caused by the absorption of a substance, (Mason, 1996, Paustenbach & Galbraith, 2006). This technique has the advantages of measuring the effective dose of a chemical to tissues (tissue dose) or, if measured in the target tissue, the target tissue dose and providing information on the combined effects of genetic and acquired susceptibility.

Biological monitoring is typically used for determination of (i) metals in blood and urine (mercury, arsenic, lead); (ii) parent compound in adipose tissue, milk, urine and blood (dioxins, PCBs, benzene); (iii) specific metabolites (S-phenylmercapturic acid for benzene) in urine and (iv) volatile compounds in exhaled breath (parent compounds or metabolites). Examples of biochemical effect monitoring include measurement of adducts of a specific chemical to DNA and protein (albumin, haemoglobin), messenger RNA expression and measurement of transcribed protein levels" (Keshava *et al.*, 2005, Terasaka *et al.*, 2004, Hemstreet *et al.*, 2000, Vanden Heuvel *et al.*, 1993, Whyatt *et al.*, 1995).

Biological effect monitoring and abnormal clinical parameters

Following exposure, early, often reversible, biological effects are monitored through measurement of specific biomarkers of effect, whereas expression of clinical parameters that are indicative of disease are monitored through biomarkers of disease. Biological effect monitoring has been used for measurement of (i) cholinesterase activity in blood (ii) sister chromatid exchange / chromosomal abberations (iii) microalbuminuria. A number of environmental and physiological factors can influence biomarkers of effect and therefore measurement within an individual or group of individuals (population) is representative of a 'normal background' value. This value, although fairly arbitrary, can potentially be used to distinguish a minor biological effect level from one that may be clinically relevant; it is important to note that the prognostic ability of any biomarker of effect requires initial validation within a high risk clinical cohort (Mueller *et al.*, 1997). In addition, biomarkers of effect are often used in conjunction with biomarkers of exposure to establish dose-effect relationships.

Biomarkers are influenced by a number of factors, including an individual's genotype and phenotype. *Biomarkers of susceptibility* may be used as an indicator that an individual has an inherent or acquired limitation in their ability to respond to a specific exposure challenge (Mason, 1996), and may therefore potentially have an altered health risk. Expression of certain isoforms of cytochrome P450, glutathione transferases, iron-status and nutritional status have all been used as biomarkers of susceptibility.

Requirements for Human Biomonitoring

Human biomonitoring provides a number of advantages over other risk assessment methods, including air and surface contamination monitoring, in that it allows evaluation of an internal dose that can potentially be related to early biochemical and biological effects (ECETOC, 2005). However, in comparison with environmental monitoring, validated biomonitoring methods are only available for a limited number of substances. In order to ensure accuracy of HBM data adherence to a number of specific requirements is recommended:

- *biological matrices* - blood and urine are the most commonly analysed samples in HBM as they are easily accessible in sufficient quantities, through relatively non-invasive procedures that pose no adverse risk to the subject. Additionally, there are evaluated SOPs for analysis with these matrices and reliable reference values for interpretation of results. Although hair, nails, teeth, saliva and exhaled air have also been investigated for use in HBM, applications of these are less well defined; however, for measurement of methyl mercury intake or exposure to inorganic arsenic, hair and nails are the most appropriate matrices (van Wijngaarden *et al.*, 2006, Karagas *et al.*, 2002, Wilhelm *et al.*, 2005).
- *biomarker relevance and specificity*- for biomarkers to be used effectively in occupational and environmental risk assessments they must be *relevant* and *specific.* Biomarkers should allow dose monitoring, biochemical effect monitoring and biological effect monitoring. Currently utilised biomarkers with proven diagnostic reliability and applicability to public health assessments have been summarised in a recent paper (Angerer *et al.,* 2007). The author provides a comprehensive list of biomarkers of exposure for dose monitoring of metals, polyaromatic hydrocarbons (PAHs), phthalates, polychlorinated dibenzodioxins (PCDD), polychlorinated dibenzofurans (PCDF), polychlorinated biphenyls (PCB), pesticides, aromatic amines, perfluorinated substances, environmental tobacco smoke (ETS) and volatile organic compounds (VOC).
- *biomarker validity* –refers to both analytical (measurement validity) and epidemiological (internal and external validity) aspects of validity. As findings from HBM surveys have the potential to impact on regulatory requirements, the integrity of the results must be assured at the analytical stage through use of standard operating procedures (SOPS) such as those published by The Deutsche Forschungsgemein-schaft (Angerer and Schaller, (1985-2006) and appropriate internal and external quality controls (WHO, 1981). Reliability and reproducibility of analytical methods are tested and published in 'Analyses of Hazardous Substances in Biological Sciences'. The internal and external validity of currently used biomarkers of biochemical effect such as haemoglobin and DNA adducts and biomarkers of

biological effect such as chromosome aberrations and micronuclei (Au, 2007) are also comprehensively discussed by Angerer (2007).

- *interpretation* - clear criteria are needed for accurate interpretation of HBM data. In Germany, reference and HBM values are devised by the German HBM Commission; exposure guidance values are given in 'The MAK Collection for Occupational Health and Safety' (available at http://www3.interscience.wiley.com/cgi-bin/mrwhome/104554790/HOME) and in the UK, BMGVs are set by HSE (available at http://www.hse.gov.uk/). These are all discussed in greater detail in later sections.

Ethics of biomonitoring

As biomonitoring necessitates the collection of human samples e.g. blood and urine, ethical issues including confidentiality, sample storage and disposal as well as strategies for dealing with potential high exposures and communication of data must be considered. In occupational biomonitoring such ethical issues are well established. However, although the need to establish ethical guidelines for use of biomonitoring data from broader population studies has been acknowledged, these are currently still under discussion and at present each programme of work addresses these issues in isolation at regional or national level.

Communication of biomonitoring data

Biomonitoring studies have a number of stakeholders ranging from, study participants and their families, researchers/investigators to other members of society. Much of the data produced through biomonitoring is personal and may even relate to an individual's health risk and as such, has the potential to be misinterpreted or misunderstood. It is essential therefore that biomonitoring protocols should incorporate a defined communication strategy to be implemented through all stages of the study.

1.2 Biomonitoring Initiatives

HBM has traditionally been applied in occupational settings, where correlations between biomonitoring values and personal air monitoring data, or early and reversible biological effects have been used to set biological limit values (estimated levels of exposure associated with no adverse health effects) for a number of substances. However, due to advances in increasing sensitivity in analytical techniques, HBM is now used, with increasing frequency, to monitor environmental exposures, providing the unique challenge of interpreting potential adverse health effects in a non-homogeneous population exposed at levels significantly below those assessed in animal experiments (ECETOC, 2005).

In a meeting organised by the Health and Environmental Sciences Institute (HESI) Biomonitoring Technical Committee, an international group of scientists from government, academia and industry reviewed global biomonitoring initiatives (Angerer *et al.*, 2006). The group identified that, to date, a number of environmental biomonitoring initiatives have been established around the world with the aim of collecting and interpreting selected biomonitoring values for exposure risk assessment in non-occupationally exposed populations (Angerer, 2007). At present the various national biomonitoring programmes are primarily used to collect data to identify trends and assess performance of public health measures. However, when sufficient data becomes available it may be possible to utilise the data to determine potential adverse health effects following exposure to environmental chemicals at those levels (National Research Council. Committee on Human Biomonitoring for Environmental Toxicants, 2006). Whilst for the majority of environmental chemicals this is still in the future, the application of biomonitoring to assess blood lead levels resulted in the successful phasing out of lead in petrol, with concurrent reduction in lead-based diseases (CDC 2009).

European Perspective

The European Commission (EC) has developed an Environment & Health Action Plan (2004 2010) through the SCALE (Scientific evidence, focused on Children, meant to raise Awareness, improve the situation by use of Legal instruments) initiative, to ensure a continual Evaluation of the progress made; (EC. Technical Working Group on Integrated Monitoring, 2004; EC 2004). A pilot project is currently being developed with the aim of monitoring levels of lead, cotinine and methyl mercury in European population groups, with possible inclusion of substances such as phthalates and acrylamide at a later date. Current biomonitoring initiatives in Europe include;

- German Environmental Survey (http://www.umweltbundesamt.de/gesundheit-e/survey/index.htm)
- Biomonitoring programme in humans on environmental health conducted by the Flemish Ministries of Environment and Health (http://www.milieu-en-gezondheid.be/index.html)
- Polish biomonitoring programmes (Indulski *et al.*, 1999, Heinrich-Ramm *et al.*, 2000, Jakubowski & Trzcinka-Ochocka, 2005)
- French biomonitoring programme (Huel *et al*., 2002)
- Portuguese biomonitoring programmes.

United States Perspective

There are currently several ongoing initiatives to assess exposure of the US population to a number of environmental chemicals. A recent report on these initiatives was published as the fourth National Report on Human Exposure to Environmental Chemicals (CDC, 2009). The report was based on

measurements from the Centres for Disease Control and Prevention (CDC) most prominent biomonitoring programme, the National Health and Nutrition Examination Survey (NHANES) which gathers data on around 250 chemicals in the blood and urine of the general population of the US. Through the NHANES biomonitoring programme, blood levels of lead, cotinine, and dioxins have all been shown to be successfully reduced in the US population, following implementation of specific legislation. For other environmental chemicals, including brominated flame retardants, perchlorate, and perfluorinated chemicals, exposure data is currently being collected (Angerer *et al.*, 2006, Needham, 2008).

The US Environmental Protection Agency (US EPA) is responsible for the development and implementation of regulations to protect public health. In order to facilitate this role, the US EPA has conducted several field-monitoring studies to identify environmentally-related health problems, develop risk mitigation strategies and assess their effectiveness. These studies include;

- National Human Exposure Assessment Survey (http://www.epa.gov/nerl/research/nhexas/nhexas.htm/);
- Agricultural Health Study / Pesticide Exposure Study (http://www.aghealth.org/);
- Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants (http://www.epa.gov/heasd/ctepp/index.html/; Wilson, *et al*., 2004).

The US EPA are also currently developing exposure and dose models such as the Stochastic Human Exposure and Dose Simulation model (http://www.epa.gov/heasd/products/sheds_multimedia/sheds_mm.html/; Zartarian *et al*., 2002) to facilitate estimation of exposure from environmental measurements.

In a further initiative, the US National Research Council (US NRC) established the Committee on Human Biomonitoring for Environmental Toxicants in 2004 (National Research Council. Committee on Human Biomonitoring for Environmental Toxicants, 2006). This committee, comprised of a multi-disciplinary team, has the specific remit of addressing all issues related to the interpretation of data relating to biomonitoring, toxicology, epidemiology, risk assessment and communication, analytical chemistry, medicine, occupational and children's health.

1.3 Types of Biological Monitoring Guidance values (BMGVs)

Reference and HBM values

The German Human Biomonitoring Commission was established in Germany in 1992 in order to provide expert advice to the Federal Environment Agency in developing scientifically-based criteria

for the application of human biomonitoring (HBM). The principles and procedures employed by the commission have been previously summarised (Ewers *et al*., 1999) but in general, a consistent assessment of internal exposure to environmental contaminants is achieved through derivation of two kinds of guidance values, reference and HBM values (Schulz *et al.*, 2007).

***Reference values*:** have been defined as '*the upper margin of the current background exposure of the general population to a given environmental pollutant*' (Angerer *et al*., 2007). Reference values are not toxicologically-derived biological exposure limits but are a statistical description of the background exposure of a given population at a given time. As environmental conditions and populations are subject to change, reference values are updated on a regular basis. Reference values are generally used to compare exposure levels of either individuals or groups to a given 'background' exposure and are typically based on analyses of blood or urine from a representative sample of the general population. Reference values are derived from analytical data within the framework of the German Environment Surveys (http://www.umweltbundesamt.de/gesundheit-e/survey/index.htm; Seifert, *et al*., 2000) using statistical analysis as set out in IUPAC guidelines (Poulsen *et al*., 1997). The reference value is taken as the '*95th percentile of the measured pollutant concentration levels in the relevant matrix of the reference population'*, or in cases where there is sufficient data and it is appropriate to do so, reference values for subgroups not being exposed are defined (e.g. cadmium in non-smokers). The reference values set by the Commission are not health-based values and therefore exceeding these levels does not imply an increased health risk. Conversely, an increased health risk cannot be ruled out if the level of pollutant is below the reference value. Reference values in blood, urine and human milk have been established for a number of compounds, as detailed in Table 1.

***HBM values*:** HBM values are derived by the Human Biomonitoring Commission following review by an expert panel of toxicological and epidemiological studies. Two levels of HBM values are defined (Schulz *et al*., 2007):

- ***HBM-I values:*** determine the concentration in biological material at which, according to current knowledge, no adverse health effects are considered to occur.
- ***HBM-II values:*** determine the concentration in biological material above which, according to current knowledge, there is increased risk of adverse health effects.

At the HBM-I level and below, there would be no need for intervention to reduce exposure of an individual, and is regarded as the 'no action' level. However at the HBM-II level and above, urgent reduction in exposure would be recommended and medical advice given to an individual. This level is therefore regarded as the 'action level'. At levels between the HBM-I and HBM-II values, verification of measurement is confirmed and sources of exposure are identified and reduced, or preferably eliminated.

Table 1: Compounds for which a reference range has been established in a biological matrix by the German Human Biomonitoring Commission

Compound	Media for which Reference value established
Metals	
Lead	B
Cadmium	B+U
Mercury	B+U
Nickel	B+U
Uranium	B+U
Platinum	U
Arsenic	U
PCBs	
Beta-hexachlorocyclohexane (β-HCH)	B; HM
Hexachlorobenzene (HCB)	B; HM
Organochlorine Pesticides	
DDT	HM
PCP	S+U
DDE	B
Metabolites	
Organophosphates	
DMP, DMTP, DEP	U
Pyrethroids	
cis-Cl_2CA; trans- Cl_2CA; 3-PBA	U
DEHP	
5oxo-MEHP; 5OH-MEHP	U
Polycyclic aromatic hydrocarbons	
1-OH-pyrene	U

B = blood only; B+U=blood and urine; U = urine only; HM=human milk; S+U=serum and urine

HBM values in blood and urine have been established for only a limited number of compounds (Schulz *et al*., 2007), as detailed in Table 2. The small number of HBM values established to date reflects the lack of available data from human health-effect studies for many compounds, which currently prohibits HBM derivation. In an attempt to overcome this shortcoming, the Human Biomonitoring Committee proposes to evaluate the use of toxicokinetic data and models to estimate dose-specific contaminant levels in blood. Biological levels will be estimated at exposure doses equivalent to the tolerable daily intake (TDI), acceptable daily intake (ADI), lowest observed adverse effect level (LOAEL) and no observed adverse effect level (NOAEL) for a number of chemicals, for which at present HBM values cannot be derived.

