

Environmental Health Risk Assessment

*Guidelines for assessing human
health risks from
environmental hazards*



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Objectives

This document provides a national approach to environmental health risk assessment.

Risk assessments are being undertaken for a wide variety of projects by governments and industry. Environmental health agencies need to be able to assess their content and approach against a benchmark. The document presents a general environmental health risk assessment methodology applicable to a range of environmental health hazards. The focus is on chemical hazards in the first instance but the core methodology can also be applied to physical (e.g. radiation, noise) and microbiological hazards. The core methodology is intended to be able to accommodate specialised 'modules' that will deal with issues such as physical and microbiological hazards and mixtures as they become available. The links to risk management and community consultation/risk communication will be identified.

Due to the complexity and scale of the environmental health risk assessment process a concise 'cookbook' is not practicable. Similarly, the situation-specific issues are often sufficiently complex and 'situation-specific' that a manageable and complete algorithm for decision-making cannot be drafted; the document provides a series of guidelines and checklists to assist the decision-making process. Where possible, the document is prescriptive about certain aspects of risk assessment. Having specific requirements for the content of investigations and having them presented in uniform, coherent and logically developed reports will enable more efficient, accurate, timely and transparent decision-making and a greater consistency of environmental health decision-making across Australia.

Audience

The document is primarily intended to be used by environmental health agencies reviewing risk assessments, by people preparing risk assessments for environmental health agencies and by those regulatory agencies reviewing risk assessments. It is also intended to be of assistance to a broader audience seeking information about processes of environmental risk assessment in Australia.

Risk assessors should have a basic grounding in epidemiology and toxicology.

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Summary

Risk Assessment

Intuitive risk assessment and risk management have been fundamental for human survival and evolution. Those who appreciated risk were more likely to survive and reproduce whereas those who could not were more likely to perish from environmental hazards (Thomas and Hrudey, 1997).

A specific quantitative concept of 'risk' has only been appreciated in relatively recent times. Estimates of risk based on probability only developed in the late seventeenth century.

In considering risk as either a prediction or expectation, there are various elements:

- a hazard (the source of danger);
- an uncertainty of occurrence and outcomes (expressed by probability distributions);
- possible adverse health outcomes;
- a target;
- a time frame; and
- the importance of the risk for people affected by it (Thomas and Hrudey, 1997).

Risk assessment provides a systematic approach for characterising the nature and magnitude of the risks associated with environmental health hazards. All activities, processes and products have some degree of risk. The ultimate aim of risk assessment is to provide the best possible scientific, social and practical information about the risks, so that these can be discussed more broadly and the best decisions made as to what to do about them.

Risk assessment has been used in various forms for many years in Australia although it may not always have been called 'risk assessment'.

The use of risk assessment as a tool in the decision-making process has become increasingly important over the last two decades as it has become evident that situations cannot be judged simply as either 'safe' or 'unsafe'.

Risk assessment takes into account factors relevant to the situation such as the current or proposed human activities, physico-chemical and bioavailability characteristics of chemical hazard(s), the infective doses of microbiological agents, and the opportunities for exposure to the agent.

Generic risk assessments and assessments of potential risk may be made in situations such as determining environmental standards for additives or contaminants in soil, air, water and food or to determine whether particular products such as pesticides and pharmaceuticals can be used. Situation-specific risk assessments can be undertaken where there is an actual or potential environmental hazard such as contaminated land or industrial emissions from a proposed factory and should take into account factors relevant to those particular circumstances.

Health risk assessment is intended 'to provide complete information to risk managers, specifically policymakers and regulators, so that the best possible decisions are made' (Paustenbach, 1989, p. 28). Good risk assessment is dependent upon a high degree of scientific skill and objectivity and should be distinguished from the risk management process which selects options in response to health risk assessments and which incorporates 'scientific, social, economic and political information' and which

'requires value judgements e.g. on the tolerability of risk and reasonableness of costs' (ANZECC/NHMRC 1992, p. iii). Risk assessment should provide a 'credible, objective, realistic and balanced analysis' (US EPA, 1992).

