Regulatory Toxicology and Pharmacology 51 (2008) S16–S26

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Guidelines for the communication of Biomonitoring Equivalents: Report from the Biomonitoring Equivalents Expert Workshop

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ARTICLE INFO

Article history:
Received 15 January 2008
Available online 22 May 2008

Keywords:
Biomonitoring
Biomonitoring Equivalents
Risk communication
BEs
Transparency
Exposure guidance values

ABSTRACT

Biomonitoring Equivalents (BEs) are screening tools for interpreting biomonitoring data. However, the development of BEs brings to the public a relatively novel concept in the field of health risk assessment and presents new challenges for environmental risk communication. This paper provides guidance on methods for conveying information to the general public, the health care community, regulators and other interested parties regarding how chemical-specific BEs are derived, what they mean in terms of health, and the challenges and questions related to interpretation and communication of biomonitoring data. Key communication issues include: (i) developing a definition of the BE that accurately captures the BE concept in lay terms, (ii) how to compare population biomonitoring data to BEs, (iii) interpreting biomonitoring data that exceed BEs for a specific chemical, (iv) how to best describe the confidence in chemical-specific BEs, and (v) key requirements for effective communication with health care professionals. While the risk communication literature specific to biomonitoring is sparse, many of the concepts developed for traditional risk assessments apply, including transparency and discussions of confidence and uncertainty. Communication of BEs will require outreach, education, and development of communication materials specific to several audiences including the lay public and health care providers.

1. Introduction

The traditional risk assessment paradigm for evaluating health risks associated with exposure to environmental chemicals—a four-step process including hazard identification, exposure assessment, dose–response evaluation and risk characterization—has been in use for over two decades (NRC, 1983). A large body of literature on risk communication associated with this paradigm is available. Interested parties, including regulators, health care providers, and the general public, have some familiarity with the types of information they obtain when

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doi:10.1016/j.yrtph.2008.05.007

risks are evaluated using this paradigm (e.g., cancer risk of one in one million associated with exposure to a specific chemical at a specific exposure concentration). Increasing interest in biomonitoring—the assessment of chemicals in human body fluids or tissues as opposed to in the environment—has created a large database on chemical concentrations in humans. However, the ability to interpret these data in terms of human health is, with few exceptions (e.g., lead), severely limited.

Biomonitoring Equivalents (BEs) are screening tools for interpreting biomonitoring data in a public health risk assessment paradigm. In this regard, BEs provide a simple tool for rapidly delineating portions of populations that have biomonitoring levels exceeding readily accepted exposure guidance values such as the United States Environmental Protection Agency's (US EPA) Reference Dose (RfD) and for identifying populations with biomonitoring levels below the exposure guidance values. The development of BEs brings to the public a relatively novel concept in the field of health risk assessment and presents new challenges for environmental risk communication. The risk communication literature for the traditional risk assessment paradigm can be drawn upon to inform the current issues related to communication of information surrounding the development of BEs. However, to a great extent, new ground must be broken as risks in the context of chemicals in the body, rather than chemicals in the environment, are addressed. Interpretations relevant to public health based on biomonitoring rather than environmental data will likely be perceived as more personal because human exposures are measured internally and are not based on hypothetical exposures to chemicals in the environment. Emotionally charged expressions such as "chemical trespass" (Schafer et al., 2004) and "body burden" (PBS, 2001) have been used to describe the presence of chemicals in the body, making objective communication of scientific information on risk and safety difficult. The National Research Council (NRC, 2006) has noted that "We do not know how to convey the biomarker-presence-does-not-indicate-health-effects message effectively." With the development of a framework for deriving BEs, a first step can be taken to directly address this problem. A careful evaluation of the extent to which BEs can be used to interpret biomonitoring information as it relates to human health, as well as the limitations on interpretation, is necessary.

An Expert Panel was convened (The Biomonitoring Equivalents Pilot Project Derivation and Communication Expert Workshop, 24–27 June 2007) to discuss issues related to BE derivation, interpretation and communication, and the results of the Panel deliberations are described in this paper and accompanying papers in this journal issue. This paper is focused on the deliberations and conclusions of the Expert Panel on BE Communication, which explored the multitude of issues that complicate the presentation of information on BE derivation, and devised methods that would enable successful development of BE communication information. These methods are not chemical-specific, but rather have application to communication of BE-related information in general. The goal is to convey information to the general public, the health care community, regulators and other interested parties regarding how chemical-specific BEs are derived, what they mean in terms of health, and the challenges and questions related to interpretation and communication of biomonitoring data that cannot be addressed by the BE concept at this time, but which may be the subject of future research efforts within the BE framework or through complementary approaches.

Key communication issues addressed by the Expert Panel and described in this paper are:

(1) What definition of the BE accurately captures the BE concept in lay terms?
(2) How do population biomonitoring data compare to the BE?
(3) What message(s) should be conveyed regarding biomonitoring data that exceed BEs for a specific chemical?
(4) What is the confidence in the BE?
(5) What are key questions of interest to the various audiences that might form the basis for a communication document, and what types of information are needed to address these questions?
(6) What are key requirements for effective communication with health care professionals?

Many of these issues appear straightforward, but in fact require comprehensive assessments of the data used to derive individual BEs (Hays et al., 2008) and possibly novel approaches to communication, particularly in light of the fact that the literature on biomonitoring-specific communication is scarce (Zober and Will, 1996; Pedersen et al., 2007; Angerer et al., 2006; Frank, 1996; NRC, 2006; ECETOC, 2005).

2. What definition of the BE accurately captures the BE concept in lay terms?

Ideally, specified levels of environmental chemicals in the body that provide guidance on risk (e.g., levels thought to be without appreciable risk) would be derived from a robust set of studies of health effects in humans related directly to measured levels of the chemical in a specific biological medium (e.g., blood and urine). Such levels exist for a limited number of environmental chemicals. In the absence of such a database, estimates of chemical concentrations in the body consistent with existing exposure guidance values such as US Environmental Protection Agency (EPA) Reference Doses (RfDs) and Reference Concentrations (RfCs) can serve as screening values for interpretation of measured concentrations in the body.

