

Chapter 14: Biomonitoring

13.2.7 Administrative requirements for the use of Monte Carlo methods

The range of total acceptable exposures and risk will need to be defined on a situation-specific basis after consultation with stakeholders. Depending on how it is applied, the Monte Carlo method may lose much of the conservatism usually inherent in point estimates.

Regulatory authorities in Australia are likely to require the following of assessments using Monte Carlo methods:

- meeting the 14 principles of good practice detailed above
- providing adequate information to the authority to enable review of the assessment – this may require providing the software (and underlying formulae) and data
- a demonstration of the relevance of the exposure data to the site (data from other countries or cultural backgrounds may not be relevant)
- an explanation of the data and method that will be able to be understood by the relevant community (usually the most difficult aspect)
- using data that accounts for age and gender differences and takes into account susceptible populations.

On a large site divided into housing lots, the results for specific housing lots that may be affected by atypically elevated concentrations should not be obscured by averaging or Monte Carlo techniques applied to the entire site. In many instances, Monte Carlo methods will only be relevant to large sites or sites where direct measurements of exposure are not practicable. Before the use of Monte Carlo is commenced for any situation being assessed, the assessor should check with the relevant regulator or government authority about whether such use is

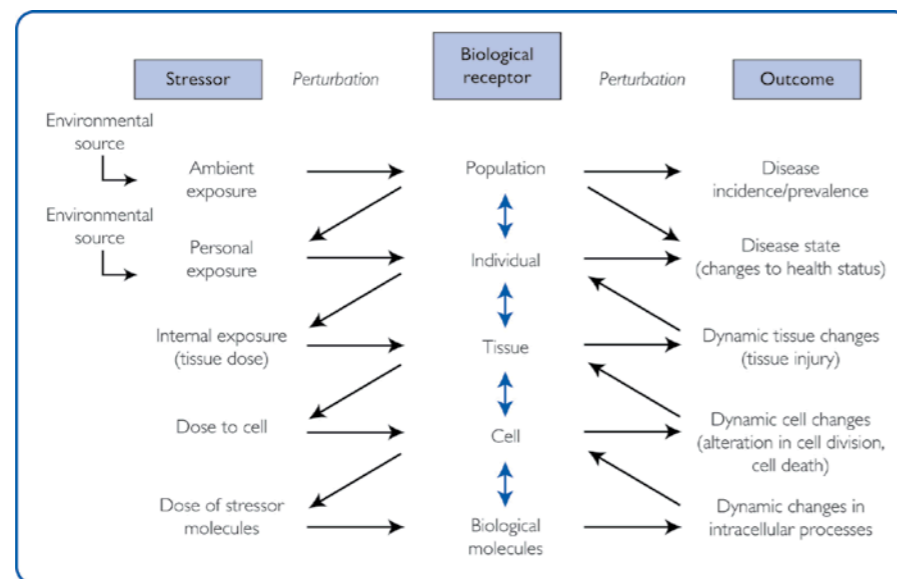
considered appropriate. Most regulators are likely to discourage the use of this technique, in the main due to the difficulty in explaining it to the affected community and the lack of robust probability distributions for parameters of interest.

Since the outputs of Monte Carlo analyses are distributions of risk estimates and other parameters, some guidance will be needed on where to define the cut-offs for risk assessment purposes. This is likely to fall into the realm of policy settings to be determined by government authorities. As noted above, UK guidance on establishing guidance values (GVs) for contaminated land exposure assessment (CLEA) is already showing signs of ‘back-peddalling’ on the use of probabilistic approaches, such as Monte Carlo analysis.

13.3 INTEGRATION OF EXPOSURE WITH EHRA OUTCOMES

As part of the NRC review of toxicity testing developments for the 21st century (NRC 2007), Hubal (2009) commented on the role that developments in exposure sciences must play in developing new paradigms of EHRA. In particular, the development of models that could be used to define exposures at levels ranging from environmental to cellular (target tissue doses) would be important for integrating animal testing data with the new generation of scientific tools using genetic, *in vitro* and *in silico* techniques for profiling chemical toxicity and individual susceptibility. A depiction of the interrelationships in such a model is shown in Figure 31.