Risk assessment gathers and organises information and may enable:

- risks at a point in time (including baseline risks) and changes in risk over time to be estimated and allows judgement as to whether action is necessary;
- Health Guidance Values to be established for public health hazards;
- assessments of new or exotic risks;
- a comparison of the potential health impacts of various environmental health interventions (thus enabling cost-effectiveness estimates);
- the identification and comparison of different factors that affect the nature and magnitude of the risk;
- risk-based standards setting for regulatory exposure limits and clean-up standards;
- prioritising issues according to their levels of risks;
- questionable theories, methods and data to be challenged and addressed by providing a clearly documented and open process (Covello and Merkhofer, 1993);
- better appreciation of the tradeoffs and opportunity costs which occur when addressing one source of risk;
- consistent, transparent appraisal and recording of public health risks; and
- risk based policy making.

Risk assessment may not always provide a compelling or definitive outcome and will often be limited by the data available.

Risk assessors should appreciate that the community may see risk assessment as an excuse for polluting behaviours.

A preliminary situation-specific risk assessment can be undertaken by choosing to apply environmental health criteria, which are derived using risk assessment techniques and can be applied generically to a range of situations. Where the level of a hazard exceeds the risk-based environmental health criteria, more detailed situation-specific health risk assessment may be used to determine the nature of action required to address the risks. The action may range from informing the community to requiring large-scale remediation measures.

While this document is about environmental health risk assessment, it recognises that environmental health risk assessment is complemented by the process of ecological risk assessment.

Environmental Health Risk Assessment Methodology

There are several models of risk assessments and various definitions for the relevant terms. This document uses a model developed by and for environmental health agencies and uses a model compatible with WHO models. It is comprised of:

- issue identification;
- hazard identification;
- dose–response assessment;
- exposure assessment for the relevant population; and
- risk characterisation.

These five stages are linked and dependent on the preceding stages when they are part of a risk assessment.

Issue Identification identifies issues for which risk assessment is useful and establishes a context for the risk assessment by a process of identifying the concerns that the risk assessment needs to address. The determination of the ‘problems’ is necessary to establish a context for the risk assessment and assists the process of risk management.

Issue Identification involves determining:

- what is causing the identified problem;
- why the problem is a problem;
- how the problem was initially identified;
- what types of (adverse) health effects might be caused by the problem;
- how quickly and for what duration the problems might be experienced; and
- what the public perceptions of the hazard are (Health Canada, 1999, p. 12).

Hazard Assessment comprises Hazard Identification and Dose–response Assessment

Hazard Identification involves determining:

- what types of (adverse) health effects might be caused by the problem; and
- how quickly the problems might be experienced. (Health Canada, 1999, p. 12)

Dose–response Assessment evaluates both qualitative and quantitative toxicity information to estimate ‘the incidence of adverse effects occurring in humans at different exposure levels’. (US EPA, 1989, p. 1.6) Where available, human and animal evidence will be assessed as part of this process.

Exposure Assessment involves the determination of the frequency, magnitude, extent, duration and character of exposures to a hazard. Estimates can be made for past, present and likely future exposures. There is also the identification of exposed populations and particularly sensitive sub-populations, and potential exposure pathways. Environmental monitoring and predictive models can be used to determine the levels of exposure at particular points on the exposure pathways. The contaminant intakes from the various pathways under a range of scenarios can then be estimated (US EPA, 1989).

Given this information, Risk Characterisation details the nature and potential incidence of effects for the exposure conditions described in the exposure assessment. An integral part of this stage is to evaluate the uncertainties and assumptions in the risk assessment process. The nature and magnitude of the uncertainties should be clearly detailed so that they can be taken into account in the risk management of a situation. The uncertainties may be addressed by gathering further information, or by incorporating safety factors.

The process of risk assessment should enable consistent application of methodology to be made by the specialists undertaking the process. Expert professional judgement can be an integral part of the process. Situation-specific risk assessments should not lead to significant variations in the estimated risks of similar situations (Langley and El Saadi, 1991).

The situation-specific process is a multi-disciplinary task and requires considerable expertise. People involved in specific components of the environmental health risk assessment process should be adequately qualified and experienced and have a broad understanding of health risk assessment and management and the practical realities of environmental health practice. Professional skills that may be used include environmental health, engineering, history, chemistry, planning, statistics, occupational hygiene, occupational and public health medicine, toxicology, health science, communication, sociology, psychology, economics and epidemiology. While it is unlikely that one person will have the breadth of skill to undertake all components of the health risk assessment, there must be a single person coordinating and taking responsibility for the assessment.

In many instances, situation-specific health risk assessments may not be necessary as the nature and magnitude of the risks will be quite apparent, there may be no population at risk, or decisions on risk management may be made on other grounds. In such cases, the significant resources required for a detailed risk assessment would be better directed to risk management steps (ANZECC/NHMRC, 1992, p. 20).