The BE values represent the concentration of a chemical in the body, typically measured in blood or urine, that are consistent with selected exposure guidance values, based on the current understanding of the pharmacokinetic properties of the chemical. An example of a useful exposure guidance value is EPA's RfD, which is "an estimate of a daily oral exposure for a given duration to the human population including susceptible subgroups that is likely to be without an appreciable risk of adverse health effects over a lifetime" (http://www.epa.gov/IRIS/gloss8_arch.htm). The BE is an interim screening value that can be revised, for example, if and when the scientific and regulatory communities reach consensus on acceptable concentrations in human biological media based directly on epidemiological data.

Different public health and regulatory agencies (and in some cases different offices within one agency) derive guidance values using different methods, resulting in more than one guidance value that could be considered appropriate for BE derivation. Thus, a range of BE values may be derived for a given chemical. The definition of the BE is:

A Biomonitoring Equivalent (BE) is the concentration or range of concentrations of a biomarker of exposure for an environmental chemical consistent with existing exposure guidance values.

It is necessary to define certain terms within the BE definition, including "biomonitoring" and "biomarker of exposure". The Centers for Disease Control and Prevention (CDC) definition is used for biomonitoring (http://www.cdc.gov/biomonitoring/). The standard definition from the International Union of Pure and Applied Chemistry (IUPAC) (Nordberg et al., 2004) is used for biomarker of exposure. The two key terms used in the BE definition are as follows.

2.1. Biomarker of exposure

Biomarker that relates exposure to a xenobiotic to the levels of the substance or its metabolite, or of the product of an interaction between the substance and some target molecule or cell that can be measured in a compartment within an organism.

2.2. Biomonitoring

The direct measurement of people's exposure to toxic substances in the environment by measuring the substances or their metabolites in human specimens, such as blood or urine.

The following is put forth as the definition for "exposure guidance value" as it pertains to BE derivation:

2.3. Exposure guidance values (EGVs)

Concentration of chemical in air, water or food or a daily oral dose of a chemical set by a regulatory agency or authoritative body and designed to be protective of human health (i.e., exposures at or below this value are believed to be without appreciable health risks) and is used as a guide for making risk management decisions (e.g., concentrations of chemical to be achieved during clean-up of a contaminated site, etc.).

For communication to the general public, the terminology in the BE definition and corresponding IUPAC definitions are not sufficiently accessible. Thus, the following definition will be used for this purpose:

> A Biomonitoring Equivalent is an estimated concentration or range of concentrations of an environmental chemical in humans consistent with existing exposure guidelines.

In addition to providing a generic definition for the term BE, for each chemical-specific BE it is useful to have a generic description of the method used to derive the value. The basis for the BE can be communicated with a simple diagram showing the origin of the toxicological data (e.g., human, rodent, etc.) and the method used (e.g., inclusion of uncertainty factors), as shown generically in Fig. 1. Fig. 1 is used as the initial template, with only the relevant portions shown for any given chemical. More detailed schematics of the methods and approaches used to derive BEs may be more appropriate for technical audiences; examples are shown in the accompanying chemical-specific dossiers in this issue.

There are numerous sources of exposure guidance values that can be used as the basis for BE derivation including RfDs, Tolerable Daily Intake (TDI) values, RfCs, and MRLs (Minimum Risk Levels). These guidance values can refer to different routes of exposure (oral, inhalation, and dermal), different health endpoints and different exposure durations (e.g., chronic and acute). The BEs are derived from the "Point of Departure" (POD) defined as the "...point on a dose–response curve established from experimental data, e.g., the benchmark dose, generally corresponding to an estimated low effect level (e.g., 1–10% incidence of an effect) or a No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL). Depending on the mode of action and available data, some form of extrapolation below the POD may be employed for low-dose risk assessment or the POD may be divided by a series of uncertainty factors to arrive at a reference dose" (USEPA, 2007a). The value in notating the BEs with superscripts and/or subscripts was considered so that the variations in the underlying guidance would be transparent. However, it was felt that this would unnecessarily complicate the communication of the BE, and that the interested reader should instead be referred to the related chemical-specific derivation document. In addition, the exposure guidance values on which the BEs are based, along with details such as the populations considered by the guidance values (e.g., general population, sensitive subpopulations, and infants), should be available to the reader via a hyperlink to an appropriate website. Given that some BEs are derived starting with the PODs, it was recognized that a notation to differentiate between BEs associated with the exposure guidance values and BEs associated with PODs would be required. Therefore, use of BE_{POD} is acceptable for use in the technical BE dossiers and for communicating to technical (risk assessment) audiences.

Information on BEs developed for the general public and health care providers must include a statement on the restrictions associated with the use of the BE. We provide language here that mirrors the language used by the American Conference of Industrial Hygienists (ACGIH) to describe limitations on their Threshold Limit Values (TLVs®) (ACGIH, 2001):

> BEs are guidelines to be used by environmental and health professionals. BEs are intended for use only as guidelines or recommendations to assist in the evaluation of general population or special population biomonitoring data. BEs are not intended to be used for assessing biomonitoring data from individuals, or for diagnostic purposes. In addition, BEs are not bright lines between safe and unsafe levels of chemicals in the body. BEs are not regulatory standards.

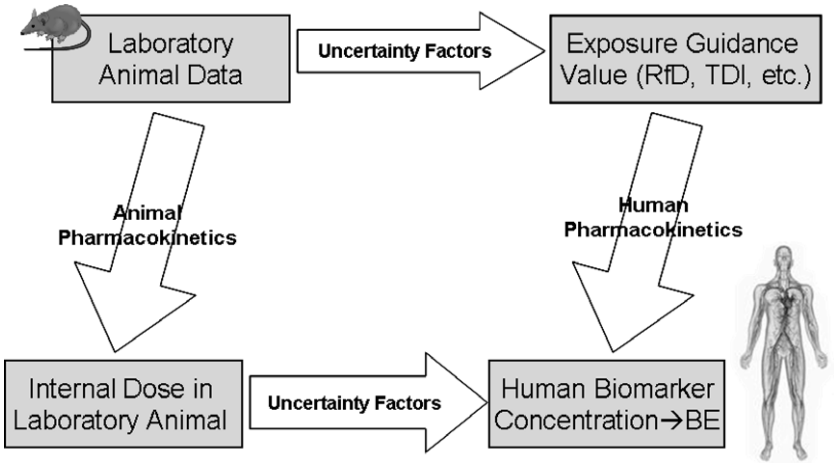

Fig. 1. Generic description of method for deriving the BE. See the BE derivation guidelines (Hays et al., 2008) for further discussion of this figure.