Table 2: Compounds for which HBM values have been established by the German Human Biomonitoring Commission

Compound	Media for which HBM value established
Metals	
lead	B+U
cadmium	B+U
mercury	B+U
Organochlorine Pesticides	
pentachlorophenol	S+U
Metabolites of DEHP	
5oxo-MEHP; 5OH-MEHP	U

B+U = blood and urine; S+U =serum and urine; U = urine only

Exposure Guidance Values

Exposure guidance values are estimates of exposure to chemicals that are considered not to appreciably increase health risk of an exposed population. These values are set by regulatory agencies and authoritative bodies through a risk assessment process. They are designed to protect all groups within the general population, including sensitive subpopulations with chronic exposure. Many BMGVs utilise Acceptable Daily Intake (ADI), Tolerable Daily Intake (TDI) and Provisional Tolerable Weekly Intake (PTWI) data in their derivation. International scientific committees such as the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) allocate ADIs to substances in the food chain such as food additives, veterinary drugs and pesticides, that can be controlled (IPCS, 1987 & 1990). JECFA also derives TDIs, both daily and weekly, for contaminants (IPCS, 1987) and, for contaminants with long half lives in the body (i.e not cleared rapidly) PTWIs. The term *tolerable* is used to emphasise that the level is only permissible, and not acceptable, as some contaminants will be consumed as a consequence of eating other foods e.g. pesticide residues in vegetables. Contaminants given a PTWI may accumulate within the body over a period of time e.g. cadmium, and is concerned more with prolonged exposure rather than day to day variation in intake. The term p*rovisional* reflects the lack of reliable data available on effects of human exposure to these contaminants (IPCS, 1987). For trace elements that do not accumulate in the body but which are also essential nutrients, JECFA establishes Provisional Maximum Tolerable Daily Intakes (PMTDIs) where the lowest value of the range represents that which is essential to maintain good health and the highest value represents the PMTDI (IPCS, 1987). The International Programme on Chemical Safety (IPCS) task groups are responsible for reviewing Environmental Health Criteria (EHC) documents and derive TDIs which are designated as Tolerable Intakes (TIs) in EHC 170 (IPCS, 1987) and are equivalent to ADIs set by JECFA and JMPR.

Other established criteria commonly used to derive BMGVs include, Reference dose (RfDs) which is set by the US EPA and defined as the maximum acceptable oral dose of a toxic substance; Reference concentration (RfCs) which refers to the concentration of a chemical in air that is very unlikely to have adverse effects if inhaled continuously over a lifetime; Minimum risk levels (MRLs) which are derived by the ATSDR (Agency for Toxic Substances and Disease Registry) as an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure; NOAEL (no observable adverse effect level) which refers to the highest tested dose or concentration of a substance at which no adverse effect is found, where higher doses or concentrations resulted in an adverse effect.

JMPR bases ADIs on No Observed Adverse Effect Level (NOAELs) determined from toxicology studies (IPCS, 1994). Although the procedure is the same for contaminants, veterinary drugs and pesticides, the level of the NOAEL will vary considerably depending on substance and for some (eg. food additives) the ADI will be based on an observed effect, even if it is not known whether it is adverse. When NOAELs are available from several studies, the overall NOAEL used to determine the ADI is the one from the animal study showing toxic effect at the lowest dose.

The ADI is based on multiple-dose animal studies, usually carried out over long time periods. As the ADI is intended to define safety over a lifetime of exposure, large safety factors are 'built in' to ensure that intake above the ADI over a shorter period of time is unlikely to result in harmful effects (as long as intake over extended period doesn't go over ADI). JEFCA and JMPR use the term 'safety factor' whereas other bodies use 'uncertainty factor' - they are both used to provide a safety margin and are generally derived in the same way. The NOAEL is divided by a safety factor to establish the ADI, with a safety factor of 100 generally being employed. This figure is based on the assumption that humans are 10x more sensitive to a substance than experimental animals, and that there is a 10-fold range in sensitivity within the human population. However, other safety factors have also be employed, such as those using physiologically based pharmacokinetic (PBPK) models (Renwick 1993) as proposed by IPCS (IPCS, 1994) and probabilistic approaches (Baird *et al*., 1996). Committees deriving ADIs may also employ safety factors other than 100 when the available studies are inadequate; toxicokinetic and toxicodynamic data are available; where there is evidence of irreversible toxicity (eg developmental toxicity); where a susceptible group of individuals has been identified; where human studies are available; when substance is a contaminant of food stuffs (Herrman & Younes, 1999).

Environmental Exposure Guidance Values: Although biomonitoring is often described as the 'gold standard' of environmental exposure assessment (Needham *et al.*, 1999), very few biomonitoring-based reference values exist for exposure of the general population to environmental chemicals, where exposures may be many orders of magnitude below that found in an occupational setting.

Epidemiologic studies have been used to link exposure and health effects but these cannot provide definitive levels of chemicals that result in a biological health effect. However, risk assessments could be facilitated if biomonitoring levels could be compared to existing screening criteria such as RfDs, MRLs, TDIs and other PODs (points of departure). Approaches have been, and are being, developed with one such approach, proposed by Summit Toxicology, of Biomonitoring Equivalents (BEs). The aim of developing BEs is to "*integrate existing risk assessments with available pharmacokinetic data to estimate the concentration of a biomarker of exposure consistent with current exposure guidance values such as the EPA Reference Doses (RfDs) or Health Canada's tolerable daily intakes (TDIs)*" (Hays *et al*., 2007). BEs provide a screening tool for assessment of biomonitoring results of a population for public-health risk, however they are not intended for assessment of an individuals biomonitoring results or for diagnostic purposes. BEs provide a screening level assessment for comparison with biomonitoring levels that can evaluate whether measured levels are of low, medium or high priority for risk assessment follow-up and further risk management procedures.

Derivation: Exposure guidance values based on chemical risk assessments are used to derive chemical and biological media-specific BEs, equivalent to the exposure criteria e.g. BE_{RfD} would provide a biological monitoring equivalent to the RfD and a BE_{MRL} would correspond to the MRL. Several steps are involved in deriving BEs:

- ***Exposure Guidance Value Selection*****:** exposure guidance values including RfDs and RfCs (USEPA), MRLs (ATSDR) and TDIs (WHO; Health Canada) are the most appropriate for use as the starting point for BE derivation.
- ***Target Analyte Selection:*** analyte should be a *specific* marker of exposure to the chemical of interest; be *relevant* to the toxic end point of interest and /or to exposure; be *stable*, whether it is the parent c*ompound or metabolite; have an acceptable* (less-invasive) method of sampling; have robust analytical methodologies for measurement; be *interpretable* from a health risk context.
- ***Source Data Requirements*****: s**everal sources can be used to derive BEs, including, extrapolation from occupational biomonitoring standards; use of human exposure PK studies and one-compartment steady-state models; use of multi-compartment and physiologically-based pharmacokinetic (PBPK) models; use of animal pharmacokinetic studies.

Overall reliability of the derived BE is however dependent on the assumptions that internal measures of dose are superior to external measures for predicting potential health effects; that the regulatory guidelines used to derive BEs are robust; the analyte measured is relevant to prediction of potential toxicity and that the assessed exposure is chronic steady-state, and at the regulatory guideline. However, even when taking these limitations into account, BEs are likely to be no more uncertain

than existing regulatory exposure guidelines, and in some aspects offer improved estimates. To date, BEs have been derived for 2,4-Dichlorophenoxyacetic Acid (2,4-D; Aylward & Hays, 2008); Toluene (Aylward *et al.*, 2008); Acrylamide (Hays & Aylward, 2008); Cadmium (Hays *et al.*, 2008); Trihalomethanes (Aylward *et al*., 2008b).

Occupational Exposure Guidance Values: Biomonitoring of human exposure through measurement of chemicals in biological samples has the advantage of assessing total exposure from all routes and sources, providing an internal dose that can be directly related to the concentration of chemical reaching target organs. For this reason, biomonitoring has been used for some time to assess exposure and evaluate health risk in an occupational setting and there are frameworks available for when to use human biomonitoring (when substances are significantly absorbed through the skin or when exposure control relies on respiratory protection). In the UK there are different types of BMGVs based on health, biological equivalents to inhalation exposures, 'background levels' and good occupational hygiene practice, depending on the hazard and available information. Biomonitoring-based reference values called biological exposure indices (BEIs) started to be developed in the United States in the 1980s and represent levels of chemicals in a healthy worker exposed through inhalation to levels at the Threshold Limit Value (TLV). Germany has similarly developed biological monitoring reference values called biological tolerance values (BATs) and the World Health Organisation, biological action levels (BALs). In the EU, SCOEL are in the process of establishing guidelines for setting and explaining different kinds of occupational biological guidance values (BGVs) which take into account those already in use in Germany (BATs), the US (BEIs) and the UK (BMGVs) as well as others.

Table 3 provides a summary of the derivation of human environmental and occupational exposure guidance values.

Table 3: Summary of current exposure guidance values

Acronym	Basis	Organisation
Environmental		
HBM1	RfD/Tox/Epi	HBM Commission
HBM2	Tox/Epi/Occ	HBM Commission
Reference/Clinical Ranges	Population ranges	Various
BE	RfD/RfC/MRL/TDI	Summitt Toxicology
B	Tox	WHO
Occupational		
BMGV	Tox/90th percentile ref range	HSE
BAT	Tox/Air	MAK/DFG
BEI	Tox/Air	ACGIH
BLV	Tox	SCOEL
BALs	Tox/Air	WHO
EKA	Tox/Air	DFG
BLW	Tox/Epi	DFG
BAR	Ref/Tox	DFG

RfD=reference dose; RfC=reference concentration; T=toxicology data; Epi=epidemiology data; Occ=occupational data; Ref=reference range

1.4 Interpretation of Human Biomonitoring Data

Assessment of human exposure to environmental chemicals forms an integral part of the risk assessment process. Traditionally, exposure is measured, and an applied dose for a given cohort estimated. The applied dose is subsequently evaluated against established criteria such as; reference doses (RfDs) or concentrations (RfCs), minimal risk levels (MRLs), tolerable daily intakes (TDIs) or a Unit Cancer Risk (UCR). There are however, some uncertainties involved with estimating environmental exposures, which often leads to overestimation of actual exposures (Gosselin, 2006; Ewers, 1996 & 2004). Advances in analytical measurements have allowed the detection and quantitation of hundreds of chemicals and their metabolites in biological samples of individuals at increasingly lower levels. However, the ability to interpret these measurements in the context of biological effect has not developed alongside the analytical technologies. As the results from a number of biomonitoring initiatives (described previously) become widely available, there is an increasing need to be able to interpret the results in terms of a public health risk. Such interpretation is

essential to achieve efficient communication of any health concern to exposed individuals or populations. In addition, it will also impact on decisions regarding risk management and enable prioritisation of resources (Meek, 2008).

In an attempt to address the key issues that affect interpretation of HBM studies, The European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) published "Guidance for the Interpretation of Biomonitoring Data (ECETOC, 2005). The document details several considerations that need to be applied to any biomonitoring data prior to its use for evaluation of health risks (Figure 2);

- sample analytical integrity;
- account of toxicokinetics;
- relevance of data for health effects;
- how data align with other available information
- supporting evidence from epidemiology studies

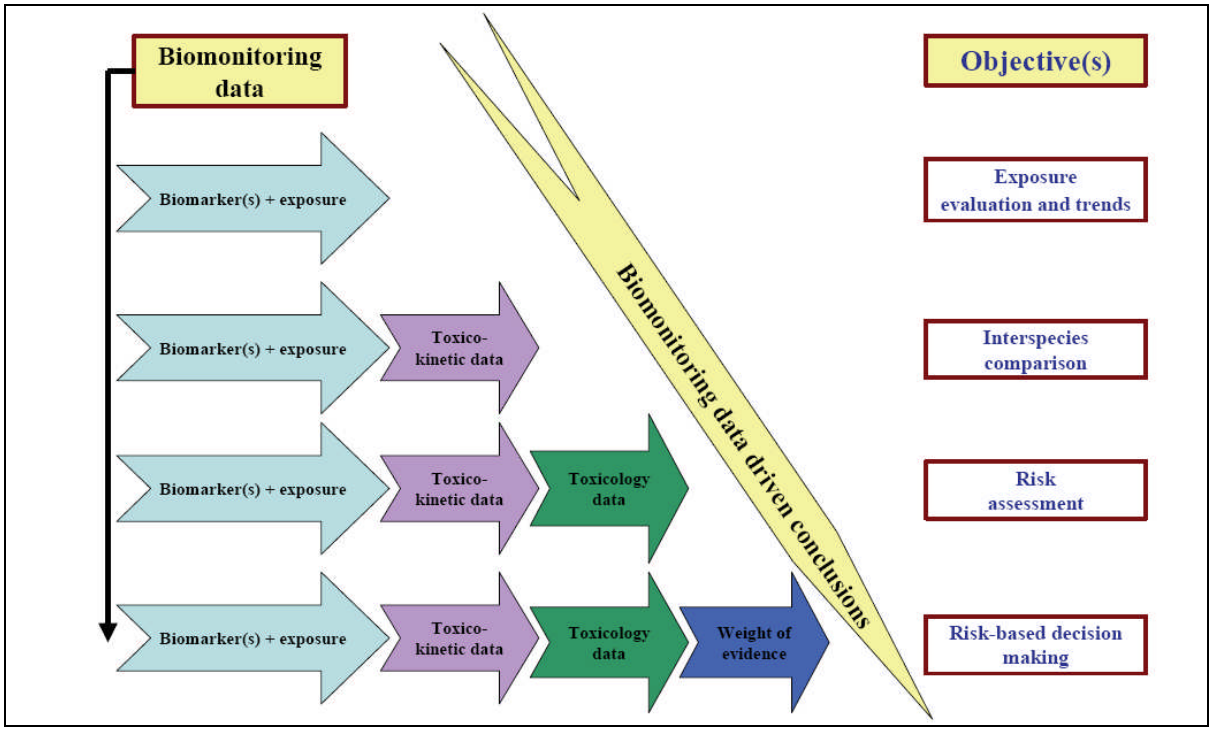

Figure 2: Evaluation of health risks using biomonitoring data (ECETOC, 2005. Permission for reproduction of figure received from ECETOC, however it should be noted that this does not constitute endorsement of this report by ECETOC).