The level of risk can be described either qualitatively (i.e. by putting risks into categories such as 'high', 'medium' or 'low') or quantitatively (with a numerical estimate or probability density distribution). Current risk assessment methods do not enable accurate quantitative estimates of risk for low levels of exposure to environmental hazards. Numerical estimates of risk will rarely be feasible because of limitations in toxicological and exposure data which will be reflected in the uncertainty assessment, but quantification may be possible for some components such as exposure assessment. Clearly defined qualitative categories can enable reliable and effective risk management decisions.

It should be recognised that, as a consequence of testing limitations (for example, not every square metre of a contaminated site nor every item of food in the marketplace will be tested), situation-specific health risk assessment is a screening process where there may be low rates of false negatives and false positives. 'Risk assessment is based on probabilities rather than absolutes and this should be reflected in decision-making' (*ibid*, p. 34). Uncertainty is usually caused by inadequate knowledge but can also relate to:

- parameter uncertainty (measurement errors, random errors, systematic errors);
- multiple uncertainty (errors arising from the incorrect models or reality); and
- decision-rule uncertainty (not knowing how to interpret predictions) (Finkel, 1990)

Variability occurs when a single number is used to describe something that actually has multiple or variable values such as bodyweight or susceptibility to adverse affects, or something that varies over time such as the population of an area. Variability occurs as a result of differences between the characteristics of different people or populations. Uncertainty arises as a result of lack of data. Both uncertainty and variability need to be considered in risk assessments.

Key Principles in Environmental Health Risk Assessment

There are a number of key principles for environmental health risk characterisation (EPA NSW, 1998; US EPA, 1995):

1. Actions should always adequately protect public health and the environment, putting these responsibilities before all other considerations.
2. Risk assessments should be transparent. The nature and use of default values and methods, assumptions and policy judgements in the risk assessment should be clearly identified. Conclusions drawn from the evidence should be separated from policy judgements.
3. Risk characterisations should include a summary of the key issues and conclusions of each of the other components of the risk assessment, as well as describing the likelihood of adverse health effects. The summary should include a description of the overall strengths and limitations (including uncertainties) of the assessment and conclusions.
4. Risk characterisations (and risk assessments) should be consistent in general format, but recognise the unique characteristics of each specific situation
5. Health risk assessment must be undertaken with an appreciation that the health risk assessment is often part of a larger assessment that encompasses ecological risk assessment.
6. To protect public health and the environment an appropriate degree of conservatism must be adopted to guard against uncertainties.
7. Ensure that comparisons have been made against environmental health criteria that have been endorsed by the relevant Commonwealth, State or Territory environmental health agencies.
8. Where there are no Environmental Health Criteria for a particular agent refer to the administrative authority at the relevant Commonwealth, State or Territory level.
9. Ensure that human health risk assessments are undertaken, where necessary, according to methods in this document, or its revisions as published from time to time
10. When deriving environmental health criteria use toxicological data or exposure criteria from agencies or organisations relevant to the State or Territory (e.g. local or Commonwealth health agencies such as NHMRC, or the enHealth Council) or to which Australia is party (e.g. World Health Organization). (See Toxicity Assessment Section 5.4)
11. Ensure that human health risk assessments are undertaken using national toxicological assessments (e.g. NHMRC) or WHO assessments or, where neither has been made, methods agreed to by the administrative authority for contaminated sites at the relevant Commonwealth, State or Territory level.
12. The risk assessor's knowledge of the peer-reviewed scientific literature relevant to risk assessment and the practical aspects of risk assessment should be up-to-date.
13. Variations in risk assessments as a result of particular statutory requirements, resource limitations, and other specific factors should be explained as part of the risk characterisation. For example, a reason will be required to explain why certain elements are incomplete.

Risk Management, Risk Communication and Community Consultation

Risk assessment may lead into risk management. Risk management is about a broader evaluation of the results of the risk assessment and takes into account not only scientific data, but also social, economic and political considerations. It is important that the basis of decision making is clearly documented.

Public involvement should be an inherent part of risk assessment and management not only because they have a right to know but also because they have local knowledge such as sources of exposure, patterns of behaviour and local concerns that may be missed by generic risk assessments and models. The nature and extent of the risk must therefore be communicated in terms understandable by all parties.

Risk communication about the estimated risks is an essential process that should be incorporated before and throughout risk assessment and management. It is the deliberate exchange of information about the nature, severity, or acceptability of risks and the decisions taken to combat them.