3. Comparison of population biomonitoring data with the BE

An important use of the BE is as a screening value for comparison with human biomonitoring data. The comparison of biomonitoring data to the relevant BE value can assist risk managers in assessing the potential need for research, exposure reductions, or assessment of other alternatives. Such a comparison may provide information to the public as well. While comparisons with population data can provide valuable information regarding general exposures to a given chemical, there are important limitations that must be considered.

3.1. Individual data

Numerous private laboratories advertise their ability to measure environmental chemicals in blood, urine, or other human tissues and fluids. Thus, individuals may obtain measures of an array of chemicals in their bodies. While it may seem enticing to use a BE to try to interpret these individual measures, it is generally not scientifically valid to use the BE as an interpretive tool for individual biomonitoring data. One principal reason is that the level measured in an individual will be influenced by a large number of factors, and typically only one measurement is available. This is especially the case for chemicals with short half-lives in the body, where daily (or even hourly) fluctuations in biomarker levels in an individual will not be captured by the one measurement and may misrepresent the typical level in the individual (i.e., single measurements should not be used to establish baseline levels for an individual because all human health parameters fluctuate). ACGIH has described factors that can impact a worker's biomarker levels (ACGIH, 2001), some of which are applicable to general population exposures to chemicals in the environment:

- Physiological makeup and health status: body build, diet, metabolism, body fluid composition, age, gender, pregnancy, medication, and disease state.
- Exposure: work rate intensity and duration, skin exposure, temperature and humidity, co-exposure to other chemicals, work habits, community and home air pollutants, water and food components, personal hygiene, smoking, alcohol and drug intake, exposure to household products, or exposure to chemicals from hobbies or from another workplace.
- Methodological: specimen contamination or deterioration during collection and storage; bias of selected analytical method.

In addition, the BE value is based on PODs and exposure guidelines that are not derived for individuals and are not meant to serve as bright line values separating "safe" and "unsafe". For example, a BE based on an RfD will have the same underlying definitional aspects as the RfD from which it was derived. As previously noted, the RfD is defined as an "estimate of a daily oral exposure for a given duration to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime." It is derived from a "....suitable point of departure, with uncertainty/variability factors applied to reflect limitations of the data used" (USEPA, 2007b). As is clear from this definition, there are various aspects of the RfD that make it unsuitable for application to interpretation of individual "safe" levels, including: (i) "estimate of daily dose", which does not necessarily account for episodic exposures and peak exposures; (ii) "likely to be without appreciable risk" which leaves open to interpretation the actual risk level which cannot be known; (iii) uncertainty/variability factors, which can span several orders of magnitude, and are meant to account for uncertainties stemming from such factors as interspecies extrapolation and susceptible populations; and (iv) a duration of exposure (lifetime) which is unlikely to be accurately reflected by a single biomarker measurement.

3.2. Workplace population data

BEs are analogous to the Biological Exposure Indices (BEIs) developed by ACGIH in that both are designed to represent biomonitoring levels estimated to be related to exposures at an EGV (TLVs in the case of BEIs). BEs developed for workplace standards were recognized as potentially valuable for comparison to biomonitoring studies conducted among workers, but BEs derived from workplace standards would not be considered appropriate for comparison to biomonitoring studies from general populations. If BEs are developed for workplace standards, the difference between BE and BEI values should be noted.

3.3. General population data

The most appropriate data for comparing to BEs are general population data, as populations capture a large range of variation and also best reflect the effectiveness of large-scale (i.e., population-scale) interventions (e.g., removing lead from gasoline). In comparing this type of data to a BE, the population's characteristics should be described and the data's original reference cited. The difficulty in comparing the BE to population data is related to the quality of the population data: how will the public know whether the data are of high quality and that the selection of the data for comparison was not biased? One source of high quality US population data that can be used is CDC's data published in their biennial National Report on Human Exposure to Environmental Chemicals (CDC, 2007). There may be instances where it will be useful to compare the BE to data from a smaller region or smaller special groups (e.g., groups with atypical exposures) and best professional judgment will need to be applied.

Graphical representation of the BE comparison to population data should be included in the communication material. Log scale graphics are to be avoided whenever possible due to the difficulty the general population will have in interpreting such a graphic.

4. Interpreting biomonitoring data that exceed chemical-specific BEs

In order to interpret concentrations of chemicals in humans in comparison to BEs, it is important to describe the objectives of deriving BEs and what purposes BEs are and are not meant to serve. BEs provide a tool for interpreting human biomonitoring data in relation to existing exposure guidance values. BEs are not diagnostic tools, and as stated previously should not be used to provide clinical interpretation of an individual's biomonitoring data. Thus, exceedances need to be discussed in the context of population data. BEs are not risk assessment values, as they do not provide information on sources, frequency, or duration of exposure, and as such, exceedances would not necessarily trigger remedial activities. However, values such as RfDs can provide a model for communication regarding BE exceedances, because for exposure at levels slightly above the RfD, it is not anticipated the exposed individuals will experience adverse health effects, given the conservative factors built into the RfD. Similarly, measured biomarker concentrations slightly above levels consistent with existing exposure guidance values will not necessarily result in adverse health effects. The definition of a guidance value called the Provisional Tolerable Monthly Intake (PTMI) sheds light on why this is so (FAO/WHO, 2001): "The PTMI is not a limit of toxicity and does not represent a boundary between safe intake and intake associ-

ated with a significant increase in body burden or risk. Long-term intakes slightly above the PTMI would not necessarily result in adverse health effects but would erode the safety factor built into the calculations of the PTMI. It is not possible given our current knowledge to define the magnitude and duration of excess intake that would be associated with adverse health effects." The derivation of BE values with demarcated regions of low, medium, and high priority for risk assessment follow-up provide a similar basis for general evaluation, with the degree of elevation above the low-priority region, as well as the duration of that elevation, related to the degree to which built-in safety factors may be eroded (Fig. 2).