1.5 Current Challenges and Future Direction of HBM

At present, biomonitoring provides valuable information on exposure of the general population to a wide variety of environmental chemicals. HBM has the advantage of measuring total internal dose resulting from the uptake of a chemical following exposure from different sources and uptake from different routes. Repeated measurements over a period of time can be used to reflect trends in exposure and assess success of risk management procedures. However, there are also several scientific and technical limitations that remain to be addressed (Borgert, 2005).

HBM data provides only a 'snap-shot' of levels of chemicals in the body at a given point in time and does not provide information on the source, magnitude, frequency and duration of exposure. Indeed, the CDC are careful to point out that "*the measurement of an environmental chemical in a persons blood or urine does not by itself mean that the chemical causes disease*". In order to interpret BM data in a health risk context, guidelines on 'safe biomarker levels' need to be derived, perhaps employing PBPK modelling in combination with 'no-effect' or minimal risk toxicity benchmarks. Biomonitoring surveys can be expensive, with large cohort studies currently underway in many countries. However, alternative approaches using Postal Survey techniques have been successfully employed (Levy *et al*., 2007). Albertini et al (2006) identified several areas of improvements that are needed to reduce the uncertainty associated with interpretation of biomonitoring data. Suggestions include, improving the understanding of predictive relationship between measures of exposure, dose and effect; added emphasis on the validation and precision of biomarker measurements; characterisation of a baseline for biomarkers; improvement in the understanding of the origin of biomarkers and their relationship to disease; assess inter and intra-individual variability; identification of new candidate biomarkers. HESI also suggest several challenges for the future for biomonitoring, including, assessment of natural chemicals e.g. phytoestrogens and glycoalkoids; looking at aggregate exposures; use of biomarkers to inform cumulative risk assessment; addressing public misunderstanding about relationship between presence of chemical and occurrence of human health effects (Angerer *et al*., 2006). Effective communication of biomonitoring results has also recently been highlighted, with recommendation that it should be included as a strategy during project planning, developing as the study continues (Sepai, 2008).

The integration of health and exposure data is the definitive tool in public health. The ultimate goal of any biomonitoring programme must be to collect human health, environmental exposure and biomonitoring data in a fully integrated system. The utility of HBM for public health protection is determined by the ability to interpret the data produced against set criteria; therefore the aim for the future of biomonitoring is to develop a framework for this purpose building on current scientific

knowledge and best practice across Europe and the US. An accepted framework is urgently needed to help scientists, regulators, and stakeholders to design appropriate HBM studies, interpret HBM data (both for groups and individuals) and to take appropriate action. This appropriate action will include the usual range of risk management options, including risk communication to the public. (Sepai, 2008).

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2.0 Aims and objectives

Human biomonitoring (HBM) is a useful tool to aid the assessment of exposure to many chemical substances but currently our ability to detect hazardous substances (or their metabolites and effects) may often exceed our understanding of the biological relevance of these results. As detailed in Section 1 of this report there are a number of well-established frameworks for developing and using biological guidance values (BGVs) in the occupational health field but these are for a limited number (<100) of data-rich substances that have been in use for some time. BGVs for new substances, and those with undefined dose-response relationships, are difficult to derive and the problems are compounded at environmental levels that are far below doses used in toxicity studies or those encountered in the occupational setting.

There have been a number of published reviews of how to use and interpret human biomonitoring data (ECETOC, 2005; IPCS, 2001) as well as several published arguments on setting BGVs (Hays *et al*, 2007; Albertini *et al*, 2006). As stated earlier, the principle objective of any biomonitoring programme is the collation of data relevant to human health and environmental exposure in a fully integrated system that facilitates interpretation of the data produced against set criteria

The primary objective of the project reported here was to develop a practical and scientifically-defensible framework for establishing different types of environmental monitoring BGVs for a wide range of anthropogenic and naturally-occurring environmental contaminants. The framework also aimed to address suggested uses of BGVs and their implications for public health.

In order to achieve these aims, it was considered essential that the framework defined minimum data requirements for the derivation of BGVs and reflected the reliability and confidence that could be placed upon derived BGVs which is dependent on the information available. It was also considered important that the developed framework is broadly acceptable and useful to all stakeholders and, just as importantly, would define guidelines where the setting of such guideline values is uninformative or even misleading.

The specific objectives of the project were:

- to investigate the feasibility of proposing different types or approaches to BGVs based on distribution of exposure in the population, hazard and risk; this would be achieved by addressing biological monitoring (BM), as well as biochemical effect monitoring (BEM) *where possible*.

- to investigate the utility of BGVs expressed as ranges and probabilities as well as single values
- to develop a set of criteria for establishing when and how to derive environmental BGVs
- to develop a framework, using the established criteria, for the interpretation of HBM data and define types of environmental BGVs depending on their application. The study also aimed to explore the various ways in which types of BGVs can be defined, and the way they may influence public health choices
- to explore how REACH data might be used to aid BGVs. It has been proposed (Appendix V to draft REACH Implementation Project-RIP 3.2) that biomarker Derived No Effect Levels (DNELs) could be established from biomonitoring data using the same methodologies being used for derivation of health-based biological limit values. In principle, there are two situations where establishing a biomarker DNEL may be preferable.

    1. a clear dose-response correlation exists between biomarker levels and the effect(s) in humans or in animals

    2. a clear relationship exists between an external exposure metric, which is linked to the effect(s), and the biomarker in the same species

    In addition, REACH increases the need for exposure assessments and also the need to verify that the controls proposed under REACH actually work. BM data could aid exposure assessment or be used as a feedback loop. In the future it might be asked for as part of the package. In the short-term, data generated for REACH may simply aid the development of BM methods and sampling strategies and possibly aid in the development of BGVs

- to explore the feasibility of different BGVs for different sub-groups of the population
- to test the proposed framework using example compounds or classes of chemicals
- to ‘peer-review’ the proposed framework using an advisory group of experts
- present the framework to key stakeholders in a workshop
- to include in the framework, a glossary of internationally-accepted terms and words used in biomonitoring to avoid misunderstanding and confusion
- publish findings and proposed framework in peer-reviewed scientific literature and present at an appropriate scientific conference.

3.0 Methods

The project was divided into 5 work packages, as detailed below. Overall project management was undertaken by IEH with project partners involved with developing different aspects of the framework, according to their expertise, and with testing the framework.

Workpackage 1: Development of framework criteria

- project start up meeting
- literature searches on existing guidance values and procedures
- review of literature and draft working paper

Workpackage 2: Development of framework

- draft framework based on outcomes of WP1
- consult advisory group on draft framework and revise as needed

Workpackage 3: Testing of framework

- prioritise substances to use to test compounds in conjunction with Cefic
- test framework using model compounds

Workpackage 4: Workshop

- organise workshop
- present framework at workshop

Workpackage 5: Reporting and publications

- re-draft paper according to outcomes of workshop
- produce final draft of framework
- issue final report and peer review paper

Project advisory group

It was considered essential that, in order to gain the widest academic and regulatory acceptance, the study should included the support and advice of an expert advisory group. Details of the project advisory group involved with this study are shown in Table 4.

Table 4: Project advisory group members

Name	Organisation	Country	Specialism
Dr Sean Hays	Summit Toxicology	US	BEs
Dr Larry Needham	National Centre for Environmental Health	US	Biomonitoring
Ms Bette Meek	Health Canada / University of Ottawa	Canada	Chemical Risk Assessment
Dr Marek Jacubowski	Nofer Institute of Occupational Medicine Poland	Poland	Biomarkers
Dr Silvia Fustinoni	University of Milan	Italy	Biomonitoring
Dr George Loizou	HSL	UK	PBPK Monitoring
Dr Peter Farmer	University of Leicester	UK	Biomonitoring / adducts
Dr Ludwine Casteleyn	Environment and Health	Belgium	Human biomonitoring
Prof Conrad Brunk	University of Victoria	Canada	Risk Assessment and Communication
Dr Daniel Goldstein	Monsanto	US	Toxicology
Dr Herman Autrup	University of Aarhus	Denmark	Epidemiologist
Dr Peter Boogaard	Shell International	Netherlands	Technical aspects of biomonitoring
Dr Lesa Aylward	Summit Toxicology	US	BEs / interpretation

Input was sought from advisory group members following the initial drafting of criteria and framework structure as described in WP1 and WP2. The initial draft of criteria that was sent for comment included consideration of:

- How to select the appropriate biomarkers
- How to define the type of BGV - exposure related or health-based or risk-based
- How and when to derive BGVs based:
    - Occupational data
    - Environmental human biomonitoring data
    - Guidance values based on animal toxicology data (use of hazard/ dose responses, pharmacokinetics, bench mark doses, uncertainty factors)

  - ADIs
  - Guidance values based on epidemiological data
- Criteria for a minimum/optimal set of BGVs
- Strategy towards obtaining these BGVs for data poor and data rich compounds
- Dealing with sensitive groups
- Prioritising compounds for derivation of BGVs

The initial draft of framework structure that was sent for comment is shown in Figure 3.

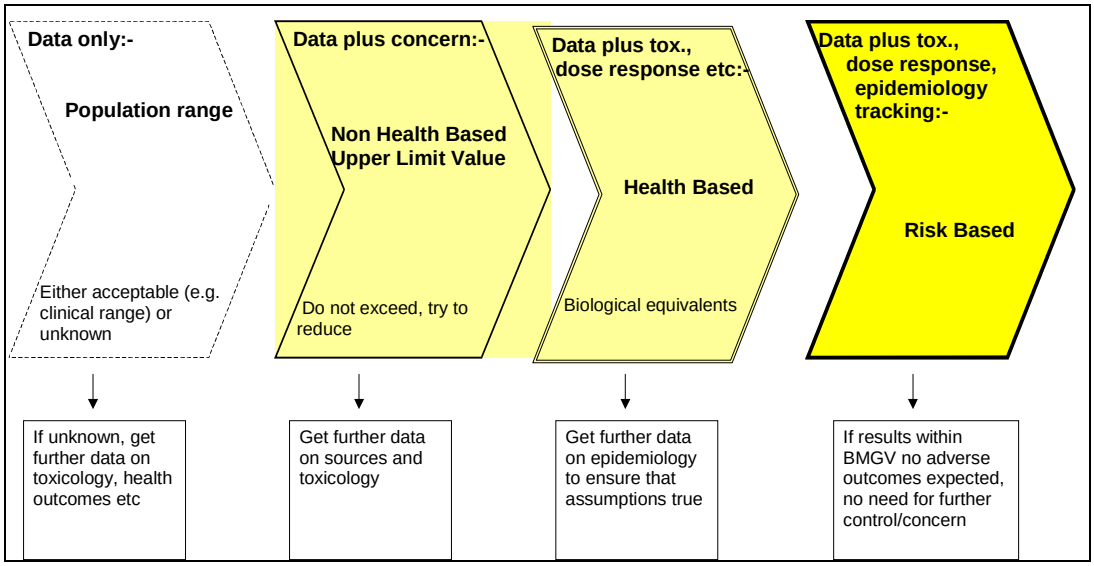

Figure 3: Initial draft t of framework structure

Input from advisory board members was also sought during a 2-day workshop. Comments from members on the draft protocol, scope and framework of the study were used to produce the finalised proposed framework structure, as detailed in Section 5.

4.0 Workshop Summary

Introduction

Following review of the framework structure in accordance with comments received from the expert advisory panel, a number of modifications and clarifications were made to the frame work structure. Based on this revised BGV framework, documents were prepared for 12 agreed model chemical compounds (detailed in full in Annex 3).

The revised framework as a whole, and applicability and discussion of the 12 worked examples in particular, formed the basis of a 2-day workshop held at Woburn, UK on 17th – 18th June 2009. The workshop was attended by experts from the project advisory board and other invited expert participants (full list of all participants in Annex 1).

Day 1 - 17th June 2009

Workshop Introduction:

Professor Len Levy (LL) introduced the aims of the project and associated workshop, which he outlined as; to investigate the feasibility of proposing different types or approaches to BGVs based on distribution of exposure in the population, hazard and risk; to present the framework to key stakeholders; to demonstrate utility of the framework through a number of worked examples.

Session 1: Project from the perspective of CEFIC-LRI

Dr Peter Boogaard, Shell Health

The 'framework project' was described in context of the overall Cefic-LRI programme as a whole in this talk by Peter Boogaard (PB). The Cefic-LRI programme was initiated by chemical industries in the EU, Japan and USA following the publication of white papers on 'State of the Science – Human Biomonitoring' in 1998. As part of the phase 2 programme, three projects were commissioned by Cefic-LRI in 2004 to look at background levels of biomarkers and establish inter- and intra-individual variation of these. Following this, in phase 3 a call for projects to interpret biomonitoring guidance values was issued, of which the 'framework project' was one of four commissioned. PB concluded that the main challenges for the future were to further develop concepts of BGVs established to date, to obtain a global perspective of this approach and to seek acceptance of the findings and create links with computational methods.

Session 1 Discussion

It was acknowledged by the Workshop participants that the Cefic-LRI initiative was a comprehensive programme that had maintained close contact with both scientific and regulatory communities. As a

whole, the projects had been successful and had resulted in multiple publications, tools for risk-based management of exposure to environmental chemicals and tools for registrants to comply with the EU REACH regulations.

Session 2: Introduction to Biomonitoring Values

Dr Sean Hays, Summitt Toxicology

In a continuation of the background information of the project, Sean Hays (SH) presented an overview of available methods of interpreting biomonitoring data. Currently, biomonitoring investigations are used to survey the general population, including development of reference ranges, or to study targeted populations to identify susceptible or highly exposed populations. SH stressed the importance of defining the end-user of the BGV, as the communication of the overall message may change depending on the audience.

The majority of environmental BGVs have previously been based on hazard, where 'detection+hazard=risk'. However, the limitations of this approach are that it is governed by detection limits and knowledge of dose response relationships. It penalises chemicals for which there is a lot of data; under this approach 'new chemicals' with limited amounts of data will not be adequately considered. SH considered that this method of interpretation was equivalent to Levels 1 and 2 of the proposed framework.

SH continued with a description of quantitative approaches used for the interpretation of biomonitoring studies, which include the use of reference ranges (Levels 1 and 2), risk assessments (Level 3) and epidemiology studies (Level 4). Although reference ranges (e.g. NHANES and German reference values) are relatively easy to establish, they do not provide information regarding health risk and they need to be continually updated as circumstances change. Although epidemiology studies may provide more robust information regarding health risk, they require a lot of data and are usually occupational-based studies and therefore reflective of a highly exposed and thus a relatively narrow section of the total population.

In the interpretation of biomonitoring data, it is natural to look for potential relationships between biomarkers and health endpoints. However, SH stressed that it was important to bear in mind that some health conditions may influence biomarker concentration and therefore for a relationship to be causal, the risk factor under consideration must precede the onset of disease. In addition, many other factors may contribute to the health endpoint of interest, which may not be included in the biomonitoring data collection.