Figure 31: Proposals for integrating exposure with outcomes of EHRA



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14.1 BIOMARKERS

The term ‘biomarker’ has been used in recent times to describe the measurements used in biological monitoring. The term refers broadly to almost any measurement reflecting an interaction between a biological system and an environmental agent, which may be chemical, physical or biological (WHO 1993b, 2001). Three classes of biomarker are identified by WHO (2001):

- **Biomarker of exposure:** an exogenous substance or its metabolite or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured in a compartment within an organism
- **Biomarker of effect:** a measurable biochemical, physiological, behavioural or other alteration within an organism that, depending upon the magnitude, can be recognised as associated with an established or possible health impairment or disease
- **Biomarker of susceptibility:** an indicator of an inherent or acquired ability of an organism to respond to the challenge of exposure to a specific xenobiotic substance.

For many environmental pollutants, the flow of events between exposure and health effects is not well understood. Biomarkers help address this problem by improving the sensitivity, specificity and predictive value of detection and quantification of adverse effects at low dose and early exposure (Fowle 1989; Fowle & Sexton 1992; NRC 1992). Sensitive sub-populations can be better pinpointed by biomarkers that measure increased absorption rate or a more severe biological response to a given environmental exposure (Fowle & Sexton 1992; Hemminki 1992; Lauwerys 1984; NRC 1992).

14.1.1 Why biomonitoring?

Biological monitoring is a measuring procedure whereby validated indicators of the uptake of contaminants, or their metabolites, and people’s individual responses are determined and interpreted. Whereas environmental monitoring measures the composition of the external environment around a person, biological monitoring measures the amount of contaminant absorbed into the body.

Biological monitoring may be direct (e.g. the measurement of lead in blood) or indirect (e.g. the measurement of the breakdown product of nicotine and cotinine in urine). Biological monitoring may measure a biological effect, such as enzyme depression, or a physiological effect, such as tremor. The monitoring may be used to identify whether exposure has occurred at all, or the amount of exposure.

If biological monitoring is practicable, it will be more valuable than environmental monitoring in determining the level of risk from an environment, as it will measure whether exposure is occurring and the level of exposure (Langley 1991b). It can be useful in identifying highly exposed individuals or sub-populations.

The prerequisites for biological monitoring (Aitio et al. 1988) are as follows:

- The substance and/or metabolites need to be present in a tissue, body fluid or excretion suitable for sampling.
- Valid, accurate and practicable methods of sampling and analysis are available.
- The results of testing can be interpreted in a meaningful way for individuals and groups.
- An appropriate management strategy has been devised for sampling, analysis, collation of results, interpretation of results, and follow-up.

The use of biomonitoring data in environmental risk assessment was reviewed at an international biomonitoring workshop in 2004, at which six case studies illustrated the applications and utilities of this technique in environmental health surveillance (Albertini et al. 2006).

Further reviews of the application of biomonitoring to risk assessment have been presented by Doerr (2007), Angerer et al. (2006) and Swenberg et al. (2008).

One of the difficulties traditionally associated with the interpretation of biomonitoring data has been the absence of validated values representing specific levels of exposure or linking to levels of effect. This issue was addressed by an international panel convened to develop a series of biomonitoring equivalents (BEs) (Hays et al. 2008). This panel established some guidelines on what should be taken into consideration in establishing BEs, including consideration of toxicokinetics and internal dose metrics, integration of human and animal data, and the choice of suitable tissues and analytes. This expert group devised a series of flow charts (Figure 32) illustrating how animal and human data could be integrated, depending on the extent to which pharmacokinetic data in either species are well understood.