The general public and others will still likely be interested in interpretation of population biomonitoring data that exceed chemical-specific BEs. Analogies from the medical realm exist that can be used to assist in the interpretation of exceedances. Cholesterol provides a useful analogy for interpreting exceedances of BEs; while it is an endogenous substance and not an environmental chemical, the public is generally aware that cholesterol is present in the body and that cholesterol can be used as a biomarker for potential health risks. Further, a discussion of cholesterol can be used to bring forth to the public underlying concepts that are transferable to environmental chemicals—such as "dose–response" and "acceptable" or "normal" levels. People generally understand that there is a "dose–response" relationship between increasing blood cholesterol and the risk of heart disease (i.e., while high cholesterol levels are a risk factor for coronary heart disease (CHD), elevated levels do not mean that CHD is inevitable, but rather that the risk of CHD is greater) (NCEP, 2005). They also understand that the range of "normal" values may change over time as new knowledge is developed. People further understand individual variability, in that not everyone with a high fat diet has high cholesterol levels (Clifton et al., 1990; Robinson et al., 2006). Thus, a generic description of blood cholesterol may be a valuable tool for communicating information about biomonitoring levels exceeding the BE.

BEs as screening metrics of environmental exposure and exceedances can therefore inform decision makers regarding the priority of the chemicals for further attention. However, BEs as risk management tools are only as robust as the underlying PODs/guidance values and pharmacokinetic models on which they are based. The range of the BEs (either resulting from BEs established for different exposure guidance values or resulting from the range between BE-$_{POD}$s and BEs for the same exposure guidance value) will inform the risk manager regarding the uncertainty of the BE estimate, with a large band suggesting greater uncertainty.

The use of BE values to identify levels of low, medium, and high priority for risk assessment follow-up is recommended. Such follow-up may include additional assessment or investigation of exposure pathways and exposure levels, additional collection or assessment of toxicology or health effect data, assessment of potential exposure interdictions or public health education measures, risk-benefit assessments, or other risk assessment or risk management actions, as determined to be appropriate by public health agencies. The use of only three levels of priority provides the public with a simple scale that can be used to interpret population-based biomonitoring results. For chemicals associated with non-cancer health endpoints, the definition of the priority levels in relationship to the derivation of underlying exposure guidance values is as follows (Fig. 2):

- High priority for risk assessment follow-up is associated with biomonitoring levels that exceed the biomarker concentration estimated to be associated with the human equivalent POD (termed the human equivalent BE$_{POD}$). This biomarker concentration may have been estimated based on one of two starting points:
  (1) From the POD in an animal toxicology study (animal no-adverse-effect-level) in combination with appropriate duration adjustment factors and interspecies uncertainty factors to account for presumed animal-to-human differences in intrinsic sensitivity to the chemical as well as, where appropriate, presumed animal-to-human differences in pharmacokinetics.
  (2) Directly from human toxicology or epidemiology data when such data serve as the basis for the exposure guidance value.
- Medium priority for risk assessment follow-up is associated with biomarker concentrations below the human equivalent POD, but are above the BE value derived consistent with the

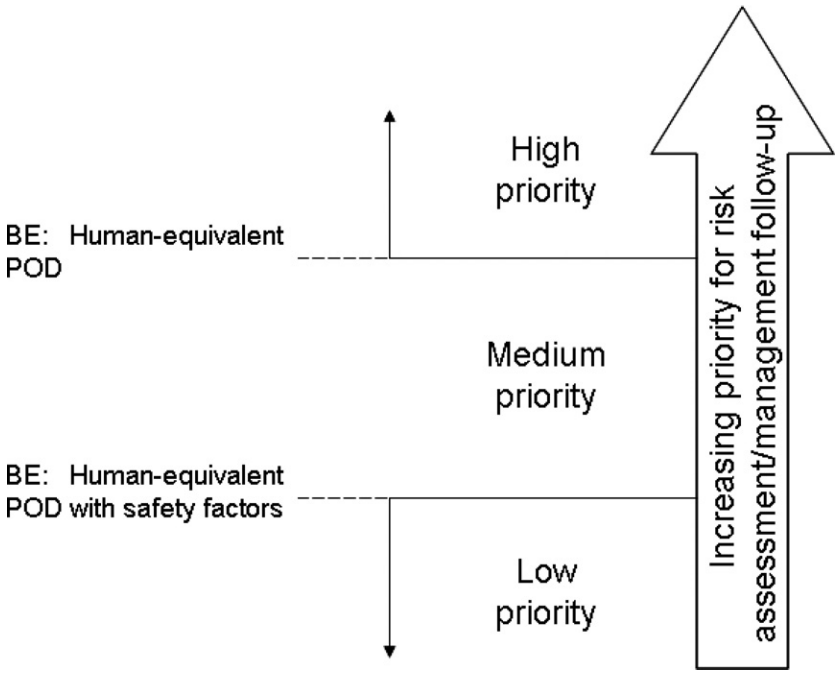

Fig. 2. Interpretation of population biomonitoring data exceedance of BEs.

exposure guidance value. The BE value corresponding to the exposure guidance value is derived from the human equivalent BE_{POD} in combination with appropriate within-human (intraspecies) uncertainty factors. These uncertainty factors account for presumed interindividual differences in intrinsic sensitivity to the chemical, and, where appropriate, for presumed interindividual differences in pharmacokinetics.

- Low priority for risk assessment follow-up is associated with biomarker concentrations below the biomarker concentrations consistent with the exposure guidance value (BE). These concentrations are consistent with exposures deemed of low risk under the conventional chemical risk assessment paradigm.

The derivation of these cut-points and selection of appropriate uncertainty factors are discussed in detail in the accompanying paper presenting BE derivation guidelines (Hays et al., 2008).

5. How should the level of confidence in the BE be expressed?

Confidence in the BE is related to uncertainties associated with aspects of the science that underlie the BE derivation, including understanding of the mode of action that determines the relationship between the measured biomarker and the critical dose metrics related to adverse effects of the chemical, and to the robustness of the pharmacokinetic data and models utilized in the derivation of the BE. Because of the technical nature of these issues, the more appropriate place for a detailed discussion of these uncertainties is in the BE derivation documentation (Hays et al., 2008). This discussion, however, needs to be converted to a description of confidence that can be understood by those outside the scientific community. It is critically important that communication materials include discussions of uncertainty (NRC, 2006), and according to Frewer (2004), "Uncertainty should be communicated in explicit and understandable ways, and should be focused on the need of the target audience; experts may have underestimated the ability of lay audiences to understand uncertainty, and lack of clear information on uncertainty has increased public distrust—communication about uncertainty may increase the communicator's credibility. Risk communication needs to focus on sources *and* magnitude of uncertainties." It is important that the level of confidence in the BE is captured so that risk managers, health care providers, and the general public may reliably use the BE to gauge the level of concern that may be applied to measured human exposures. Adequate documentation regarding the confidence in the BE must be developed.