One aspect of the Hill Criteria (often used as a guideline to explore causality between exposures and ill-health) is used to explain the concept of temporality, which states that 'exposure must precede the

onset of disease in time'. One weakness of cross-sectional studies/surveys such as NHANES is that exposure and disease are measured at the same time, making it very difficult to establish cause and effect. In addition, chemical concentrations in biological matrices can be highly transient, therefore making any one measurement representative of a 'snap-shot' in time only. SH also described how existing risk assessments can be utilised to interpret biomonitoring data in a public health context. However, this approach also has certain disadvantages, including a reliance on *in vivo* animal study data and use of default approaches to extrapolate data.

When deriving biomonitoring values, four factors need to be taken into account, namely, *derivation, confidence assessment, interpretation* and *communication*. Derivation should consider the use of animal versus human PK data, choice of biomarker to reflect the mode of action and dose metrics, with a half life >12 hours being preferable. Evaluation of confidence is needed as not all BGVs will attain the same level of confidence. Communication of biomonitoring data will also vary depending on whether it is seen as being 'personal' e.g. blood levels usually cause greater level of concern than levels in air. The communication message will need to differ between audiences and depending on whether a public health or diagnostic message is being put forward.

SH concluded his presentation with an explanation of Biomonitoring Equivalents, an approach developed to allow derivation of guidance values that capture most of the issues described previously. SH and colleagues have concurrently developed models for confidence, interpretation and communication which impact on derivation guidelines and vice versa. SH stressed that BEs are not a diagnostic criteria for interpreting biomonitoring data from individuals; they allow interpretation which focuses on "low" to "high" priority for risk assessment follow-up.

In summarising, SH put forward some points for consideration as follows:

- BGV categories: keep them simple and understandable
- judgments in derivation will always be questioned
- guidelines: flexibility but also able to achieve consistency
- confidence, interpretation and communication are what most people will be interested in

Session 2 Discussion

Bette Meek (BM) commented on the use of uncertainty and variability factors in risk assessment, stating that although a Mode of Action (MoA) approach had been favoured in the past for risk assessment, for some chemicals, such as benzene, the MoA appears not to correlate with exposure. With this in mind, is it better to look for a biomarker that correlates with exposure or biological effect? SH replied that he considered that there was a need to move away from a focus on biomarkers

of exposure to markers that can be interpreted in risk assessment. Conrad Brunk (CB) added that the application of uncertainty factors is an internal communication issue within the scientific community and stressed that this area needs clarification prior to any communication with the public. Any audience in receipt of biomonitoring data will wish to know whether it offers diagnostic or public health assurance, i.e. people will focus on issues such as 'am I getting sick' and 'is the population getting sick'.

SH explained that the BE model incorporated two confidence scores and utilised a decision tree to derive values, which are dependent on whether a combination of human and animal data or human or animal data in isolation are used. The BE model also contains a communication model. However, SH stressed that BEs are not diagnostic for an individual as there is no clear line of effect; the model is used as a risk prioritisation screening tool to show which chemicals are of greatest concern.

With reference to the model BGV framework, SH commented that it should be kept as simple as possible, especially with regards to interpretation and communication as all judgements made using the framework were likely to be challenged. SH suggested further discussion regarding use of the word 'concern' in Level 2 of the first draft framework, at a later stage in the workshop.

Session 3 Presentation of Framework

On behalf of the project team, John Cocker (JC) outlined the aims and objectives behind the development of the framework for proposed HBM guidance values. JC described how the proposed framework was developed to recognise the utility and limits of HBM data; this was achieved by recognising existing BGVs and their context; aiding the interpretation of BGVs; promoting the development of new BGVs; prioritising substances requiring more data; aiding an understanding of HBM.

The proposed framework allows for consideration of the type and quality of available HBM and toxicology data which determines the type of BGV, its relevance (or otherwise) to health and the action to be taken if it is exceeded. A tiered approach of four levels was considered to be most appropriate, with categorization governed by the type and quantity of data available for a chemical. JC described in detail the criteria for each level of the framework, with the appropriate suggested action to be taken for compiling additional data.

The workshop continued with examples of substances that fit the criteria for the different levels in the framework.

Samarium

Kate Jones (KJ) presented the first of the model compounds, samarium, used to illustrate the utility and limitations of a framework Level 1substance. Samarium belongs to the Rare Earths (REs) and has several industrial and medical uses including being used in carbon arc lighting, in permanent magnets and as chelates in bone cancer therapy. The element is found in mineral and does not exist in a free form and most sources of environmental exposure are probably restricted to emissions from manufacturing and mining activities; little is known about environmental levels of exposure at present. Data on the toxicity of samarium is very limited (HSL study on 8 samples) and there is no published biological monitoring data from either occupational or environmental exposure. Read-across from data relating to similar REs suggest that samarium will have low acute toxicity and the use of samarium chelates in cancer therapy suggest little immediate health concern following environmental exposure. Occupational exposure to samarium may result in inhalation of dusts with unknown consequences, but with possible pneumoconiosis.

KJ concluded by proposing that within the proposed framework, samarium was a Level 1 compound and that further work is needed to identify a reference range and to determine toxicokinetics.

Discussion

Alistair Hay (AH) enquired whether there is currently any health surveillance on workers using samarium and KJ responded that there is not. Joe Lunec (JL) asked how many of the 8 samples measured by HSL were below the level of detection and KJ replied that 6 of the 8 samples taken had detectable levels. LL asked what would be needed to trigger further action for samarium, and if a compound is in Level 1, is there always a requirement for it to move up levels? CB commented that it is usually a political push triggered by public concern that gets chemicals onto the public health agenda, rather than a scientific push. BM stated that it is extremely difficult to systemise political factors and the potential for exposure should be one of the most important factors however, much care needs to be taken when communicating that a hazard is unknown as this in itself is likely to raise concern.

It was agreed by participants that samarium was representative of a Level 1 compound.

Toluene Di- isocyanate

Ovnair Sepai (OS) presented the second of the model compounds, toluene Di- isocyanate (TDI), used to illustrate the utility of the framework at Level 2. Sources of exposure to TDI include products such as plastics, foams, spray paints, glue, DIY products and varnishes; greater than 95% of TDI used is comprised of a mixture of 80:20 2,4 and 2,6 TDI. Some toxicological data is available for TDI and commercial grade TDI is carcinogenic in rats and mice and has been classified as an IARC Group 2B

carcinogen, a respiratory irritant and sensitizer in the EU and elsewhere. Main routes of exposure are dermal and inhalation and TDI has been shown to be absorbed rapidly within the respiratory tract. Following exposure, health effects have been reported to include acute respiratory irritation, occupational asthma, reduced lung function and chronic rhinitis. Although distribution of TDI is not well understood, metabolism occurs through rapid hydrolysis to amine and conjugated acetylated derivatives, or conjugation to proteins, these conjugates are then excreted into urine. Experimentally, excretion into urine has been shown to be biphasic, with the first phase between 1.6 – 1.9 h and the second phase at 5h; half-life in plasma is longer at 10 days which is probably due to formation of plasma adducts. In chronically exposed workers, half lives in urine of 5.8 – 11 days and in plasma of 21 days have been shown. Validated biomarkers of exposure to TDI and analytical capability for measurement are available and exposure limits have been set by US EPA, Sweden and HSE (UK). Control based guidance values have been adopted by HSE and the German Research Foundation (GSF). Although a dose-biomarker relationship has been shown, the dose-response relationship is debatable. Epidemiology studies are in the main occupationally related, with very few environmental studies. OS concluded that within the proposed framework, TDI was a Level 2 compound.

Discussion

Marek Jacobowski (MJ) asked, that for chemicals that are mainly local irritants, whether it was necessary to also set BGVs for other effects. OS replied that the main health effects for TDI were respiratory-related and any exposure limits that have been set will relate to these, and not skin effects. PB commented that most people regard TDI to be a sensitizer for effects on respiratory airways, and that a threshold for sensitization would be logical for this chemical. JC added that public concern regarding TDI was over the development of asthma at high levels of exposure, however as a cause-effect relationship could not be established at present, TDI needed to be classified as a Level 2 compound in the proposed framework. SH re-emphasised that he considered that communication would be an issue with compounds stated as being ‘of concern’ but for which more information was not available. Greet Schoeters (GS) commented that transparency in what is and isn’t known about a chemical is very important. SH pointed out that as you move from Level 3 to Level 4 of the framework, uncertainty is decreased as confidence increases; however he was unsure what differentiated a Level 1 and Level 2 compound. In response JC replied that for a Level 2 compound, there was greater knowledge; e.g. you may have population ranges as for chromium III. SH replied that the change through the levels was not linear and it was possible to have population data for a Level 1 compound, but with a large degree of uncertainty.

Acrylamide

Juergen Angerer (JA) presented the third of the model compounds, acrylamide (AA), used to illustrate the utility of the framework at Level 3. Exposure to AA results from occupational exposure through

use in water treatment, paper industry and building industry and from environmental exposures, such as generation during cooking. WHO has estimated AA content of foods such as fries, crisps and coffee to be between 30-3500 µg/kg; tobacco smoke is also an important source and breast milk and placental transfer has been demonstrated. Critical toxicity effects include neurotoxicity and carcinogenicity. A NOAEL of 500 -1000 µg/kg bw has been established for humans for neurotoxicity by WHO. AA has been linked in human epidemiological studies to mammary cancer, renal cancer and endometrial cancer; although a mode of action is unclear (but thought to be genotoxic). In animals, effects on CNS, thyroid, tunica vaginalis, testis, scrotum, oral cavity and mammary have been shown and IARC has classified AA as a Group 2A carcinogen. A BMDL of 300 mg/kg bw has also been proposed by JECFA. AA has established and validated biomarkers for both long-term, haemoglobin adducts (AAVal, GAVal lifetime 120 days) and short term, mercapturic acids (AAMA, GAMA $t_{1/2}$ = 14-26 h) exposure. Haemoglobin adducts, and in particular AAVal, have been used to establish population ranges (n=5-857). For carcinogenicity, a RISK based BGV of 0.022 µg/kg d=0.15 µg AAVal/l (1/10000 lifetime risk) has been established by the USEPA and a POPULATION based BGV of 0.87 µg/kg d =0.6µgAAVal/l (average population) by the UBA. For neurotoxicity, a NOAEL of 14.6 µg AAVal/l has been proposed. Ratios of the mercapturic acids, AAMA and GAMA have also been used to establish ranges in children and adults, with higher ratios determined in children. JA concluded by proposing that within the proposed framework, AA was a Level 3 compound.

Discussion

MJ commented that the value established for carcinogenic risk for the general population was very high. JA replied that although the value was based on animal experiments, similar levels of adducts in rats and humans had been reported to those established in his own studies. Dan Goldstein (DG) agreed with the classification of AA as a Level 3 compound within the framework, however he emphasised that communication is again a key issue here as AA is present within the food chain. Much conflicting advice has been given regarding intake of AA in the diet, and it is possible that the overall health gain from changing diet is still largely unknown. PB added that from the aspect of risk communication, AA was very interesting as epidemiology evidence from occupational exposures has shown no increased risk associated with high level of exposure. SH commented that for AA there was a good data set relating to neurotoxicity, which could qualify it as a Level 4 compound within the framework. However, he qualified this statement by proposing that the effects seen may have been species related and may not be repeated in humans. LL pointed out that Level 3 of the framework recommends collation of epidemiology data to validate the assumptions made, and therefore he considered that AA was categorised correctly as Level 3.

Cadmium

Roel Smolders (RS) presented the fourth of the model compounds, cadmium (Cd), used to illustrate the utility of the framework at Level 4. Cd is a by-product of zinc-, copper-, and lead-production, and is used predominantely in batteries (83% of total uses) with much lower usages in paint pigments (8%) and coatings/platings (7%). Environmental exposure to Cd occurs through cigarette smoking, consumption of contaminated food & water, inhalation of contaminated air-dust and from natural sources. Following exposure, efficiency of absorption is defined as inhalation>>oral>>>dermal; with efficiency of uptake being dependent on particle size. Body burden of Cd increases with age, reaching maximum levels between 60-70 years; smokers have around 2x the body burden of non-smokers. The kidney is the main target organ for Cd toxicity, causing tubular dysfunction, and a number of health-based limits have been established; occupational exposure limit of 5 µg Cd/g creatinine; environmental exposure limit of 2 µg Cd/g creatinine, The EU SCTEE have stated that there may not be a 'safe' level; FAO/WHO Expert Committee recommended a PTWI of 7 µg Cd/kg bw/day which was revised by EFSA to a TWI of 2.5 µg Cd/kg bw/day. Reliable and sensitive methods have been established for the measurement of Cd in blood and urine. In blood, Cd has a half-life of 2-3 months, with levels in non-smokers of < 1 µg Cd/l and in smokers of < 5 µg Cd/l, whereas inn urine, Cd has a half-life of 10-30 years, with elimination of around 0.005-0.01% body burden/day, A PBPK model has also been established for Cd by Nordberg-Kjellström. HBM Reference, HBM-I & HBM-II values. HBM data has been collected for Cd based on GerES-III (children & adults) and GerES-IV (children) and reference values for blood and urine in adults (non-smoking) and children established; Biomonitoring Equivalents have also been established. Several large-scale epidemiological studies have been carried out to establish effects on all-cause mortality; cancer; hypertension and endocrine disruption. Cd has been classified by IARC as Group 1 (*carcinogenic to humans*); USEPA as Group B1 (*a probable human carcinogen by inhalation*) and German DFG as a Carcinogen category 1. A number of risk management options have been recommended by ATSDR, including; not smoking tobacco products, good occupational hygiene, avoiding cadmium-contaminated areas and food, proper disposal of cadmium-containing products and careful handling of cadmium-containing products. RS summarised by proposing that within the proposed framework, Cd was a Level 4 compound.

Discussion

MJ commented that efficiency of the risk management options could effectively be assessed by human biomonitoring. LL asked whether the risk management options would protect from cancer and GS replied that environmental exposure to Cd has only been associated with lung cancer in one study. PB added that the route of exposure may be one of the most important factors for health effect of Cd and that cancer risk may in fact be negligible because environmental exposure to Cd is predominantly through food rather than occupational. AH asked what the oral exposure data in animals shows and PB responded that in rat studies, animals die from renal failure before they develop cancer. BM stated

that the route specificity for certain health effects would need to be clearly explained in any communication regarding Cd.