Biological monitoring should not be commenced before:

- the objective of the biological monitoring is clearly defined
- a reference range of results that is applicable for the population under study is established – this is often not available (or a control group is not available to establish a reference range); the relationship of body burden levels and exposure (or risk) are unavailable for many substances
- consideration has been given as to how results are to be managed – significant anxiety may be caused by factors such as delays in providing information and

an inability to explain the meaning of measured levels or to take action if the person is distressed by elevated levels, perceives that any measure of exposure is unsatisfactory or equates exposure to a health effect may cause

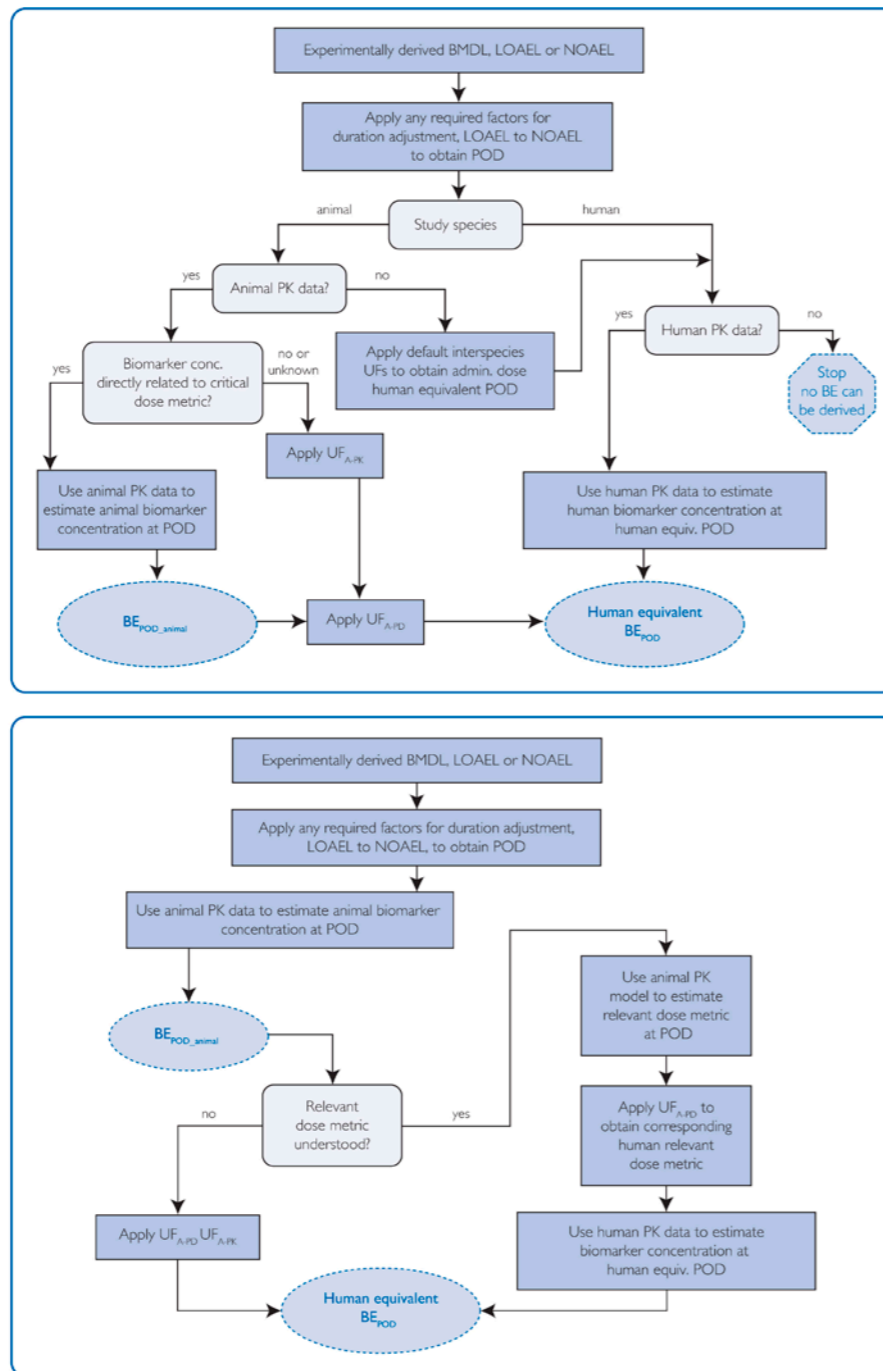
- the correct timing of sampling has been established – correct timing is critical for substances with short biological half-lives or a particular exposure is of concern
- a process has been established to enable consistent analysis and epidemiological appraisal of results
- the ethical and confidentiality aspects of collecting, maintaining and distributing information and results are fully considered
- a centralised collection point for results has been established to enable consistent analysis and epidemiological appraisal of results.