Risk communication should be seen as a process that enables all stakeholders to make an informed judgement about a risk and its management. The process must involve a frank and open presentation of all relevant background information to the stakeholders, in a manner understandable by all. This process also involves listening to stakeholders. There are three perspectives to 'risk': actual, estimated and perceived (McKone and Bogen, 1991). The estimated risk is the outcome of the risk assessment with its uncertainties. The actual level may never be known because there may not be instruments available to 'measure' it or because actions will change the course of events. All stakeholders will have their own perceptions of the risk. Good risk assessment and risk communication minimise the mismatch between these three perspectives of risk and assist in efficient risk management. They will also address disquiet and will highlight significant risks where they may not be apparent to the stakeholders.

Abbreviations

ACDP	Advisory Committee on Dangerous Pathogens
ADI	Acceptable Daily Intake (WHO)
ANZECC	Australia and New Zealand Environment and Conservation Council
ASCEPT	Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists
BMD	Benchmark Dose
BMDL	Lower confidence limit on BMD
BMR	Benchmark Risk (Response)
DOH	Department of Health (United Kingdom)
DNA	Deoxyribonucleic acid
EA	Environment Australia
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
FDA	Food and Drug Administration (USA)
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HSE	Health and Safety Executive (United Kingdom)
IARC	International Agency for Research on Cancer
ICRP	International Commission on Radiological Protection
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LED	Lowest Effective Dose
LOAEL	Lowest Observed Adverse Effect Level
MAC	Maximum Allowable Concentration
mg/kg bw/d	mg/kg bodyweight/day
MTD	Maximum Tolerated Dose
MRL	Maximum Residue Limit
MRT	Maximum Residue Tolerance
NEPC	National Environment Protection Council (Australia)
NHMRC	National Health and Medical Research Council (Australia)
NICNAS	National Industrial Chemicals Notification and Assessment Scheme (Australia)
NOAEL	No Observed Adverse Effect Level

NOEL	No Observed Effect Level
NOHSC	National Occupational Health and Safety Commission (Australia)
NTP	National Toxicology Program (USA)
OECD	Organisation for Economic Co-operation and Development
PCB	Polychlorinated biphenyl
PM₁₀	Particulate Matter 10 μ
PTWI	Provisional Tolerable Weekly Intake (WHO)
q₁*	The 95 per cent upper confidence limit of the slope estimate used for the linearised multi-stage model
QRA	Quantitative Risk Assessment
RD	Reference Dose (US EPA)
SF	Safety Factors
SAR	Structure Activity Relationship
TDI	Tolerable Daily Intake (WHO)
TWP	Technical Working Party
US EPA	United States Environmental Protection Agency
WHO	World Health Organization

Glossary

(Adapted from NHMRC 1997)

Absorbed dose	The amount of chemical that, after contact with the exchange boundary (skin, lungs, gut), actually penetrates the exchange boundary and enters the circulatory system. The amount may be the same or less than the applied dose.
ADI	Acceptable Daily Intake. The daily intake of a chemical which, during a lifetime, appears to be without appreciable risk, on the basis of all the facts known at the time. It is expressed in milligrams per kilogram of body weight per day (mg/kg/day). (WHO, 1989) For this purpose, 'without appreciable risk' is taken to mean that adverse effects will not result even after a lifetime of exposure. Furthermore, for a pesticide residue, the acceptable daily intake is intended to give a guide to the maximum amount that can be taken daily in the food without appreciable risk to the consumer. Accordingly, the figure is derived as far as possible from feeding studies in animals. (See also 'Tolerable Daily Intake' and 'Reference Dose')
Adverse effect	The change in morphology, physiology, growth, development or life span of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects of other environmental influences. Some adaptive changes are not generally considered to be adverse e.g. some changes in enzyme levels.
Adduct	A chemical moiety which is covalently bound to a large molecule such as DNA or protein. (DOH, 1991)
Agent	Any chemical, physical, biological or social substance or factor being assessed, unless otherwise noted.
Applied dose	Amount of an agent presented to an absorption barrier and available for absorption. The amount may be the same or more than the absorbed dose.
Bias	A process resulting in a tendency to produce results that differ in a systematic value from the true values. Also known as systematic error. (Beaglehole <i>et al</i> , 1993)
BMD	Benchmark Dose. The dose associated with a given incidence (e.g. 1 per cent, 5 per cent or 10 per cent incidence) of effect, the Benchmark Risk, based on the best-fitting dose-response curve.
BMR	Benchmark Risk. A predetermined incidence of adverse response that determines the Benchmark dose.
Background concentration	'naturally-occurring, ambient concentrations in the local area of a site' (ANZECC/NHMRC, 1997)
Bioavailability	The ratio of the systemic dose to the applied dose.
Biological monitoring	Measurement of a contaminant or metabolite in body tissue, fluid, blood, expired air, breast milk and sweat. It is usually used as a marker or indicator of exposure to environmental chemicals.
Biomarker	Any measurement reflecting an interaction between a biological system and an environmental agent, which may be chemical, physical or biological (WHO, 1993). Often used to describe measurements used in biological monitoring.