Session 4

Day 1 Summary Discussion

Chair: Dan Goldstein

Conrad Brunk (CB) opened the general discussion session by asking how far you can outline risk on an individual basis. The four level approach of the proposed framework reduces uncertainty at each level but, we still cannot use HBM data to do individual risk assessment, even for Level 4 substance. Should we therefore accept that individualised risk assessments are never appropriate, even though that is the theoretical endpoint of the framework. LL responded that you could associate particular groups with increased risk in the same way as we do now for people with, for example, high blood pressure. DG also added that there is an increasing importance around epidemiology data and its incorporation into risk assessment, but what do we actually do with the data? SH responded that in the 'pyramid' of approaches to interpret HBM data, epidemiology is the top of the pyramid and in the proposed framework, it is the recommendation given at Level 3 to confirm that any assumptions that have been taken regarding health effects are correct. However, in reality a general epidemiology study is likely to be carried out which will turn up many associations, and not specifically the health endpoint associated with the BGV of interest. It was also highlighted that the categorisation used in the proposed framework implies a hierarchy, with epidemiological data being the most important part of the risk assessment. Sending this framework out without endorsing epidemiology data as the 'gold standard' may be difficult to achieve. SH also acknowledged that although many bad epidemiological studies have been reported, a robust well-performed study is very powerful. LL asked whether the wording associated with the action from Level 3 should be changed to 'gather reliable human data', however it was considered that epidemiology has a specific and appropriate context in the framework. RS pointed out that epidemiological data is not meant to stand alone but must be supported by other types of data and must not usurp that data. MJ argued that epidemiological studies are very expensive and that monitoring of biomarkers should be equivalent to the best risk assessment practices. JL observed that the difference between Levels 3 and 4 of the proposed framework was one of quality of data and certainty of human health effects.

Day 2 : 18th June 2009

Session 1: 'Pet Compounds' and the framework

Several participants were asked to prepare a short presentation outlining how a compound of their own interest/choice worked with the proposed framework.

Tetrachloroethylene ("Perc")

Bette Meek (BM) presented a framework for the data rich substance tetrachloroethylene (Perc). Perc is a volatile solvent that is widely used in dry-cleaning, textile processing and metal cleaning. Exposure of the general population occurs principally in air (point sources), and through consumption of contaminated drinking water and breast milk. The metabolism of Perc has been elucidated and is complex; the predominant pathway occurs through oxidation and results in a range of metabolites that are conjugated with GSH prior to excretion. The critical non-cancer health endpoint is neurotoxicity and a reference concentration has been established for this effect. Experimentally, Perc has also been associated with development of liver tumours in mice, and mononuclear cell leukemias and kidney tumours in rats, although potency is considered to be low. Data from the NHANES study has been used to establish levels of Perc in blood of the general population and exposed subgroups (numbers < 50 to > 1000) including children in homes co-located with dry cleaning facilities. BM summarised by concluding that within the proposed framework, Perc was a Level 3 compound. In terms of the proposed framework itself, BM commented that it is useful pragmatic tool but clear guidelines are needed as to how to move between the four levels – even with these, it will still involve professional judgement and consideration of patterns across similar compounds (read-across) for data poor substances.

Discussion

CB raised a question regarding variability and uncertainty, asking whether both were down to a lack of data which, in principle, could be filled. BM replied that there was a need to collect all multimedia data possible; i.e. reference/dose/concentration and to compare it with biomonitoring data.

Methyl *tert*-butylether (MTBE)

Silvia Fustinoni (SF) presented a framework for methyl *tert*-butylether (MTBE). MTBE is a water soluble volatile compound which is used in the EU in fuel at up to 15% for octane improvement and to decrease CO emissions. However, in the US, its use has been phased out in several states following its inclusion in the Clean Act (1990). MTBE is a ubiquitous pollutant with environmental exposure through ggasoline evaporation (refueling and car tank), exhaust emissions from vehicles, consumption of water contaminated with MTBE. The estimated daily intake following environmental exposure is 0.4-6 µg/Kg/day from air and 1.4 µg/Kg/day from water. Occupational exposure results during ggasoline production (petrochemical workers), transportation and distribution (station attendants) with an estimated daily intake of 1-1000 µg/Kg/day from air. The toxicokinetics of MTBE are well defined. MTBE is rapidly absorbed into the circulation following inhalation exposure and is wwidely distributed in the body, with levels in fat being 7-10 fold higher than in blood. Metabolism occurs by oxidation via P450 enzymes and metabolites are eliminated in exhaled air (50% of inhaled dose) and in urine (40% as metabolites). Toxic effects include reversible central nervous system (CNS) effects

(sedation, hypoactivity, ataxia and anesthesia) and mild skin and eye irritation, but not sensitization. Epidemiological studies of human populations exposed under occupational as well as non-occupational conditions and experimental studies of human volunteers exposed under controlled conditions have not been able to identify a basis for health-complaints. No adverse reproductive or developmental effects in rodents at concentrations less than those that were toxic to the parent have been reported. MTBE is not genotoxic but has induced tumors in rodents primarily at high concentrations, and IARC has denoted a Group 3 classification i.e. *not classifiable as to its carcinogenicity to humans*. MRLS for inhalation and oral routes have been established by ASTDR. Several biomarkers have been identified for MTBE, with measurements of MTBE in blood and breath being most reliable. Although occupational limit values have been established, there is little data on environmental exposure levels. SF summarised by concluding that within the proposed framework, MTBE was on the whole a Level 2 compound, however some elements of knowledge were Level 3.

Discussion

PB informed participants that MTBE has a horrible taste and that the slightest spill can make water undrinkable. SH commented that on a positive note, MTBE was good at dissolving kidney stones! AH asked whether MTBE had been measured in saliva as this is an easier medium to work with than blood. SF replied that they had not tried this in their laboratories as the method they had developed using urine had proved sufficient, however SF added that in the US, measurement of MTBE in blood was favoured as this medium was considered to be closer to the mode of action of the compound. SH commented that it was not always possible to ensure that urine samples were collected in a way that would prevent VOC evaporation and that blood collection offered greater control over this. JC responded that in the UK the aim was always to collect samples in as non-invasive a way where possible; he added that he agreed with Silvia's placement of MTBE within the proposed framework. CB commented that it would be useful to consider what the communication message would be within the framework, and what follows from that.

Session 2: Communication Issues

Chair: Ludwine Casteleyn

Conrad Brunk - Communication Issues Arising with Biomonitoring Values

Communication of science, especially risk science, is fraught with well-known difficulties including a lack of scientific literacy in the lay public, and the different ways in which experts and non-experts perceive risk and safety. The communication of new sciences can be even more difficult and has a greater potential for engendering fears and inappropriate behaviour on the part of health officials and members of the public. Therefore, the first Principle of Communication is 'know your audience' as different audiences hear the same information differently. The "personal" nature of biomonitoring

data vs. environmental exposure data increases the demand for interpretation and explanation; however, high levels of uncertainty/ambiguity inherent in the interpretation of biomonitoring data make it difficult to answer these 'personal' questions.

There are, in general, three types of audience, scientists, users of the data and the lay public and challenges exist for each type. With a scientific audience challenges include, how should concepts and methods be characterised, how should different "Uncertainty Factors" be weighed and expressed and what conclusions (Risk Assessment, Risk Management, Diagnostic, Therapeutic, etc.) are properly drawn from HBM data. With an audience of public health officials (users) the primary interest is in augmenting Risk Assessment and Risk Management tools which may lead to over-interpretation of HBM data; this audience is also likely to be concerned that HBM information will lead to unwarranted expectations or fears in the general public. The interest of Physicians/Clinicians is primarily in diagnostic and therapeutic uses of HBM information and there is a tendency not to communicate HBM data if it does not have clear implications for the patient. For an audience of the lay public, understanding the difference between expert and non-expert perceptions of risk, understanding Risk Factors and Probabilities and Understanding "Uncertainty Factors/Confidence Levels" are all key challenges. However, the common assumption that lay persons do not understand probabilities may be overstated and the correct question to ask is whether they can understand the difference between "will/will not, become ill" and "higher/lower chance of getting ill" . There are also many kinds of uncertainty at every point in the establishment of BGVs and Scientists tend to be reluctant to discuss uncertainty "in public".

Empowerment and control is a further key issue for communication. A current debate amongst professionals is whether subjects taking part in biomonitoring studies have any 'right' to their own data and when access to such data is empowering or not. Several key questions that require clarification for the lay public at present are; what are the adverse health effects associated with the chemical?; what is the meaning of the fact that my/our biomonitoring levels are below/at/above the BGV/BE?; how are people exposed to the chemical, and what can they do to control levels of exposure?; where can I get more information about this?

CB concluded the talk by identifying the clear need for research with different stakeholders. Clearly, different stakeholders, expert and non-expert in science, have different backgrounds, and personal and professional interests which strongly influence the interpretation of risk messages.

Discussion

BM commented that risk assessments improve as uncertainty is discussed and that heads of science agencies are often more nervous about uncertainty than the scientists themselves. In Health Canada, communication is 'via negativa'; they state what BGVs are not, i.e. they are not a way to determine

previous exposure and are not a reliable indicator of individual health risk. LC asked when this message should be communicated to subjects, as it may be more powerful to do so when the sample is taken rather than when the results are given. CB questioned whether an overall negative message was sufficient and that the lay public may expect a positive message as well. JC argued that as the ethics approval of biomonitoring requires informed consent then any expectations should be limited during the 'informing' part of the process, at the start of the project. LL commented that it was important to think about what people actually understood by the messages given and CB added that the plan would be to test messages on lay people before giving to subjects. BM expressed the need for trained people to provide information/results to subjects, however, SH informed participants that in US it was common for results to be posted to subjects. It was considered that if this method was employed then it should be backed up with further information available on a web-site. SF commented that in Italy, reference ranges for unexposed populations were given for comparison, but this presents problems if the subject is outside of that range. CB stressed the importance of empowerment, with a key message being to show subjects what actions they can take to lower levels, which reduces fear. RS questioned the balance of risk vs exposure management; lay people will focus on risk reduction, for which advice can be given, whereas regulators will focus on exposure management. GL suggested that there were actually two groups of lay people, those invited to take part, and those outside of a study. GL also considered that lay people would not understand aggregate exposures and that they perceived discussion between scientists as disagreement; additionally GL pointed out that cultural differences would affect the way in which people react to a given message. LL argued that the public health arena had many years experience in communicating with the lay public; however, CB commented that HBM dealt with new concepts. LC stated that it was important for BGVs to have associated guidance on how they should be applied. CB asked whether all BGVs were aimed at levels of concern as they gave information on exposure for an individual; it is not surprising that people will then want to be empowered to reduce their exposure. BM added that people will want to make their own choices and all we can say, in most cases, is that there is no concern on the basis of what is known at present; people should be made aware that BGVs are only crude indicators. LL argued that people are likely to use BGVs as dividing lines, as occupational exposure limits, such as TLVs are currently also misused and therefore it need to stress the use of BGVs as a device for further activity. DG informed participants that physicians have no training in risk assessment, they look only at disease vs non-disease state or non-healthy vs healthy; although this doesn't make them the ideal people to communicate BGVs, they are trusted. GS informed participants that in the Flemish biomonitoring programme, there are 5000 participants and all results are communicated on an individual basis. Social scientists help with communication prior to the project starting and participants can opt out of knowing. Individuals are given information on what quantile they are in within reference ranges for exposure and for effect; the explanation also includes information on sources, with more detailed information provided via a web site. In her experience, lay public generally understand better than

expected. . In the Flemish biomonitoring program, individual results and group results, as well as some information on exposure sources, possibly associated health risks and exposure reduction measures are communicated to individual participants. LC commented that for environmental levels of some compounds, e.g. benzene, there has been a trend based on acceptance of risk and this could be a possible approach to take. LL replied that this would be fine provided sufficient data is available for the compound.

Session 3 : Workshop Summary

Chair: Len Levy

LL started the Workshop summary session by stating that it had become clear from all the discussion that communication is a key element running through all aspects of HBM and it is essential to incorporate the approach to be taken at the start of any HBM programme. CB agreed with the statement and added that a critical aspect of this is the reference value, how it is defined, what it represents and the level of acceptable risk it contains, and this must be made clear. For example, tolerable daily intake (TDI) is a regulatory action point for significant level of concern for exposure, that triggers regulatory involvement/response; it is therefore a judgement of risk and acceptable risk. JC argued that being within the reference range can mean that your 'risk' is the same as everyone else, however LL responded that use of the word 'risk' implies harm. CB put forward the opinion that in the interpretation of risk communication by lay persons and NGOs, there is often an inherent overall suspicion or rejection of the risk paradigm used by the scientist and regulators. LL pointed out that the experience of GS and RS with both successful and unsuccessful communication strategies could usefully be applied to the framework. CB re-emphasised the importance of scientists and social scientists working together at the beginning of a HBM study to develop an understanding of the science and subsequent communication message involved; each study would have its own stakeholders and therefore its own unique issues. CB also proposed the involvement of NGOs at the start of a study to gain trust.

The session was concluded with participants listing particular aspects of the Workshop that they considered of particular importance:

Bette Meek

- ensure transparency of risk assessment process
- draw on chemical profiling for data-poor substances for both toxicity profile and exposure.

Holger Koch

- reference ranges are important to an individual but their main concern comes down to whether a level is critical or not.

Ludwine Castelyn

- emphasis that HBM is not a standalone tool and that clinical and exposure modelling should also taken into account.

Roel Smolders

- progression of information within the framework may lend itself to addition of sublevels i.e. 3a 3b 3c etc where level 3c would indicate a priority to obtain further information to satisfy Level 4 requirements.

Alastair Hay

- important to make sure that when HBM data is reported, there is associated explanatory text
- what happens about chemicals that won't fit into Level 1 of the proposed framework?

John Cocker

- can't solve all communication issues at the end of a study – communications should be thought of at the start.
- there is a need to manage expectations of individuals at the start of a study as part of the informed consent.

George Loizou

- media coverage of HBM information and how they may use it.

Conrad Brunk

- use of the word 'concern' in Level 2 should be clarified as may be poorly communicated

Silvia Fustinoni

- important to try to make HBM simple as physicians are not comfortable dealing with HBM value interpretation.
- can learn from occupational medicine as we know that workers can understand occupational limit values.

Peter Boogaard

- different types of compounds will have different health effects and we can't treat them all in the same way.

Dan Goldstein

- the reality is that the path forward will be driven by political situations and what general population is worried about.

Greet Schoeters

- need to use a systematic approach to measuring compounds in all environments and within people so we have a full set of data for prioritisation.
- the proposed framework is useful for us as scientists but what will we do with it?