The reasons for biological monitoring include to:

- detect whether exposure has occurred
- quantitate exposure
- enable the risk of health effects to be assessed
- determine changes in exposure over time or to assess the effects of interventions such as health education or soil remediation (if serial measurements are done) or to determine exposure pathways and their relative importance, such as occupational versus domestic exposures ingestion of soil versus inhalation of dust (if combined with environmental monitoring)
- determine segments of the population at greatest risk, such as particular age groups or those living in particular locations or circumstances (if conducted as part of widespread population studies).

Results should always be available to participants in biological monitoring combined with a meaningful explanation of the results.

Figure 32: Flow charts for deriving BEs for chemicals pharmacokinetic data are available for both animals and humans along with toxicity data from both species (a) or only from animals (b)



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Several aspects must be considered:

- A good biological monitoring test result may not correlate well with environmental levels (mainly because of human factors).
- The number of substances that can be used reliably for biological monitoring is still small.
- Irritative, locally or rapidly acting substances are usually unsuitable as the systemic absorption may be minimal and/or irrelevant to the level of local reaction (e.g. SO₂, ammonia, direct skin exposure to PAHs causing skin cancer).
- The substance must be in some tissue or fluid suitable for sampling.
- Accurate, valid and practical measuring methods must be available.
- The result should be interpretable in terms of health risk.
- The results are likely to have more value for a group than an individual.

The advantages of biological monitoring are:

- the exposed person is his or her own sampler, so that many 'samples' are taken over a 100 per cent sampling time
- the evaluation of absorption can be performed over a prolonged period of time
- the sampling takes into account all the person's movements within and outside the domestic environment, and accidental and illicit exposures
- the amount absorbed by various routes is considered (not only via the respiratory route as is presumed by monitoring of atmospheric concentrations), for example, oral absorption of lead compounds or in situations where skin absorption is important
- it may show exposures where past environmental monitoring is unavailable, for example, PCBs where

the persistence of the substances acts as a long-term marker of exposure

- it enables an individualised assessment taking into consideration age, sex, personal hygiene, biotransformation and elimination.

The disadvantages and difficulties are:

- the relatively wide range of individual response to a substance and the wide 'normal' range that may have to be considered
- the lack of simple specific analytical methods of sufficient sensitivity (in many instances)
- difficulties in sample collection, for example, 24-hour urine collections
- unsuspected exposure can be shown but the source cannot be pinpointed – this will require detailed environmental monitoring
- inferences caused by occupational exposure, for example, lead exposure in battery makers and radiator repairers
- there must be a clear relationship (if only on a group basis) between the chosen biological indicator and the health risks of the substance.

Some analyses require specialised laboratories:

- There may be laboratory inaccuracy.
- If the substance has a short biological half-life, rapidly changing concentrations in body samples complicate interpretation and the body burden may be under-predicted or over-predicted.

- Transient periods of high exposure may not be detected.

Having decided a test for a substance is appropriate, further questions arise:

- Which compound should be measured? The substance, a metabolite or both?
- Which biological fluid or tissue is to be sampled?
- In relation to what period of exposure?
- How frequently should sampling be done?