Carcinogen	Chemical, biological or physical cancer-causing agent.
Carcinogenesis	The origin, causation and development of tumours. The term applies to all forms of tumours (e.g. benign and malignant).
Carcinogenicity	The ability to produce tumours, which may be benign or malignant. (IEH, 1999b)
Chronic toxicity	The ability to produce an adverse effect which persists over a long period of time, whether or not it occurs immediately upon exposure to a chemical or is delayed, or an effect which is only induced by prolonged exposure to a chemical. (IEH, 1999b)
Confidence	Weight assigned by the evaluator to the quality of the information available (high, medium or low confidence) to indicate that a chemical possesses certain toxicological properties.
Confidence limits	A range of values determined by the degree of presumed random variability in a set of data, within which the value of a parameter, e.g. the mean, lies, with a specified level of confidence or probability (e.g. 95 per cent). The confidence limit refers to the upper or lower value of the range. (DOH, 1991)
Confounding factor	A factor that distorts the apparent effect or magnitude of the effect of a study factor or risk. Such factors must be controlled for in order to obtain an undistorted estimate of a given effect. (DOH, 1991)
Critical effect(s)	The adverse effect judged to be the most important for setting an acceptable human intake or exposure. It is usually the most sensitive adverse effect, i.e. that with the lowest effect level, or sometimes a more severe effect, not necessarily having the lowest effect level. (IEH, 1999b)
Default value	A pragmatic, fixed or standard value used in the absence of relevant data.
Dermal	Of the skin, through or by the skin.
Developmental toxicity	The ability to produce an adverse effect in embryo, fetus or immature organism, which is induced and/or manifest either prenatally or postnatally before sexual maturity. (IEH, 1999b)
Dose	<p>A stated quantity or concentration of a substance to which an organism is exposed over a continuous or intermittent duration of exposure. It is most commonly expressed as the amount of test substance per unit weight of test animal (e.g. mg/kg body weight).</p> <p>The applied dose is the amount of chemical in contact with the primary absorption boundaries (e.g. skin, lungs, and gastrointestinal tract) and available for absorption. The absorbed dose is the amount crossing a specific absorption barrier (e.g. the exchange boundaries of skin, lung, and digestive tract) through uptake processes. The amount of the chemical available for interaction by any particular organ or cell is termed the delivered dose of that organ or cell. (EPA, 1992, p. 22933). The systemic dose is the dose to which the whole, or extensive parts, of the body is exposed. The absorbed dose may not be the systemic dose as substances absorbed in the digestive tract may be removed by the liver and not enter the systemic circulation.</p>
Dosage	A general term comprising the dose, its frequency and the duration of dosing. Dosage is properly applied to any rate or ratio involving a dose. Dosages often involve the dimension of time (e.g. mg/kg/day), but the meaning is not restricted to this relationship. (Hayes, 1991)