Marek Jacubowski

- use of reference ranges is important

Ovnair Sepai

- framework could be used for communication to scientists as well as the public

Sean Hayes

- important to keep the framework simple, flexible and consistent
- communication is essential
- use of the word 'concern' in Level 2 is a problem for communication

LL closed the workshop by thanking all participants for sparing time from their busy schedules to contribute to a thoroughly productive and informative workshop.

5.0 Proposed framework structure

The finalised proposed framework structure presented below incorporates amendments from the project advisory group and workshop participants.

5.1 Background

All types of BGVs are not, and should not, be the same either in derivation or application. The type and quality of available HBM data and potential health/toxicological effects will determine the type of BGV, its relevance (or otherwise) to health and the action to be taken if it is exceeded. There are essentially four proposed classes or levels of BGV (Figure 4). Each level or class of BGV may have several variants depending on the data available and application, but for simplicity we suggest only 4 levels. The criteria defining each level are described in section 5.4. The wavy line is intended to indicate that the boundaries between levels are not clear-cut.

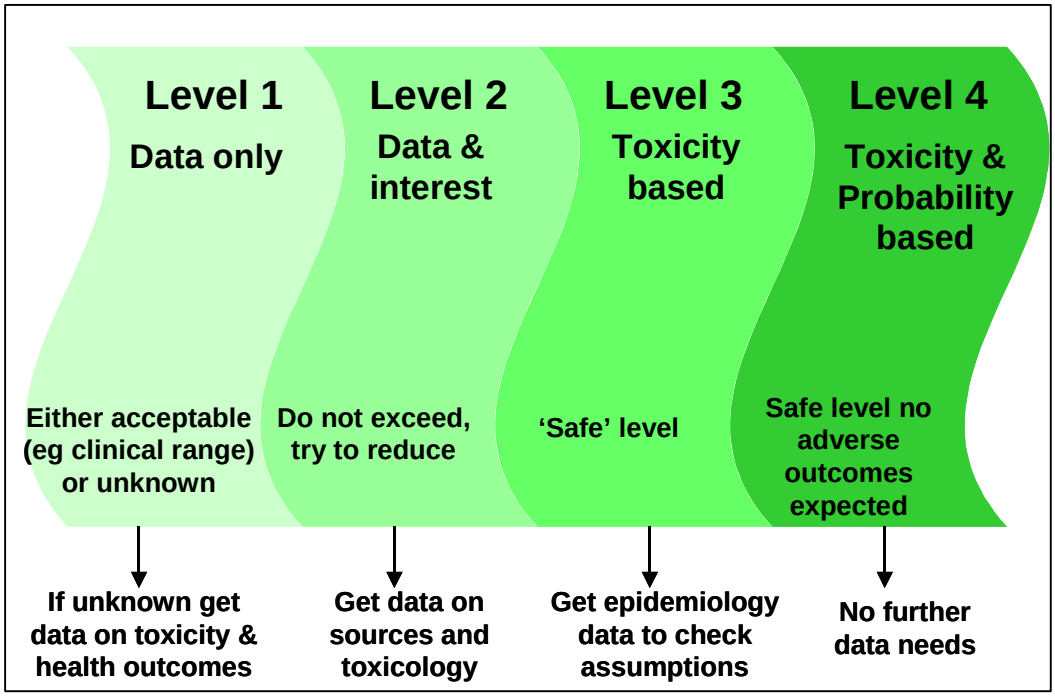

Figure 4: Classes or levels of Biomonitoring guidance values.

In the figure above, moving to the right brings an increasing confidence in a health-based guidance value, but also a need for more extensive data. Health-risk-based guidance values require a large amount of data and many years of study. As a consequence these are rare and exist only for substances with widespread exposure and significant concern. Most HBM data starts on the left hand side of the figure with very little information other than a simple range of observed values. Developing health-based BGVs will only be feasible for a limited number of "data-rich" substances. Therefore, there is a need to develop exposure-based BGVs and those that represent the distribution of

a substance in the general population such as the NHANES or German Reference Values. Although these values will not be health based, they may identify high exposure groups and provide benchmarks for exposure assessment (not risk assessment). The need to gather more data and move to the right is driven by concerns about the hazard and risk of exposure. For some substances there may be sufficient data to indicate a need for a non-health-based or control type of value for example where biomonitoring shows there is exposure and the toxicology suggests concern but a 'safe' value cannot be established; a BGV derived for the substance may help monitor exposure and efforts to reduce it. For other substances it may signal a need for further study, however, it is also possible that some substances will not need to move categories.

The objective of a BGV is to aid the interpretation of HBM results and subsequent action, either to be reassured by the outcome or to take action to either reduce exposure or, for regulators and some manufacturers, seek further information. A BGV for a dietary constituent may be a range of 'normal' or acceptable values rather than a single limit value and only BM results at the extremes of the range would need action to prevent deficiency or toxicity – even then there may be margins of safety between the population range and levels at which we would be concerned. A similar range of HBM data for a non-dietary substance may not require a BGV if the substance is not hazardous but may prompt regulators to review toxicity data and seek further information if it is. If sufficient data is available, a health-based or biomonitoring equivalent BGV may be derived based on some form of acceptable dose.

For some substances, the most basic toxicity data may suggest that exposure should be avoided or kept to a minimum. This is likely to apply to substances of no known biological value to the body or where there is no threshold of exposure where we can be sure that there is no concern for human health (e.g. genotoxic carcinogens). However, since most toxicity data is either on non-humans or *in vitro*, PK or PBPK modeling may be important in interpreting data for the human scenarios. In these cases a BGV might be derived based on the mean, median or 90% value of the HBM data with action to reduce exposure being proportional to the level found above the BGV.

5.2 A Tiered Approach

The need for and type of BGV should be proportional to the hazard and possible exposure (Figure 4)). A tiered approach could be proposed based on a hazard and probability of exposure. Hazardous substances (e.g. carcinogens, mutagens, highly toxic substances) with a high probability of widespread exposure (numbers of people exposed, concentrations they might be exposed to) would point to a need for a BGV to help control and reduce exposure. Substances with little hazard (very low toxicity) may not require any form of BGV. If exposure from a natural source far outweighs anthropogenic sources a background range BGV may be most appropriate. A health–based BGV is

generally desirable but is only possible if sufficient data is available. In most cases availability consists of HBM and very limited toxicity data. Nonetheless, even in these circumstances biomonitoring may still be worthwhile as a first step towards data gathering and assessing exposure.

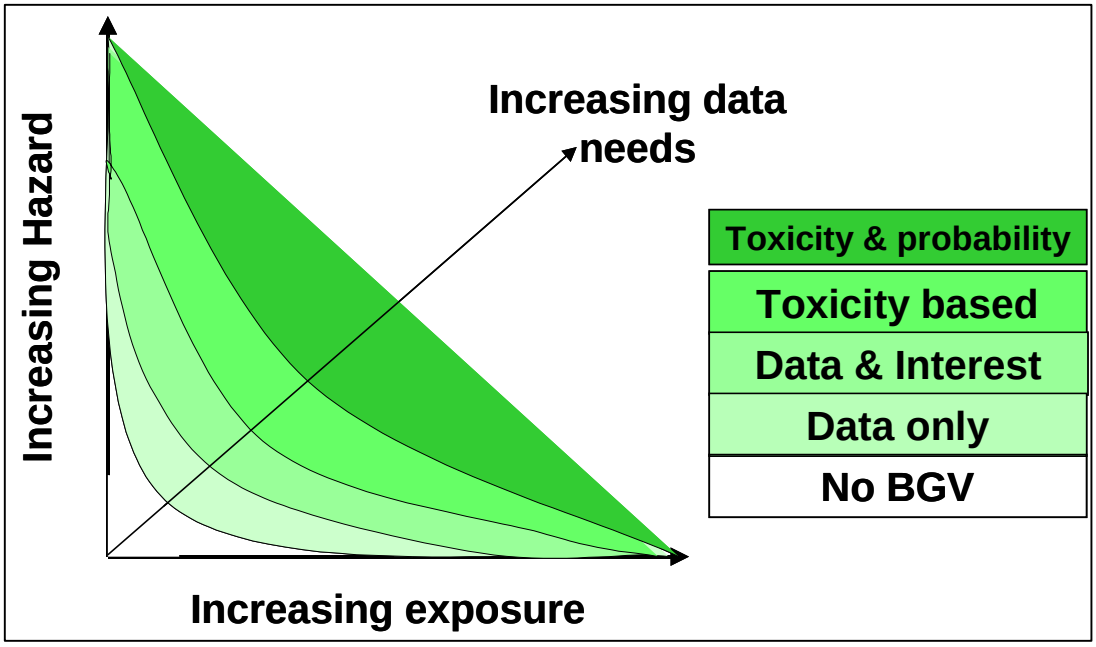

Figure 4: Type of BGV is proportional to hazard and possible exposure.

5.3 Communication issues

Often, in risk assessment and risk management, the communication of risk is considered to be a bolt-on extra with not much thought as to how this might be perceived by the stakeholder groups. Part of this problem relates to the communication of risk in general, and part to the history of biomonitoring (BM). In terms of the latter, BM has been developed for many industrially-used chemicals over many years, and management, occupational health professionals, exposed workforces and regulators have generally developed a mature attitude towards the use of BM as a risk assessment/management tool alongside air monitoring. Workers, often through their Trade Unions and occupational health professionals, have usually been involved in using BM and also in the setting of acceptable standards whereby risk/exposure reduction may be required. More recently however, many of these BM techniques have been used on the general population as part of national schemes or for research and other purposes. In these circumstances, the perceptions and attitude of the public and researchers may be very different to those of workers and occupational health professionals. As an obvious difference, the public may feel that they did not give 'permission' for themselves or members of their family to be exposed to an environmental/ industrial chemical that may have reported harmful properties, and for which they accrue no personal benefit.

How the public perceive risk and their attitudes towards risk are essential knowledge required by all those involved in risk assessment and management of chemicals (and physical agents) in the

environment. The scientist views risk in measured probabilities but, the public may not perceive risk in the same way. The social scientist will tell us that for the general public, risk perception (and hence attitude towards risk) is a social construct and will thus vary according to context. This can be quite hard for the physical scientist to understand. The social scientists often teach that risk perception depends on at least three primary factors; individual personality, cultural beliefs and current intuitional beliefs. Again, these are not always fixed and are context influenced.

One further point to consider in risk-related issues is what makes a good risk communicator. We are told that the key features are professional competence and trust. Sadly, as many a risk assessor has found to their cost, trust carries far more weight than competence. The lessons to be learnt from history are that good risk assessors/communicators must be able to understand and use all these skills. As a simple example, you have to listen, or learn to listen, to those who take a different stance to you on risk issues, even if you diametrically oppose their views.

As part of this project we explored, during the Workshop in particular, factors which should be considered when communicating BGVs to the general public.

5.4 Framework criteria

The criteria used within the framework to determine the type of BGV required for a compound includes the following considerations:

- selection of the most appropriate biomarkers
- definition of the type of BGV i.e. exposure-related / health-based / risk-based
- consideration of data from all sources including:
    - occupational data
    - environmental human biomonitoring data
    - guidance values based on animal toxicology data (use of hazard/ dose responses, pharmacokinetics, bench mark doses, uncertainty factors)
    - ADIs
    - guidance values based on epidemiological data
- definition of criteria needed for a minimum/optimal set of BGVs
- strategy towards obtaining these BGVs for data poor and data rich compounds
- consideration of how to deal with sensitive groups

- communication issues associated with different types of BGVs, different uses, different audiences, including limitations of data (how many, when collected) and of biomarker (half-life, specificity)

Framework Level 1 – Biomonitoring Data only (not health-based)

This level of the proposed framework represents the very earliest stage of biomonitoring. Criteria for inclusion in Level 1 include:

- available analytical method for the substance (or its metabolites)
- detection in a biological fluid (eg. blood and urine)
- data on toxicity of the substance or the meaning of results is not available.

Questions arising for such a substance at this stage are likely to include (not necessarily in this order):

- is the method of detection specific and reproducible?
- what are the levels/range seen?
- what are the sources of the substance and possible routes of exposure?
- is the correct substance/metabolite being measured in the most appropriate matrix at the optimum time?
- what is the metabolism and toxicokinetics of the substance?
- is there a need for further investigation?

Answering these questions requires further information which may depend on whether there is any 'concern' regarding the substance based on 'read-across' or QSAR from other related substances; if a 'concern' exists it may indicate the need for a Level 2 BGV. The most likely outcome for a Level 1 substance would be to start to define a reference range or reference value (95^{th} percentile). Levels above or below the 'normal' range may help identify sources of exposure or help to define levels associated with (ill-) health. The utility of this type of value is limited. Regularly exceeding the limits of the BGV/range might point to the need for further work but little can be said about health consequences.

Level 2 – Biomonitoring data plus some interest (not health-based).

This level follows on from Level 1 for substances where there is some interest surrounding the health effects of the substance. Criteria for inclusion in Level 2 of the framework include;

- good quality biomonitoring data
- some reason for 'concern' regarding potential health effects based on hazard information

- health effects following exposure
- some basic metabolism and toxicokinetic data
- insufficient data to propose a health-based BGV

Questions arising for such a substance at this stage are likely to include (not necessarily in this order):

- what are the levels/range seen in other members of the population
- what are the sources of the substance and possible routes of exposure?
- is the correct substance/metabolite being measured in the most appropriate matrix at the optimum time?
- what is the metabolism and toxicokinetics of the substance
- are there any health effects seen at the levels found
- can a BGV be established to help control and reduce exposure and risk
- are there trends in time or space?

Answering these questions again requires further data and this will be driven by the level of 'concern' over potential health effects associated with exposure to the substance. Examples of this type of BGV include the reference ranges for minerals and essential elements, where too high a level may lead to toxicity and too low a level to deficiency. Level 2 could also include control-based BGVs as used for occupational exposure, where workers may be exposed to hazardous substances such as carcinogens and respiratory sensitizers but where there is insufficient data to propose a Level 3 health-based guidance value.

Level 3 – Toxicity data (health-based).

Level 3 substances are distinguished from Level 2 substances through the amount of toxicology data available. Criteria for inclusion in Level 3 of the framework include:

- good quality biomonitoring data
- some reason for 'concern' regarding health effects following exposure
- good metabolism and toxicokinetic data
- insufficient data to propose a epidemiology-based BGV

For a Level 3 BGV there must be sufficient data available from animal or (preferably) human studies to be confident that a health-based BGV can be proposed. If extrapolating from animal studies, there should be sufficient data to show the animal study was in a relevant species with similar routes and

rates of metabolism. The biomarker chosen should reflect the dose and preferably the metabolites or flux in the metabolic pathway leading to toxicity. If PK or PBPK models are available they can help in these extrapolations. There should be confidence that the correct biomarker has been measured in the appropriate matrix with analytical techniques that are sufficiently sensitive, accurate and precise. Examples of this type of guidance value from the occupational field are the ACGIH BEIs and the DFG BATs. In the environmental area they include the Biological Equivalent (BEs) values. Regularly exceeding this type of BGV is unlikely to result in ill-health but may (at least in the occupational area) suggest that systemic exposure should be reduced.