The value of distinguishing among different types of uncertainty has been noted (Frewer, 2004) and examples of this type of uncertainty assessment have been reported. The Netherlands National Institute for Public Health and the Environment (RIVM) developed a matrix covering each area of potential uncertainty for use in assessing and communicating uncertainties (Janssen et al., 2005). The World Health Organization (WHO, 2006) assessed separate sources of uncertainty (e.g., the level of uncertainty, appraisal of knowledge base, the subjectivity of choices) and ranked characteristics of uncertainty as high, medium, or low.

Distinguishing among different types of uncertainties could lead to the identification of areas where improvement in the database is needed. These may be as simple as instances in which data could be developed to support assumed values or cases in which the biological plausibility of a given assumption could be supported with additional evidence. In both of these instances, the value of improved information should be made apparent. For situations where appreciable effort may be required to refine estimates of a parameter value, the quantitative impact of that parameter must justify the expenditure of resources.

In communicating the confidence in the BE, the following points should be made: first, scientific data are subject to a number of sources of uncertainty. Second, the choice of uncertainty factors applied in the derivation of the exposure guidance value involves the application of scientific judgment and policy considerations. Similarly, for cancer the choice of the model used for the analyses involves scientific judgments and policy considerations. Thus, the BE, based on scientific data and uncertainty factors or cancer modeling, is also subject to uncertainty. Third, the pharmacokinetic data or model used in the derivation of the BE inevitably carries with it uncertainty, and the degree of uncertainty varies with the robustness of the data or model. Therefore, it is useful to broadly categorize the confidence in the BEs as high, medium, or low, with assessments of the level of confidence in the overall database, as well as assessments of confidence in understanding regarding the mode of action and the relationship between the biomarker and the critical internal dose metric. In order not to overstate the precision of the BE, the BE should normally be expressed in only one or two significant figures along with a simple scale showing low, medium, and high levels of priority for risk assessment/management follow-up.

Confidence in the communicator is critical to successful communication with the public. Successful public communication requires honesty and transparency, with all of the relevant facts made freely available, along with any assumptions that have been made to deal with uncertainties or data gaps. In particular, the public will want to know how much precaution has been invoked in estimating the BE in the face of scientific uncertainty. Peer review can enhance the credibility of and confidence in BE values presented to the public. In documenting the BE derivation, it will be useful to include a prioritized list of data gaps and, more importantly, data needs that would permit a better estimation of the BE. Finally, definitions of uncertainty and variability should be included in the confidence section, which would serve to enhance the public's understanding of the concept of uncertainty.

6. Key questions for communicating information related to BEs

In addition to providing the BE value(s), comparing population biomonitoring data to the BEs, descriptions of the interpretation of exceedances of biomonitoring data, and a narrative/graphic discussing the confidence in the BE, several additional topics will likely be of interest to the general public. These topics, given in the form of queries, are: (i) what health effect is the BE based on? (ii) How are people exposed to the chemical? (iii) Where can I get more information? These questions, along with recommendations for shaping responses as part of the communications documentation, are given here.

6.1. What health effect is the BE based on?

BEs are based on exposure guidance values that are derived with the goal of minimizing the likelihood of any adverse health effect occurring from the chemical exposure. To this end, exposure guidance values based on non-cancer endpoints examine available data on all adverse effects known to result from exposure to a chemical in tested species based on available scientific studies. The most sensitive observed effect is identified, and the highest identifiable exposure that does not produce an observable impact on this endpoint is identified as the POD for derivation of an exposure guidance value. This endpoint is not necessarily the health impact of greatest concern, but protection from the most sensitive (lowest dose) outcome will necessarily protect against outcomes at higher doses, which may be of lesser or greater concern. The POD is then reduced by application of a series of inter- and intra-

species uncertainty factors to account for presumed differences in sensitivity between animals and humans (with humans presumed to be more sensitive) and within human beings (with a portion of the population presumed to be more sensitive by severalfold than the typical member of the population). Finally, in many cases, exposure guidance values include additional uncertainty factors designed to protect against the possibility that an untested endpoint might occur at lower exposure levels than the most sensitive endpoint previously identified and adjustments for less than lifetime exposures (when applicable).

In the case of cancer risk-based exposure guidance values, typical guidance values (for example, risk-specific doses or, in this case, risk-specific BE values) are based upon extrapolation of a dose identified to cause a low but detectable increase in cancer in experimental animals to a level considered to present a very low risk (for example, an upper bound estimate of a one in a million risk level).

A tenet of risk communication is that if the type of harm elicits feelings of dread, this should be acknowledged (OECD, 2002; Leiss, 2004). It is anticipated that BEs will bring forth a range of reactions and sentiments, depending upon the health effect to which they are linked and whether population data show exceedances above the BE. However, it is important to communicate to the public an understanding of the numerous elements of conservatism (i.e., health-protective assumptions) incorporated in this process. Noncancer exposure guidance values and therefore BEs derived from such values are based upon downward extrapolation of exposures shown to cause minimal (e.g., from benchmark dose analysis) or no observable health effects, and cancer-based exposure guidance values similarly identify exposures that present *de minimis* risk levels. The BE documentation provides a summary of the toxicological no-observed-adverse-effect-levels identified as the basis for the derivation of the exposure guidance values for each chemical.

6.2. How are people exposed to the chemical?

According to the National Research Council (NRC, 2006), providing a sense of individual control reduces perceived risk. In addition, risk communication should "empower individuals to make informed decisions about hazards within their control" (Russel, 1991). A minimum necessary component of risk communication is the specification of what is known about exposures and whether sensitive populations including children are likely to be exposed (OECD, 2002). Neither biomonitoring data nor BE values provide any information on sources or routes of exposure. However, the existence of biomonitoring data—with or without concomitant BE values—may prompt people to think more carefully and be more interested in their own potential sources of exposure. Providing information on sources of exposures may be a useful way of contributing to an individual sense of control, and a clear comprehension of potential sources and routes of exposure to a chemical may assist in understanding the import of a biomonitoring result. However, as noted by Anderson et al. (2006), "[k]nowledge gaps are more typical than is established science, especially when children are the exposed population.…." While interested parties may desire information on specific products, activities, etc. associated with increased exposures, whether to adults or to children (including *in utero* exposure), such information is often not available or may vary by population subgroup, geographic region, or lifestyle factors.