14.2 CHOICE OF TISSUE OR FLUID

The biological samples used for monitoring may be (Fao & Allesio 1983):

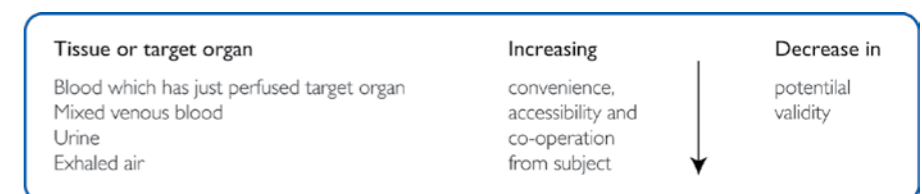
- blood, urine, fat, saliva, sweat, faeces
- hair, nails, teeth
- expired air.

Physiological response to the exposure may be estimated by determining changes in:

- the amount of a critical biochemical constituent
- the activity of a specific enzyme
- a particular physiological function such as lung function.

Choice of biological tissue or fluid for a hypothetical substance is represented in Figure 33.

Figure 33: Choice of biological tissue or fluid for a hypothetical substance



14.2.1 Blood

Depending on the biological half-life of a substance, blood analysis may provide an indication of exposure from recent hours to several years. Levels are often transient if the half-life is not prolonged. The process of blood-taking may be unacceptable for some people, including children.

When the volume of distribution is high, concentrations in blood are often too low to be measured. Samples may require careful procedures, such as plasma separation and freezing. Substances measurable in the plasma may not be responsible for the toxic effect which, instead, arises from a metabolite.

14.2.2 Urine

Only a limited number of substances can be measured in urine because of degradation of the parent substance to breakdown products. Urine samples, in general, provide a more integrated assessment of exposure than blood for periods of recent hours or days. Twenty-four-hour sample collections may be more appropriate than spot samples but many people find these collections onerous. First morning urine samples have been found to be effective for representing 24 hour urine samples. (Froese et al. 2002, Bader et al. 2004, Zhang et al. 2009). Urine samples require rapid processing and cooling.

14.2.3 Hair and toenails

Hair and toenails can provide an integrated measure of exposure over a more prolonged period than blood or urine. They are only useful for chemicals known to accumulate in those tissues and they are inappropriate tissues for biological monitoring on or near contaminated environments. External contamination of the hair cannot be adequately removed during sample preparation and an

accurate measure of excretion via hair cannot be performed. Hair analysis may be useful for assessing intake from purely dietary sources when there is no general environmental contamination.

14.2.4 Breast milk

Collecting breast milk is usually easy and acceptable to nursing mothers. Breast milk provides an integrated exposure for very lipid soluble compounds for time periods related to the biological half-life of the substance. Breast milk measurements of PCBs, organochlorine pesticides and dioxins have been used for exposure assessments. The concentrations must be standardised for fat content and may vary according to the period since breastfeeding first commenced.

14.2.5 Expired air

Expired air is used to determine exposures to ethanol (e.g. traffic breathalyser) and some solvents and can be correlated to blood concentrations based on the Henry's Law constant of the substance being measured.

14.3 CHOICE OF A TEST

Optimally, a biological monitoring test would give a result that reflected the exposure, the concentration of the substance in the target organ and the risks of adverse effects (Friberg 1985). Few tests are available that approach this ideal (Langley 1991a). Furthermore, what is of most importance is 'not so much the choice of medical test as much as the way the testing program is organised, the way the results are evaluated and communicated, and the way abnormalities are pursued' (Silverstein 1990).

In Australia, exposures from contaminated soil for example will be generally low, creating problems in accurate

measurement at low levels and the possibility of results being overwhelmingly influenced by other sources of exposure (e.g. the influence of cadmium in food, tobacco smoke and the occupational environment will generally be far greater than the influence of cadmium contamination of soils).

For many substances, biological monitoring is impracticable because:

- analytical techniques are not available or are inaccurate at low levels or in the tissues or fluids being tested
- insufficient information is available on inter- and intra-individual toxicokinetics and thresholds of health effects to enable risk assessment of results
- insufficient epidemiological studies have been done to determine normal ranges.

The correct choice of biological tissue or fluid is important. Rarely can the concentration in the critical organ be measured and compared with concentrations that give rise to effects.