Level 4 – Toxicity and probability data (health-based).

Level 4 substances are distinguished from Level 3 substances by the extent of the data available. Criteria for inclusion in Level 4 of the framework include:

- good quality biomonitoring data
- some reason for 'concern' regarding health effects following exposure
- good metabolism and toxicokinetic data
- good data from epidemiology studies

A Level 4 substance should have extensive data on metabolism, toxicology and mechanisms of action; in addition good quality biomonitoring data and epidemiology studies to link the levels of ill-health with levels of exposure/biomarkers should be available. Although this is the most useful level for interpreting biomonitoring data in terms of health and giving a risk estimate, the quantity of data required is such that there are likely to be few substances in this level. Substances reaching Level 4 are likely to have both a toxicological cause for concern and be commercially important with large numbers of people potentially exposed. Exceeding this type of BGV can be interpreted in terms of a risk (probably small) of ill-health.

5.4 Framework proforma

To aid with interpretation of criteria for inclusion into each Level of the framework, a 'proforma' detailing individual elements for consideration at each level was prepared. This document also included a glossary of internationally-accepted terms and words used in biomonitoring to avoid misunderstanding and confusion. The framework proforma is detailed in full in Annex 2

Part B: Testing of proposed framework

1.0 Summary of tested compounds

Following development of appropriate criteria for each level of the proposed framework, worked examples using 12 model compounds were prepared by members of the project team; each document was then reviewed and edited by a least two members of the project team. The summary section from each of these documents is given below with an indication of proposed Level within the framework, with full documents detailed in Annex 3. The applicability of the proposed framework structure and the levels assigned for each of the model compounds was additionally discussed at the project workshop, as detailed previously in Part A Section 4.

1.1 Acrylamide (prepared by Juergen Angerer, IPA)

Most probably AA is carcinogenic to humans. Because AA is an unavoidable constituent of food and is taken up in relevant concentrations by everybody, AA poses a health risk that must be minimized according to the ALARA principle.

The main sources of AA exposure are food and tobacco smoke. The uptake of a non –smoker is calculated to be between 0.3 and 0.8 µg/kg bw/d on average. Smokers take up two- to threefold higher doses. For the estimation of internal exposure the Hb-adduct of AA (AAVal) is a reliable and broadly approved parameter that can be determined down to 0.01 µg/l blood. The great advantage of this parameter is that it represents the AA dose taken up in the last 4 months. This enables a very reliable estimation of the internal AA exposure even of individual persons. Moreover this Hb adduct is an indicator of cancer risk. In Germany reference values for AAVal have been established for adults (1.2 µg/l) and for children (1.8 µg/l). The NOAEL for neurotoxic effect is 14.6 µg AAVal/l blood.

The average internal exposure of the general population is estimated at 0.6 µg AAVal/l. This concentration should be kept as low as reasonably practical to minimise cancer risk. Unborn children, suckling babies and children are the most susceptible groups. AA uptake can be reduced by avoiding smoking and AA rich food.

The mercapturic acids of AA and GA are the main metabolites of AA, which are excreted with urine. The concentrations of AAMA and GAMA in urine represent the exposure of the last two days. Up to now the database is not sufficient to establish reference values for AAMA and GAMA.

Free AA and GA in serum are markers which because of their very short half lives and further short comings are not suitable for HBM.

Designated as Level 3 or 'Toxicity based' BGV in the proposed framework at environmental levels of exposure.

1.2 Benzene (prepared by Ruth Bevan, IEH)

Proposed level of BGV

There is sufficient data available from human and animal studies to propose a *Level 4 or 'Toxicity and Probability based' BGV for benzene at environmental levels of exposure.*

Exposure evaluation

- sources of benzene exposure in ambient air include
  - cigarette smoke
  - petrol (combustion and evaporation)
  - petrochemical industries
  - other combustion processes
- mean ambient air concentrations of benzene in rural and urban areas is around 1 $\mu g/m^3$ and 5 – 20 $\mu g/m^3$ respectively.
- inhalation is the dominant route of exposure in humans

Health risk evaluation

- the most significant effects following chronic exposure to benzene are haematoxicity, genotoxicity and carcinogenicity
- long-term exposure to excessive levels can also result in bone marrow depression manifesting as leukopenia, anaemia, thrombocytopenia which can subsequently develop into pancytopenia and aplastic anaemia.
- genotoxic effects include chromosomal aberrations, sister chromatid exchanges and micronuclei
- carcinogenicity effects following chronic benzene excessive exposure include development of leukaemia in humans with other multisite tumours being seen in animals

1.3 Cadmium (prepared by Roel Smolders, VITO)

Cadmium has frequently been included as a target pollutant in both research and surveillance human biomonitoring projects across Europe and the World. Its primary pathways for uptake, toxico- and pharmacokinetic properties, and associated health effects are well understood and have extensively been validated under different exposure scenarios. Reference values and health based HBM-values to

estimate exposure of and effects in the general population are documented. Epidemiological studies have confirmed the in vivo and in vitro findings on the Cd exposure-dose-response continuum in the general population.

Analytical methods are documented in internationally established standard operation procedures, reference materials are available for relevant human matrices and confounders are well known and accounted for.

Generally, urinary Cd concentrations are an excellent biomarker to describe exposure to Cd and can directly be related to associated health effects. The kidney has been identified as a key organ in Cd-associated health effects. Increased excretion of low-molecular weight proteins are the earliest manifestation of Cd nephrotoxicity. And while these early changes may be reversible, tubular damage may progress to glomerular damage and eventually to renal failure if Cd exposure is prolonged.

Because all these aspects of Cd exposure, biomonitoring, and toxicity are well known, urinary Cd is designated as *Level 4 or 'Toxicity and Probability based' BGV at environmental levels of exposure*.

1.4 Cypermethrin (prepared by Kate Jones, HSL)

The toxicology of cypermethrin and its toxicokinetics and metabolism has been reasonably described in both animals and humans. Biological monitoring based on urinary metabolites is well established and reported at environmental levels, with an external quality assurance scheme available.

The German Human Biomonitoring Commission has already established a reference range of urinary metabolites for the German population. There are also plentiful data from the NHANES studies in the US and other smaller studies from other countries, indicating that a Level 2 (Non Health Based Upper Limit Value) guidance value could be set.

Although there are reported human volunteer studies available and an ADI has been established, the data is probably too limited to warrant a Level 3 (toxicity based) guidance value. The generic nature of the urinary metabolites also complicates the setting of a Level 3 guidance value.

On balance, cypermethrin is designated as *Level 2 or 'non-health based upper limit value' BGV at environmental levels of exposure.*

1.5 Di(2-ethylhexyl)phthalate (prepared by Holger Koch, IPA)

There is sufficient data available from studies of exposure to DEHP in animals and humans to be able to propose a *Level 3 toxicity-based BGV for DEHP at environmental levels of exposure.*

Both human and animal metabolism and toxicokinetics of DEHP are well described.

Exposure of the general population to DEHP is omnipresent and well documented by human biomonitoring data. Analytical methods are sensitive and selective enough to ensure a reliable detection of specific phthalate metabolites in all urine samples of the general population. Blood is, due to the contaminating interference, not an apt matrix for monitoring the body burden of the general population.

The oxidised metabolites, 5OH-MEHP, 5oxo-MEHP and 5cx-MEPP are the biomarkers of choice because of their (compared to MEHP) extended half-life, higher concentrations, non-susceptibility to contamination and suspected toxicity.

Toxicity based guidance values have been established for acceptable/tolerable levels of DEHP in air at the workplace (e.g. MAK value) and also for environmental exposure (e.g. TDI, RfD). Using these as a basis and the available extrapolation/PBPK models it is possible to derive Biological Equivalent Values for oxidised DEHP metabolites in urine.

There are insufficient data to describe the long-term effects of environmental exposure to DEHP (although new epidemiological studies have been or are currently conducted and indicate subtle effects even at environmental exposures) or to propose a probability-based guidance value.

Based on the most relevant NOAEL determined in the Risk Assessment Report on DEHP of the EU, with the inclusion of Margins of Uncertainty (MOS), Tolerable Daily Intake (TDI) values can be derived (50 µg/kg/day for the adult general population). These TDI value can be translated into biomarker data (metabolite level in urine when this TDI is reached), as done by the Human Biomonitoring Commission of the German Federal Environmental Agency:

Table: HBM I values derived for the sum of the oxidized DEHP metabolites 5OH-MEHP and 5oxo-MEHP**:**

Population	TDI [µg/kg bw/day]	urine volume [L/kg bw/day]	HBM I value [µg/L] in morning urine*
children (6-13 years)	50	0.030	500
women (childbearing age)	20	0.020	300
all other	50	0.020	750

* Calculation method: Tolerable daily intake x concentration in urine (f = 0.4) x the ratio of molecular weight (293/390) to urine volume (ml/kg bw).

1.6 Lead (prepared by Roel Smolders, VITO)

There is abundant information from environmental, animal, and human studies to propose a *Level 4 or 'Toxicity and Probability based' BGV for Lead at environmental levels of exposure.*

Lead is probably the best studied environmental pollutant with respect to the use of HBM values in hazard identification, hazard/risk assessment, risk reduction strategies and risk management evaluation. While not necessarily all mechanisms or causal relationships between Pb in the environment, Pb in blood or bone, and health effects are fully understood, the epidemiological consequences of population-scale exposure to Pb through different sources is widely understood and is supported by tons of scientific evidence.

The most important sources of Pb in the environment (tetra-ethyl Pb in gasoline and Pb-containing paint) are being banned across the world, children are identified as the most susceptible subpopulation because of their particular physiological and behavioural status (they are not little adults) and the most sensitive health endpoints, both from a toxicological and epidemiological point of view, are identified.

Risk reduction and management strategies are available, have proven their efficacy, and are globally applied.

1.7 Methyl *tert*-butylether (prepared by Kate Jones, HSL)

The toxicology of MTBE is reasonably well studied although there are some studies on carcinogenicity that are currently difficult to interpret for human risk. The toxicokinetics and metabolism has been described in both animals and humans. There have been complaints from consumers about acute health symptoms associated with the use of oxygenated fuels such as gasoline containing MTBE. However it is not clear that MTBE is the causative agent and epidemiological studies of human populations have not been able to identify a basis for these complaints.

Biological monitoring is available based on a number of markers, but for environmental exposures measuring MTBE itself is preferred. Environmental exposures have been determined to a limited extent using both blood and urine samples. Methodology for measuring MTBE is well established using either headspace or solid phase microextraction coupled with gas chromatography-mass spectrometry, however there is no available external quality assurance scheme at present.

There are no environmental or occupational biological monitoring guidance values for MTBE and the data currently available are limited but it would be possible to set *a Level 2 (Non Health Based Upper Limit Value) guidance value*, based on either blood or urine MTBE (urine would be preferable).

1.8 Platinum (prepared by Roel Smolders, VITO)

Mainly urinary Pt has been included in several HBM studies, and has been identified as a potential health hazard due to its omnipresence in the environment. Major uptake routes and population HBM

reference ranges are known. Well-validated analytical techniques exist, and detection levels are generally low enough to estimate environmental exposure of non-occupationally exposed populations

However, while there is detailed information on the potential sources of Pt, very little is known about the associated health effects. Pt in itself is not very toxic, and the only real Pt-associated health effects have occurred from sensitisation and allergies to specific Pt-salts following occupational exposure.

On balance, platinum is designated as *Level 2 or 'non-health based upper limit value' BGV at environmental levels of exposure.*

1.9 Polybrominated diphenyl ethers (prepared by Ovnair Sepai, HPA)

DecaBDE *would fall into Level 2* – there is potential wide spread general population exposure, it is possible to develop reference rages in order to monitor trends in exposure and possible reduction in exposures through chemical substitution or the removal of decaBDE from the market.

The value of a level 2 BGV is to be able to monitor trends on a national and international basis.

However, there are no clear health based criteria or risk based criteria up on which to develop lever 3 or 4 biological guidance values.

1.10 Samarium (prepared by Kate Jones, HSL)

There are few data on the toxicity of samarium and no published biological monitoring data from either occupational or environmental exposure. The low acute toxicity of the REs and the use of samarium chelates in cancer therapy suggest little immediate concern for environmental exposure. Occupational exposure to samarium may result in inhalation of dusts with unknown consequences but possibly pneumoconiosis. Further work is needed to identify a reference range for samarium and its toxicokinetics.

Samarium is designated as *Level 1, or 'data only, non-health based' BGV at environmental levels of exposure.*

1.11 Toluene (prepared by John Cocker, HSL)

There is sufficient data available from studies of exposure to toluene in animals and humans to be able to propose a *Level 3'Toxicity or health-based' biological monitoring guidance value for toluene at environmental levels of exposure*. The metabolism and toxicokinetics of toluene are well described and there are methods available to determine the major metabolite hippuric acid and some of the

minor metabolites of toluene. However, other sources of hippuric acid and o-cresol that make them unsuitable for assessing the low levels of toluene found in the environment. Measurement of toluene in blood or urine is specific for toluene exposure and there are well-validated analytical methods with sufficient sensitivity and specificity to determine toluene in blood and urine at environmental exposure levels. Dose response relationships have been established between the levels of toluene inhaled and the levels of toluene found in blood and urine. Health-based guidance values have been established for acceptable levels of toluene in air both in the workplace and the environment and also for oral exposure. Using these as a basis and the available PBPK models it is possible to derive Biomonitoring Equivalent values for toluene in blood. It may also be possible to use a similar approach or the relationship between levels of toluene in blood and urine to derive BE values for toluene in urine.

The levels of toluene found in blood show that although environmental exposure to toluene is widespread, the levels found are below the biomonitoring equivalent values based on reference values from various organisations for acute and chronic exposure (tables 4 and 5 above) and therefore are of no immediate concern.

There are insufficient data to describe the long-term effects of low level environmental exposure to toluene or to propose a probability-based guidance value.