Because the derivation and application of BE values to interpretation of biomonitoring data provide no information regarding routes and sources of exposure, a detailed discussion of exposure pathways and sources is outside the scope of BE communication materials. However, where available, BE communication materials can refer readers to other established sources for such information. Such information is readily available for many chemicals (Table 1). Example sources include the chemical-specific assessments produced by the ATSDR (ToxFAQs™) (www.atsdr.cdc.gov/toxfaq.html). Information can also be found in the EPA's Toxicity and Exposure Assessment for Children's Health (TEACH) (http://www.epa.gov/teach/), Hazardous Substances Databank (http://toxnet. nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB) and (although fairly technical in nature) in European Union risk assessments (http://ecb.jrc.it/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/REPORT/). Information on household product exposures can be found at the National Library of Medicine website "Household Products Database" (http://hpd.nlm.nih.gov/index.htm); however, this database does not provide information on exposures due to ambient levels of a chemical, or dietary exposures. When reliable information is available, it is appropriate to provide a reference or electronic link to the needed information. Available information should be reviewed by the BE documentation working group to assure that it is acceptable and reasonably consistent. Ideally, more than one authoritative source should be provided, as this eliminates potential or perceived bias and greatly improves public confidence in the information provided.

The nature of the BE derivation may impact the type of source and exposure information necessary for a comprehensive understanding of a BE value. In particular, when a metabolite results from multiple primary chemical exposures or is itself present in the environment or when a biomarker (such as DNA adducts) may reflect exposure to more than one chemical entity or agent, consideration should be given to the entire spectrum of agents likely to contribute meaningfully to a particular biomarker value. Similarly, when a biomarker may result from endogenous production of a chemical (i.e., acetone and methanol) or may be the result of various disease states or therapeutic interventions, this should be acknowledged and the likely contribution to BE values estimated, if feasible.

6.3. Where can I get more information?

Sources of additional information relevant to a variety of audiences should be provided in the BE document if available. An effort should be made to identify a number of authoritative sources that, collectively, can provide information appropriate for both professional and lay audiences.

When possible, the information for lay audiences should be provided in a language or languages and at the appropriate reading level for the anticipated audience.

Table 1
Chemicals included in one example of a source for exposure information (EPA's Toxicity and Exposure Assessment for Children's Health (TEACH) (http://www.epa.gov/teach/)

2,4-Dichlorophenoxyacetic acid	Mercury (elemental)
Arsenic	Mercury (inorganic)
Atrazine	Mercury (methylmercury and ethylmercury)
Benzene	Nitrates and nitrites
Benzo(a)pyrene (BaP)	Permethrin and resmethrin (pyrethroids)
DEET	Phthalates
Dichlorvos	Polychlorinated biphenyls (PCBs)
Formaldehyde	Trichloroethylene
Manganese	Vinyl chloride

"The TEACH Web site contains summaries of scientific literature and U.S. federal regulations relevant to children's environmental health. TEACH currently focuses on information that pertains to 18 chemicals of concern. The goal of the TEACH project is to complement existing children's health resources. TEACH does not provide an evaluation or critique the validity of the relevant scientific studies; nor does TEACH derive toxicity values. Instead, the goal of TEACH is to summarize, compile, and organize information obtained from numerous resources into one online resource. TEACH is designed to support numerous efforts throughout the country that target the protection of children's health."

Authoritative and technically correct sources are important. Governmental agency, industry, academic, and/or nongovernmental organization websites that contain appropriate information should be included, with the recognition that consistency among multiple sources serves to augment the reader's confidence in the reliability of the information provided.

Appropriate sources should be identified and referenced in the communication materials for the BE. Possible sources for evaluation are shown in Table 2.

7. Key requirements for effective communication with health care professionals

One of the greatest challenges for risk communication is: "How can health providers communicate information in a clear and simple way when the nature of the information itself is complex, ambiguous, and full of uncertainties?" (Butterfield and Salazar, 2004). Furthermore, the National Research Council (2006) has suggested that "Most doctors are notoriously ignorant about environmental exposures and health issues." An additional challenge is that patients "often receive exposure information that is educationally or linguistically inappropriate for them" (Butterfield and Salazar, 2004).

Physicians may play a critical role in helping to advise, inform, and interpret biomonitoring data for the lay public, in addition to their role in the health and regulatory communities. Further, they may serve to provide medical evaluation, treatment, and screening efforts that may in some cases be appropriate for individuals in exposure ranges of high public health priority.

Physicians come to the table with knowledge of diseases and disease etiologies, considerable experience with multi-factorial disease, and at least a basic understanding of dose–response as related to therapeutic interventions. However, unless specifically experienced in environmental or occupational medicine, they may have limited knowledge in this area. Further, unless serving in a regulatory capacity, most physicians have a very limited knowledge of risk assessment and regulatory processes—often at a lay public level of understanding. Physicians inexperienced in this area will have a corresponding lack of experience communicating with patients on environmental issues.

Like other professionals, physicians desire to appear knowledgeable and wish to meet patient expectations. This has become a particular challenge in the era of Internet information, as patients may arrive with a considerable body of knowledge (correct or otherwise), and physicians may find themselves at a loss for immediate response. It is important, when possible, to provide information to the medical community in advance of their likely patient encounters in the face of an ongoing biomonitoring effort. For example, BE derivation documents should be accompanied by a short (2-page) summary of information relevant to the BE derivation and applications. Physician training should include the recognition that there are many different chemicals in the environment, and that even experts in environmental medicine must often undertake compound-specific research to address patient needs. Physicians without the requisite training regarding environmental chemicals and biomonitoring can turn to environmental medicine and occupational medicine clinics or university departments for advice and guidance.