Attempts have been made for such direct measurement, for example, *in vivo* neutron activation analysis can directly measure renal or liver concentrations of cadmium but requires specialised equipment and provides a dose of ionising radiation to the subject.

For biological monitoring based on urine analysis, simple measurements of concentrations can provide sufficient information on exposure, but in many instances, measurements of elimination rates provide more precise information. Urinary concentrations related to creatinine, or urinary flow rates may provide more accurate information, but creatinine has not been found to be worthwhile in some evaluations (Zhang et al. 2009)

Substances for which biological monitoring of general environmental exposures is practicable are detailed in Table 22.

Table 22: Substances likely to be suitable for biological monitoring

Substance	Fluid or tissue	Comments
Lead	Blood	Urinary lead does not accurately reflect either recent exposures or burden. Substantial data available on level of risk for particular blood lead ranges. Numerous Australian studies provide comparison data. Levels of concern available for both general population and groups (for example, children).
Cadmium	Urine or blood	Urinary levels tend to reflect body burden; blood levels reflect recent exposures. Urinary levels need to be adjusted for changes in urinary flow rates (results often given as µg Cd/g creatinine or µg Cd/24 hour). Laboratory inaccuracy has always been a major problem, particularly prior to 1980. Limited Australian studies to provide comparison data. Most international studies have concentrated on occupational exposures. Very limited data on children, especially for those less than 5 years. WHO (cited in Mueller et al. 1989) has set levels of concern. General diet and smoking will tend to have a major influence on levels.
Arsenic	Urine	Short biological half-life; study must be done during exposure (or at most within 1–2 days afterwards). Considerable interference from organic sources of arsenic (for example, seafood). Dietary sources from the environment not under study need to be excluded and testing for inorganic arsenic undertaken. Limited comparison data and no set levels of concern.
Mercury	Blood or urine	At equilibrium, the concentration of mercury in the blood reflects daily intake and is probably the best indicator of exposure. Total measured mercury will also include methyl mercury from fish, so that a fractionated analysis of mercury salts and alkylated mercury compounds may be required (Aitio et al. 1988). Methyl mercury exposure will not affect urinary mercury levels although urinary levels show significant diurnal variation. Some international comparison data is available.
Polychlorinated biphenyls (PCBs)	Blood, adipose tissue (fat), breast milk	Long biological half-life so that historical exposures (i.e. body burden) may be able to be monitored. Different PCBs will have different behaviours in the body and different biological half-lives. Some comparison data is available. It is difficult to obtain adipose tissue samples and blood sampling is usually preferred.
Organochlorine (OC) pesticides	Blood, adipose tissue (fat), breast milk	Long biological half-life so that body burden can be assessed. Some comparison data is available, especially for blood. It is difficult to obtain adipose tissue samples and blood sampling is usually preferred.
Organophosphonate (OP) pesticides	Blood	Plasma butyrylcholinesterase or erythrocyte acetylcholinesterase (AChE) may be monitored to assess recent exposures. Depressed AChE activity may better reflect a level where a physiological response may occur. Wide range of values reflect 'normality', so individual baseline values assist interpretation.

Adapted from: Langley (1991b).

There are a range of other substances for which biological monitoring may be available – the tests should be assessed and used on their individual merits for a particular situation. Biological monitoring has been applied to a range of situations: tobacco use (polycyclic aromatic hydrocarbons, aromatic amines and specific nitrosamines), dietary exposures (e.g. aflatoxins, N-nitrosamines, heterocyclic amines), medicinal exposures (e.g. cisplatin, alkylating agents, 8-methoxypsoralen, ultraviolet photoproducts), trichloroacetic acid for chlorinated disinfection by-products in drinking water and occupational exposures (e.g. benzene, ethylene

oxide, styrene oxide, vinyl chloride, aromatic amines, polycyclic aromatic hydrocarbons).

Besides the pesticides mentioned in Table 22 specialised tests may be available from some laboratories for pesticides such as glyphosate.