1.12 Toluene Diisocyanate (prepared by Ovnair Sepai, HPA)

TDI has been classified as a class 2B carcinogen by IARC and is known to be a respiratory irritant and sensitiser and NCOs are one of the major causes of occupation asthma. There are some plausible routes of exposure to the public through leaks and emissions near and around industrial plants manufacturing TDI as well as polyurethane production. In addition there are some concerns around indoor air quality and low level emission of NCOs from consumer products. Thus there are well founded public health concerns. The body of evidence comes from the occupational setting where human biomonitoring has been recommended as a means to monitor the effectiveness of exposure control measures. The proposed methods involve the determination of urinary markers of exposure namely the isocyanate derived amine. The Biological guidance values set are not health based.

Environmental exposures are expected to be at very low levels and possibly intermittent therefore the use of plasma adducts as markers of environmental exposure are thought to be more feasible. However, there may also be scope to include the determination of TDI-HSA antibodies as markers of past exposure.

Therefore, for TDI a *Biological Guidance Value at Level 2 – to assess exposure alone through plasma adducts would seem appropriate*. A preliminary value could be derived from data in non-occupationally exposed individuals. This is a non-health based guidance value. There is insufficient data to propose a health-based BGV.

In order to set a Level 3 – health-based BGV for TDI, the body of evidence linking the biomarker and effect needs to be addressed. The use of TDI-specific antibodies is a attractive way forward however this will require an understanding of the mechanisms of the immunological response, the antigenic moiety and dose-biomarker, biomarker-time relationships before these techniques can be applied to public health protection.

The proposed level of BGV for all the compounds used to test the framework are summarised as follows:

Level of BGV	**Compound**
Level 1	Samarium
Level 2	Cypermethrin MBTE Platinum Polybrominated diphenyl ethers TDI
Level 3	Acrylamide Di(2-ethylhexyl)phthalate Toluene
Level 4	Benzene Cadmium Lead

Part C: Conclusions and Future Direction

1.0 General conclusions

To a greater or lesser extent, many of the key findings of the development of the HBM framework have been discussed within the body of the report. This section pulls together the most salient features relevant to the aims of the study and draws conclusions, highlights any limitations of both the study itself and of the framework as well as indicating future directions that may take the framework forward. The framework is to be seen as part of an iterative process for the use of BM to monitor environmental natural and anthropometric substances in the general populations. To date, only a very limited number of countries (Germany and the US) seem to have developed systematic national BM programmes for environmental exposure which assist in underpinning public health policy. However, this activity is likely to grow and a framework, such as the one outlined in the investigation, may well change over time. This is to be expected as the framework is intended to assist in the interpretation and communication of BM information. With usage, more experience and more BM information from surveys and studies, it may well evolve to better meet the needs of those who need to interpret and explain to various stakeholders what the information might or might not mean in terms of public health.

At the current time, biomonitoring is seen as a valuable tool that is used to provide information on exposure of the general population to a variety of environmental chemicals. HBM has the advantage of measuring total internal dose resulting from the uptake of a chemical from different exposure sources and through different routes. Repeated measurements over a period of time can be used to reflect trends in exposure and assess the success of risk management procedures.

However, at the present time, there are several scientific and technical limitations of biomonitoring that remain to be addressed. Of these, integration of health and exposure data is critical, with collection of human health, environmental exposure and biomonitoring data in an integrated system being the ultimate goal of any biomonitoring programme. The utility of HBM for public health protection is determined by the ability to interpret the data produced against set criteria, also a key limitation at present. However, the absence of ‘all the answers’ should not inhibit the search for them. Rather, an accepted framework is therefore urgently needed to put the available information in perspective, manage the expectations of its use and inform the need for additional data. Ideally, such a framework would be based on current scientific knowledge and best practice across Europe, the US and elsewhere, to help scientists, regulators, and stakeholders to design appropriate HBM studies, interpret HBM data (both for groups and individuals) and to take appropriate action. This appropriate action will comprise a range of risk management options, including risk communication to the public.

The primary objective of the study reported here was to develop a practical and scientifically-defensible framework for establishing different types of environmental monitoring BGVs for a wide range of anthropogenic and naturally occurring environmental contaminants. This framework, initially developed by the research team based on their experiences and the existing literature, was modified following critical comments from an expert advisory board, tested using a number of substances (data rich and data poor) and finally, fine-tuned following presentations and discussions at an expert Workshop. It is thus felt that the primary objective was successfully achieved in a rigorous and transparent manner.

1.1Framework structure

A number of environmentally and occupationally-derived biological monitoring guidance values are currently utilised for biomonitoring. These BGVs are most well developed in the occupational context where they have been used for many decades and where exposures have been many orders of magnitude above exposures environmentally encountered. Many of the occupational BGVs are health-based but others, where exposure-effect information is not available, may be more pragmatically derived and established on good practice and used as a risk management tool in the workplace. To some extent, there are parallels to environmentally-determined BGVs. However, to acknowledge that not all types of BGVs are derived or applied in the same way, the framework developed within this study is comprised of 4 levels (Part A, Figure 3). The Level of BGV assigned to a given compound reflects the type and quality of available HBM data and potential health/toxicological effects, and its relevance (or otherwise) to health. Although moving through the framework from Level 1 to Level 4 brings an increased confidence and moves towards a health-based guidance value, in practice, assigning a substance to Levels 3 and 4 requires extensive data. Such data is only achieved through studies or surveys which may take many years to achieve (equivalent to risk assessments and epidemiology studies) and are usually only carried out for substances with widespread exposure and significant concern regarding health effects.

The majority of substances are likely to fall into Levels 1 and 2 of the framework, as HBM data is most likely to be comprised of a simple range of observed values. These two levels of the framework allow development of BGVs based on data representing the distribution of a substance in the general population and exposure-based BGVs (equivalent to NHANES or German Reference Values) to be developed. Although BGVs at Levels 1 and 2 cannot provide information relating to health, they can provide valuable data on ‘background’ levels in a given population, against which exposures can be assessed to aid identification of high exposure groups.

Each Level of BGV within the framework is associated with a possible action that may be required to move a substance to the next Level(s). It is considered that in the main, the need to undertake recommended actions would be as a result of justified interest or concern over any potential risk associated with exposure to that substance. However, for some substances it is possible that no further action or movement between Levels would be necessary. In such cases, it needs to be made clear that a substance placed in Level 1 and 2 may not be in such a category simply because of lack of information, and that there is not an automatic need to gather more BM data. It might well be the case that the substance is there because it is toxicologically of very little or no concern, human exposures are likely to be low in known and predicted circumstances and thus Level 1 may the natural and permanent home for that substance.

1.2 Framework criteria

A number of criteria are currently available for setting different types of BGVs for occupational exposures, with guidelines for their applicability and any associated action. However, such criteria have been poorly defined for environmental exposures. A further aim of the study reported here was to identify a set of robust criteria for acceptability of data, consideration of applicability and any associated action, to be incorporated within the framework

In order to aid interpretation, a framework proforma was prepared outlining criteria to be considered for individual substances; the proforma also contained a glossary to facilitate a consistent use of biomonitoring data within the framework (Annex 2). The most relevant criteria for incorporation were considered to include:

- uses, potential routes of exposure and current health concerns
- toxicity data, *including biological effect monitoring data, if available*
- selection of the most appropriate biomarkers, i*ncluding information on reference ranges, occupational guidance value, PK or PBPK models, concentration of pure compound or metabolites in blood, urine, environment, inter- and intra-variability.*
- consideration of analytical methods, *including information on methods available for measurement of biomarkers (and parent compound if relevant), detection limits, reliability, reference materials, external quality assurance, known confounders.*
- consideration of epidemiology data, *including information on any data linking external exposure with health effect, data linking biological monitoring data with health effects.*
- identification of risk management procedures

- identification of susceptible groups and populations
- communication issues associated with different types of BGVs, different uses, different audiences, *including limitations of data (how many, when collected) and of biomarker (half-life, specificity)*

1.3 Interpretation of framework BGVs

It is important to consider the objective and purposes for establishing BGVs, their utility and limitations. The framework provides robust criteria for interpreting HBM data in relation to environmental exposure and can be used to inform regulatory bodies as to prioritisation of substances for further attention. Levels 1 and 2 of the framework allow a non-health based BGV to be defined for compounds with only small amounts of HBM data (Level 1) or for which only a reference range has been established (Level 2). Consideration of risk assessment data is provided within Levels 3 and 4, with epidemiology studies included only in Level 4 of the framework; both Levels 3 and 4 provide health-based BGVs.

1.4 Communication of framework and BGVs

There are many issues with regard to communication that are not unique to Human Biomonitoring (HBM) but relate to the conduct of all types of health-related research in human subjects. The issues of greatest importance range from 'transparency' and openness with all stakeholders to risk communication. As with all such communication, it should not be treated as a bolt-on extra to be considered only at the end of the research or survey, but at all stages of the process and thus seen as an integral part of the overall activity.

On the other hand, there are issues specific to Human Biomonitoring and these are related to how biomarkers of exposure and effect are interpreted in the context of individual health risk and population health risk management. The rapid advances in analytical technologies have resulted in a vast array of exposure and effect data sets of varying size and quality. However, not only has our ability to interpret these data fallen behind but so has our ability to communicate what these biomarker levels in human tissue may mean in terms of health.

The framework developed through this project may be used as a tool to aid clear and transparent communication to a wide range of stakeholders. These stakeholders include the public at large, the study population, the scientific community as well as politicians, the media and other interested parties. Each of these audiences has a different goal, different needs and different perception of risk.

There is a need to explain that the presence of a 'pollutant' in a human tissue does not always indicate adverse health effects. The dose-response concept is often difficult to explain, however this does not mean such 'biomarker data sets' should not be made available to the general public. Indeed, it is virtually obligatory to make such information available but it needs to be done so within an appropriate context. Strategies for health risk communication should thus be developed before data is generated; in fact current research ethics approval makes it clear that such strategies are now obligatory.

Thus, the presence of biomarkers of exposure that fall into Level 1 of the framework would not be regarded as having any health risk associated with them but the aim of such data is to assess potential exposure. As was discussed in the Workshop – transparency in regards to what is and is not known about a chemical is very important. At this level there is a lot of uncertainty and this fact must be made clear to the audience.

The inclusion of more biomarkers in contemporary epidemiological studies, where the aim is to define exposure-related associations with adverse health effects is very attractive (Level 3 and 4) and of great use from a public health perspective. However, the communication issues related with such studies are increased by the presence of these same potential adverse health effects but must be addressed by the researchers. Whether or not individual risk can be gleaned from such data is a major stumbling block for risk communicators. Understanding how the audience perceive risk is of paramount importance and such 'social studies' based research should certainly be an objective in the further development of the the framework with the overall aim of advancing risk communication in the field of HBM.

1.5 Summary

The framework developed in this study has several key features;

- a robust set of criteria acceptability of data, consideration of applicability and any associated action
- all substances with HBM data can be included, and an appropriate Level of BGV identified
- guidance values used to derive the Level of BGV are considered in context of their application, thereby preventing mis-interpretation

- clear consideration is given to the interpretation of BGVs, with limitations clearly defined
- communication of BGVs to to a wide range of stakeholders including, general public, the study population, the scientific community, politicians, media and other interested parties is considered for substances at the individual level

This study has therefore successfully met its aims and produced a practical and scientifically-defensible framework for establishing different types of environmental monitoring BGVs for a wide range of anthropogenic and naturally occurring environmental contaminants.

2.0 Future Directions

2.1 Implications for biomonitoring within REACH

Although there are no specific requirements to undertake biomonitoring within the EU REACH programme, it will clearly make a very valuable tool when undertaking exposure scenarios for submitted chemical substances. BM will be able to demonstrate the level of uptake in exposed populations and individuals, although not necessarily identifying the exposure pathway. One major danger in having such information is that without some measure of normal population range, it will make interpretation of individual or even group information problematical and often, impossible, either in comparison to background levels or to any risk criteria.

Within the EU at present, a new initiative at looking at background biomarkers in the general population is underway. A consortium to perform human biomonitoring at European scale (COPHES) met in Brussels, Belgium on 1st and 2nd December 2009. This consortium comprises 35 partners coming from 27 European countries and includes governments, research institutes, the Health and Environment Alliance (HEAL) and the European Chemical Industry council (CEFIC). The COPHES project objective is to perform actions designed to develop a functional framework that contributes to definition, organization, and management of a coherent approach towards human biomonitoring in Europe, including strategies for data interpretation and integration with environmental and health data. Interestingly, they state that a potential role of HBM in supporting and evaluating current and future policy making and policies, such as REACH, and for environmental health awareness raising will be promoted within this project.

There are further suggestions that for carcinogenic and reproductive toxicology, within the REACH guidance documentation, biomonitoring may make a useful adjunct alongside human epidemiology, particularly in relation to specific biomarkers of effect and susceptibility. However, such molecular biomarkers (DNA and other protein adducts, etc.) are generally considered to be research tools at present.

2.2 Further testing of framework

Biological monitoring is, without question, a useful tool for assessing systemic exposure to environmental chemicals and its utility is enhanced by the development of guidance values. However, all biological monitoring guidance values are not equal but are derived in different ways depending on the available knowledge of metabolism, toxicity and dose-response relationships. The framework for biological monitoring guidance values proposed here is intended as an aid to monitoring the journey from initial detection and awareness of a substance to understanding the risks, if any, to health it may pose. The four levels are not sharp boundaries but simply provide milestones to assess progress.

Biological monitoring is a developing field. The sensitivity and capability of analytical instruments is constantly improving and new biological monitoring data are being generated. Developments in toxicology and mathematical modelling will aid the interpretation of results. The need for better risk assessment to aid the control of exposure to hazardous substances will continue to stimulate this area. The framework does not replace national or international approaches to developing biological monitoring guidance values but gives a perspective and places them and other research or survey BM data into a context.

The initial lack of BGVs to interpret biological monitoring results in terms of health outcomes or risk may deter the use of biomonitoring but without use, the data will not be generated. By limiting the expectations of biomonitoring in the early stages, the framework could stimulate the development and application of biological monitoring.

One of the current major developments in biological monitoring is the pan European project on harmonising biological monitoring (COPHES) and the framework may be usefully incorporated as an aid to putting the results in perspective.

One of the key aspects determining successful use of biological monitoring is the responsible interpretation of data. It is hoped that this framework provides a rational structure to identify how much is known about a substance and what level of interpretation can be applied to the data on that substance. The communication aspects of this framework are therefore important

The next step for the Framework developed in this research is to have it “road-tested” for a wider range of substances than the 12 that have been used in this study. It is hoped that this can happen within the COPHES project. In this way, the framework can be examined and modified if and as appropriate over time. It is emphasised that the framework and the associated four Levels are only a

tool intended to assist those undertaking BM and those in public health who need to assess and act upon such information as appropriate. As such, it can only be of value if it is of use for this purpose and testing may lead to helpful changes.