7.1. General biomonitoring background information for physicians

As noted previously, the BE is not intended to be used for comparison with individual biomonitoring data. However, situations may arise in which a patient obtains data on levels of a chemical or chemicals in their body and brings these data to their health care provider, requesting interpretive information. While it is impractical to incorporate all of the details of a complete physician communication effort into this document, a number of important points are given here that could be conveyed to physicians as part of a biomonitoring education effort:

- Physicians order diagnostic tests with the expectation that the results will be relevant to assessing or diagnosing the health status of the patient. Such tests, by design, provide information on parameters in a patient with clinically relevant ranges. When such test results are outside of the "normal" range, they are generally presumed to be associated with the presence of, or increased risk of, some type of illness, disorder, or pathology. However, with few exceptions, biomonitoring data are obtained independent of an effort to diagnose or evaluate disease, and lacking a known physiologically relevant range, the levels of detection are generally set by the limits of laboratory technology or by the range of existing marker concentrations—neither of which necessarily relate to any clinical endpoint. Even with tests for which a general population range is determined statistically (usually the range of values encompassing 95% of the population), it does not necessarily follow that a value in excess of this range is associated with any clinical outcome, although it may represent an unusual exposure situation requiring further investigation. Finally, chemical risk assessments are often based on subtle physiological changes observed in animal studies (e.g., increased kidney weight) as early indicators of toxic response.

Table 2
Example sources for additional chemical-specific information

Source	Reference	Comment
ATSDR (ToxFAQs™)	http://www.atsdr.cdc.gov/toxfaq.html	Many available in Spanish
EPA Toxicity and Exposure Assessment for Children's Health (TEACH)	http://www.epa.gov/teach/	
Hazardous Substances Databank	http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB	
EPA RED documents	http://www.epa.gov/pesticides/reregistration/status.htm	Pesticide information
EXTOXNET	http://extoxnet.orst.edu/	Pesticide information
ATSDR website "Case Studies in Environmental Medicine"[a]	http://www.atsdr.cdc.gov/HEC/CSEM/csem.html	
ATSDR Case Studies in Pediatric Environmental Health	http://www.atsdr.cdc.gov/HEC/CSEM/pediatric/goals_objectives.html	Mercury information
California's Occupational Safety and Health Administration		Cohen et al., 2006
National Institute of Environmental Health Sciences	http://www.niehs.nih.gov/health/topics/agents/index.cfm	
International Programme on Chemical Safety Concise International Chemical Assessment Documents	http://www.who.int/ipcs/publications/cicad/cicads_alphabetical/en/index.html	
Nongovernmental organization sites		
Industry sites		

[a] Includes arsenic, asbestos, benzene, chromium, lead, nitrate/nitrite, polychlorinated biphenyls (PCBs), toluene, and trichloroethylene.

In such cases, it may be impossible to interpret an exceedance in terms of any disease process or outcome relevant to the patient. It may not be possible to monitor such endpoints in patients and furthermore the same specific endpoint may not be the earliest observable endpoint in humans.

- The detection of a chemical in the body does not imply that a disease state or other adverse outcome necessarily has occurred or will occur. Individuals are exposed to many different chemicals, and the ability to detect them is related to advances in analytical technology, not necessarily clinical relevance. In general, extensive additional information is necessary to establish that a disease state is present, that other causes have been excluded, that dose and timing are sufficient for the detected chemical to induce the disease, that the relationship is biologically plausible, and that a disease outcome, if present, is therefore reasonably likely to be related to the detected biomarker. In most instances, the multifactorial nature of disease causation and the limits of biomonitoring make causal attribution impossible in the individual case, and even within a population. Because EPA incorporates uncertainty factors when establishing recommended exposure limits, "simple exceedance of an exposure guidance value (e.g., RfD), or the corresponding BE, does not necessarily imply that an exposure level associated with adverse effects has been experienced" (Hays et al., 2007). However, if a biomarker concentration approaches or exceeds those associated with the human equivalent POD underlying the exposure guidance value, there is a greater concern for an adverse health effect.
- The results of a biomonitoring test must be carefully considered as to their relevance, based on toxicokinetic and other considerations. A single value for a compound with a very long half-life, or a marker reflective of chronic exposure, may be interpretable in the context of a chronic exposure BE recommendation. However, a single value for a biomarker which fluctuates significantly relative to the time frame of the BE is not likely to be reflective of long-term exposure (as is also true for monitoring of environmental media). This is particularly true for lifetime-based BEs, but may be equally true even for acute exposure BEs if the half-life of the biomarker is short. When a single or limited set of laboratory determinations does not allow for appropriate determination of exposure over the time frame relevant to the BE, it is not appropriate to attempt to interpret the result. Instead, it may be necessary to either obtain more data or to rely only upon data on population averages.
- When levels vary or fluctuate, patients often over-interpret such values to reflect trends. Physicians should avoid this error—a rise or fall in many cases is simply fluctuation unless some change has occurred in the underlying exposure. Identification of a true trend would require multiple samplings over an extended period of time.
- Biomarker values can establish the presence of a chemical (or metabolite, etc.) in the body, but cannot determine the source of the exposure. If this can be determined at all, it would require ancillary information to establish one or more sources and exclude others.
- Biomarkers of long-term exposure similarly cannot distinguish the actual time of exposure (again, similar to one-time monitoring of environmental media). Even for materials with a known excretion pattern, the laboratory value cannot distinguish a distant higher exposure from a more recent lower exposure. Biomarkers of more acute exposure, which reflect relatively rapid decay in biomarker levels, can be used to ascertain that exposure has occurred within the time frame of the biomarker, but cannot distinguish details of exposure pattern within that time frame (unless multiple samples are obtained) and will of course fail to reflect any exposure earlier than the time frame for which the assay is relevant.
- An ideal biomarker would be closely related to environmental exposure and would also be closely related, both statistically and biologically, to the critical internal dose metric. However, such a marker may not be available for all chemicals. For example, if a small fraction of a compound undergoes highly variable metabolism to a new compound responsible for the adverse effect of interest, the parent compound levels may relate very well to exposure, but correlate poorly with outcome, while the metabolite level will correlate well with outcome, but is a poor index of exposure. Neither metric is intrinsically superior, and the choice of metric (if one cannot measure both for cost, technical, or other reasons) will depend upon the purpose to which the value will be put. If one wished to determine levels of environmental exposure based upon biomonitoring, a close link to the exposure is needed. If, however, one wished to perform a pharmacokinetic/pharmacodynamic-based risk assessment, a marker closely related to the adverse effect is essential, even if it is a poor metric of exposure. It is incumbent upon the health care provider to understand the nature of the biomarker used, and whether it is a reliable measure of exposure, risk, or both.
- In some instances, biomarker concentrations may be highly dependent on route of exposure. If, for example, a compound undergoes extensive first-pass hepatic metabolism, the quantity of chemical delivered orally (food and water) may produce a very different biomarker concentration than the same material delivered via inhalation. It is incumbent on the developers of the communication document for a BE to furnish the health care provider with an understanding of the exposure route assumptions, if any, relevant to the BE value determination and to consider whether the BE value or range is applicable if such assumptions have been violated.