Most organic contaminants are not amenable to biological monitoring in general environmental situations because of the low levels of exposure and the lack of comparison data compared with occupational situations. Specialised studies may make biological monitoring for some inorganic

substances practicable (e.g. manganese, radioactive isotopes).

A good knowledge of the toxicokinetics of a substance is required for the correct choice of method and interpretation of results. The duration of persistence of the agent will be important as is the volume of distribution (e.g. many very lipid soluble substances with a very high volume of distribution have such low blood levels that they can't be measured in blood but can be identified in breast milk). Individual results may be distorted if there is not constant exposure or equilibrium within the body (Langley et al. 1998).

Cytogenetic testing may occasionally be of value but is often difficult to interpret as only small numbers of cells are usually examined so that there is the potential for considerable confidence limits around the results and because there can rarely be a link made to specific agent (one exception is aflatoxin). Tests such as sister chromatid exchange and micronuclei are non-specific tests. There are problems with confounding, distinguishing recent from historical exposures, quantifying exposures and dealing with a finite background incidence of chromosomal abnormalities.

Under the National Model Regulations for the Control of Workplace Hazardous Substances (adopted by the states and territories), health surveillance is required for specified substances. Biological monitoring methods developed for some of these methods are detailed in the NOHSC series *Guidelines for health surveillance*.

14.3.1 Accuracy

Laboratory accuracy has always been a problem because of the low levels of the substance being tested and analytical problems, including those caused by the biological matrix and the risk of contamination. Gross analytical errors have occurred in the measurement of blood lead, and blood and urinary cadmium (Elinder 1985; Vahter 1982). Friberg (1985) reports that 'normal' values for aluminium in plasma and serum 'decreased' during the 10 years 1975–1985 'from several 100 µg/l to a few micrograms the only reason for this being improved analytical technique'. Aitio et al. (1988) provide a further example for the values regarded as normal average serum chromium concentrations for occupationally unexposed men. Papers published between 1956 and 1984 showed a decrease in 'normal' values from 3,600 mmol/l to 2.1 mmol/l; Aitio et al. (1988) attributed the decline to better techniques that avoided chromium contamination.

Aberrant results may need to be repeated before being accepted as 'high'. Choice of a laboratory should be governed by the presence of stringent internal and external quality control measures.

Contamination during sample collection is likely to be a significant problem unless specialised collection protocols are rigorously followed. One example is skin contamination affecting blood samples (especially capillary prick samples).

Twenty-four-hour urinary collections are likely to be impracticable during general community studies and present significant risks for contamination during collection. Inappropriate sample containers can be a significant source of inaccuracy from leaching or contamination. Without appropriate selection of containers and storage conditions, some heavy metals will adsorb to some container materials giving falsely low readings. A single laboratory is preferred for studies to minimise problems arising from inter-laboratory variations and to enable a single body of data.

14.3.2 Indicator analytes

Where there are multiple contaminants uniformly distributed in the environment and with similar environmental and biological behaviour, the measurement of one contaminant (the indicator analyte) may be a surrogate measure for other contaminants. The indicator analyte may be chosen for the ease (or accuracy) of analysis or its toxicity relative to the other contaminants. For example, if lead and cadmium are uniformly present, lead may be chosen for the ease and relative accuracy of analysis as well as the availability of levels of concern and comparison data. Alternatively, lead may also be chosen because it is the predominant contaminant. In such instances, if the blood lead results are not elevated, elevated levels of cadmium would not be expected. If high blood lead results are demonstrated, cadmium levels

may need to be assessed to determine whether there may also be a significant risk from cadmium exposure.

14.4 INFLUENCES ON BIOLOGICAL MONITORING RESULTS

Factors apart from environmental contamination to be considered in interpreting biological monitoring results include (American Conference of Governmental Industrial Hygienists – ACGIH 1990):

- changes induced by strenuous physical activity
- changes induced by environmental conditions (including heat, diet and cigarette smoking)
- changes induced by water intake
- changes in physiological functions induced by pregnancy, disease or diurnal rhythms
- changes in metabolism induced by congenital variations of metabolic pathways or induced by simultaneous administration of another chemical (induction or inhibition of activity of a critical enzyme by medication or by pre-exposure or co-exposure to another chemical).

14.5 EXPOSURE AND BIOLOGICAL MONITORING RESULTS

For toxicokinetic reasons, the relationship between exposure and biological monitoring results is often not linear. For example, with air lead levels there appears to be a greater influence on the rate of change of blood lead levels with changes at lower air lead levels than moderate air lead levels (Friberg 1985).

This is one of the reasons why monitoring blood lead is a more common approach to lead EHRA and risk management (see Section 14.8).

The physico-chemical properties of the contaminant will have a crucial influence on the bioavailability of the contaminant and hence biological monitoring results. A further crucial influence will be the characteristics of the exposed population (e.g. age, behaviours).

The physico-chemical properties of the contaminant and the characteristics of the exposed population usually will be more important predictors of biological monitoring results than a statement of the concentration of the contaminant in the soil.

14.6 ABNORMAL RESULTS

If the accuracy of an abnormal result can be confirmed (this may require repeat testing), the health risks should be assessed and medical assessment may be required. The reason for the high result should be determined, that is, the relevant exposure pathways.

There should be a clear understanding of the basis of how the 'normal' range was derived. (e.g. What populations were studied? Were they comparable to this population?). If the range is derived from normally distributed results in a general population survey and the range is two standard deviations each side of the mean, 5 per cent of this population will have 'abnormal' results. If results are being compared with health standards, how were these standards set? Do the standards incorporate a safety factor and, if so, how large is that safety factor?

14.7 HEALTH MONITORING

Health monitoring is the organised medical assessment of individuals and groups of people. The medical assessment will consist of history taking and clinical examination, and, where indicated, particular tests (e.g. lung function testing where there is a concern about the effect of air pollutant). The epidemiological aspects of health surveys are covered in Chapter 10.

In Australia, health effects are likely to be found in only a limited number of situations of environmental contamination. Subtle effects may only be able to be determined on a group basis rather than on an individual basis (e.g. subtle neurodevelopmental effects determined by sophisticated testing in groups of children with different lead exposures). Similar problems of causation relating to individual findings rather than group findings arise if the putative effects are common in the general population (e.g. headache or fatigue). Health effects are rarely as specific to an exposure as chloracne with PCB or dioxin exposure.

Health monitoring for specific health effects is warranted where environmental or biological monitoring has indicated a significant risk of effects (e.g. specific tests of renal function if urinary cadmium levels above the levels of concern are detected in biological monitoring).

When health monitoring is done, it should rarely be done in isolation from environmental and/or biological monitoring. Clearly defined health effects should be sought with specific case-definition criteria. Records of other symptoms and clinical findings should also be kept to enable epidemiological assessment of other potential health effects (Langley 1991a).

Before health monitoring is undertaken, the following issues should be considered:

- how to ensure all parties involved do not have unreasonable expectations about the ability of health monitoring to resolve issues of causation or to detect any subtle effect (the studies rarely provide such evidence because of their size and biases)
- confidentiality of information
- how and when information will be made available to participants (the information must be released to participants)
- access to information (by whom and through what mechanisms)
- interpretation of information (at an individual and group level and on what evidentiary basis)
- release of findings (which should be at a group rather than individual level for reasons of confidentiality if the results are made public)
- how the information will be used to address the relevant environmental health issues.

14.8 BIOMONITORING AND BLOOD LEAD

Since the absorption and retention of lead from various environmental matrices can be variable, biomonitoring (blood lead levels) has become the method of choice for data inputs into health risk assessments and for managing environmental health risks associated with lead, particularly in children.

14.8.1 Adult lead exposures

These may be estimated using the US EPA adult lead model methodology (US EPA 2003c). This model focuses on adult women and incorporates lead exposure, uptake into the body and biokinetic transfer into the blood and developing foetus.