7.2. Talking to patients about BEs and biomonitoring

There are few clinical indications for ordering biomonitoring analyses for patients in the general population in the absence of information suggesting a toxic exposure. However, patients may come to physicians with biomonitoring data that they have obtained independently. The following should be considered by the physician in assisting patients in interpretation of such biomonitoring data.

(1) *Consideration of why the data were obtained by the patient.* Does the patient have a suspicion regarding the air or water at their place of residence due to odors, tastes, or a nearby facility? Is there an occupational exposure about which the patient is concerned? Such information will provide important context in evaluation of the biomonitoring data and may lead the physician to refer the patient to an occupational medicine specialist or to a local or state public health agency for additional information.

(2) *Consideration of the concentrations measured in the context of available data for the general population.* As discussed above, CDC is compiling significant databases of biomonitoring data that provide information on the concentrations of many chemicals in the general US population (www.cdc.gov/nceh). Such information is relevant for the interpretation of individual biomonitoring data. For example, if biomarker concentrations in a patient are substantially elevated over those generally found in the general population, further evaluation and investigation (beginning with a repeated measurement at an accredited and reputable laboratory) may be appropriate if those values also exceed the "low" priority BE range, perhaps in conjunction with local or state public health agencies or in conjunction with an occupational physician.

As discussed above, BE values in general are appropriate for screening of population-based biomonitoring data, but not for assessment of measured concentrations in individuals or for diagnosis of any condition. With that caveat in mind, physicians may find BE values useful in assisting patients with interpretation of biomonitoring data that the individual obtains independently or with concerns about media reports of biomonitoring results. Detailed patient guidance for particular chemicals must, by definition, be chemical-specific and is beyond the scope of this document. Nonetheless, a number of important generalizations can be made regarding advice which is likely to be appropriate for individuals or groups with biomonitored level of chemicals at low, medium, or high priority levels.

7.2.1. Low priority

Individuals with levels in this range have biomarker concentrations consistent with exposures at or below existing exposure guidance values. For these individuals, risk attributable to the exposure is negligible to zero (i.e., for threshold effects they are far below threshold), and specific advice regarding the exposure itself or regarding risk mitigation related to the exposure is not warranted. The primary role of the health care provider is to provide context and reassurance.

7.2.2. Medium priority

Individuals in this category have biomonitoring levels higher than those in the low priority category, but are generally below levels that are expected to be associated with adverse effects in humans. For such individuals, two types of advice may be appropriate. First, they might be provided with chemical-specific, practical advice regarding actions they may take in order to reduce exposure, if such information is available and the actions are reasonable. It is not clear that such action is necessarily warranted or beneficial; nonetheless, this may afford the individual a modicum of choice and an opportunity for control of exposure. Second, if there are multi-factorial health endpoints of concern with a particular chemical, the patient might be advised as to lifestyle or other changes that might mitigate risk. For example, if cardiovascular disease is an endpoint of concern for a particular compound, it may be helpful to point out that via exercise, addressing cholesterol issues if necessary, and managing blood pressure, they may compensate for some small degree of risk attributable to chemical exposure.

7.2.3. High priority

In this category, it is essential to properly advise the patient as to what, precisely, a "high priority" for risk assessment follow-up means in the context of a particular chemical and the likelihood that effects will occur in humans. This is especially important with cancer endpoints, as a high public health priority indicates only that a theoretical 1:10,000 cancer risk has been exceeded. The overall risk of cancer mortality (not necessarily specific cancers of concern for the chemical at hand) is influenced by many different exposures and risk factors for cancer overall can be mitigated to a far greater degree by recognized health practices such as colonoscopy. Within this category, there are again three types of advice that might be given. First, immediate re-testing should be conducted to determine whether the measurement represents a repeatable level. Second, specific instruction for reduction in exposure may be appropriate if this can be achieved with practical interventions. The utility and practicality of this type of intervention is dependent upon routes and sources of exposure and by many other factors, and must be determined on a case-by-case basis. Third, there may be utility in screening for particular medical conditions either on a one-time or ongoing basis so that early intervention can be provided. However, such screening is probably warranted only for compounds that are not highly transient in the human body, when adverse human health effects have been clearly linked to the chemical, and when appropriate screening tests exist. For example, elevated cadmium biomarker concentrations might suggest screening tests for kidney function, because elevated cadmium exposure is linked with such responses in humans and cadmium is relatively persistent in the body. However, a one-time measurement of a blood chloroform concentration in the "high priority" range is unlikely to be informative either of long-term exposure or of a specific health outcome that could be effectively evaluated through the use of screening tests, since chloroform is highly transient in blood and the BE value is based on subtle liver toxicity in a dog study.

8. Conclusions

While the risk communication literature specific to biomonitoring is sparse, many of the concepts developed for traditional risk assessments apply. These include transparency, discussions of confidence and uncertainty, and materials that are readily comprehensible to a wide range of audiences. Communication of BEs will require outreach, education, and development of communication materials specific to several audiences including the lay public and health care providers. These guidelines should be used to help shape how these communications materials are developed.

Disclaimer

This work was reviewed by EPA and approved for publication, but does not necessarily reflect official Agency policy. Mention of trade names or commercial products does not constitute endorsement or recommendation by EPA for use.

Conflict of interest disclosure statement

The authors declare that they have no conflicts of interest.

Acknowledgments

The BE pilot project was supported by the following organizations: the U.S. Environmental Protection Agency, Health Canada, the American Chemistry Council, Crop Life America, Responsible Industry for a Sound Environment, the Soap and Detergent Association, and the American Petroleum Institute. In addition, the authors thank the Steering Committee: John H. Duffus, Monty Eberhart, Bruce Fowler (advisor), George Johnson, Mike Kaplan, Bette Meek, David Moir, David J. Miller, Larry L. Needham, (advisor), and Babasaheb Sonawane.

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