Dose–response assessment	Determination of the relationship between the magnitude of the dose or level of exposure to a chemical and the incidence or severity of the associated adverse effect. (IEH, 1999b)
Dose–response relationship	The correlative association existing between the dose administered and the response (effect) or spectrum of responses that is obtained. The concept expressed by this term is indispensable to the identification, evaluation, and interpretation of most pharmacological and toxicological responses to chemicals. The basic assumptions which underlie and support the concept are: (a) the observed response is a function of the concentration at a site, (b) the concentration at a site is a function of the dose, and (c) response and dose are causally related (Eaton and Klaassen, 1996). The existence of a dose–response relationship for a particular biological or toxicological response (effect) provides a defensible conclusion that the response is a result of exposure to a known substance.
Endpoint	An observable or measurable biological event used as an indicator of the effect of a chemical on a biological system (cell, organism, organ etc.).
Environmental health	Those aspects of human health determined by physical, chemical, biological and social factors in the environment. Environmental health practice covers the assessment, correction, control and prevention of environmental factors that can adversely affect health, as well as the enhancement of those aspects of the environment that can improve human health.
Environmental monitoring	The monitoring of the concentration of substances in the physical environment of air, water, soil and food.
Epidemiology	The study of the distribution and determinants of health-related states or events in specified populations, and the application of the study to the control of health problems (Last, 1988)
Expert	An expert has (1) training and experience in the subject area resulting in superior knowledge in the field (2) access to relevant information, (3) an ability to process and effectively use the information, and (4) is recognised by his or her peers or those conducting the study as qualified to provide judgements about assumptions, models, and model parameters at the level of detail required. (NCRP, 1996).
Exposure	Contact of a chemical, physical or biological agent with the outer boundary of an organism, e.g. inhalation, ingestion or dermal contact.
Exposure assessment	The estimation (qualitative or quantitative) of the magnitude, frequency, duration, route and extent (for example, number of organisms) of exposure to one or more contaminated media for the general population, for different subgroups of the population, or for individuals.
Exposure pathway	The course a chemical or physical agent takes from a source to an exposed organism. An exposure pathway describes a unique mechanism by which an individual or population is exposed to chemicals or physical agents at or originating from a site. Each exposure pathway includes a source or release from a source, an exposure point, and an exposure route. If the exposure point differs from the source, a transport/exposure medium e.g. air or media (in cases of inter-media transfer) also is indicated. (US EPA, 1989, p. 62)

Exposure route	The way a chemical enters an organism after contact e.g. by ingestion, inhalation, or dermal absorption. (EPA, 1992, p. 22933)
Extrapolation	For dose–response curves, an estimate of the response at a point outside the range of the experimental data. Also refers to the estimation of a response in different species or by different routes than that used in the experimental study of interest.
Factor	A single factor or product of several single factors used to derive an acceptable intake. These factors account for adequacy of the study, interspecies extrapolation, inter-individual variability in humans, adequacy of the overall data base, nature and extent of toxicity, public health regulatory concern and scientific uncertainty.
False negative	A result that is erroneously negative.
False positive	A result that is erroneously positive.
Gene	The DNA molecule of inheritance of characteristics including susceptibility to disease.
Genotoxic	Agents for which a direct activity is the alteration of the information encoded in genetic material. (Butterworth, 1990)
Genotoxic carcinogen	A chemical which induces tumours via a mechanism involving direct damage to DNA. (IEH, 1999b)
Genotoxicity	A broad term describing the ability to produce damage to the genetic material (DNA) of cells or organisms.
Guidance values	Values such as concentrations in air or water, which are derived after appropriate allocation of Tolerable Intake (TI) among the possible different media of exposure. Combined exposure from all media at the guidance values over a lifetime would be expected to be without appreciable health risk. The aim of a guidance value is to provide quantitative information from risk assessment for risk managers to enable them to make decisions concerning the protection of human health. (WHO, 1994, p. 16)
Guideline dose	The average daily intake of a chemical, which, during a lifetime, is unlikely to result in cancer, based on a comprehensive expert assessment of the best information available at the time. The guideline dose is derived by regulatory authorities using cancer risk assessment according to guidelines developed by national health advisory bodies.
Hazard	The capacity of an agent to produce a particular type of adverse health or environmental effect, e.g. one hazard associated with benzene is that it can cause leukemia; or The disposition of a thing, a condition or a situation to produce an adverse health or environmental effect; or an event, sequence of events or combination of circumstances that could potentially have adverse consequences (adapted from ACDP, 1996).
Hazard identification	The identification, from animal and human studies, <i>in vitro</i> studies and structure-activity relationships, of adverse health effects associated with exposure to an agent. (IEH, 1999b)
Health	Health is a state of complete physical, mental and social well being and not merely the absence of disease or infirmity (WHO, 1946).

Health investigation level	The concentration of a soil contaminant (arrived at using appropriate sampling, analytical and data interpretation techniques) above which further appropriate investigation and evaluation will be required to determine whether a significant health risk exists
Health risk assessment	The process of estimating the potential impact of a chemical, biological, physical or social agent on a specified human population system under a specific set of conditions and for a certain timeframe.
Health risk management	The process of evaluating alternative actions, selecting options and implementing them in response to health risk assessments. The decision making will incorporate scientific, technological, social, economic and political information. The process requires value judgements, e.g. on the tolerability and reasonableness of costs.
Hormesis	Demonstrated beneficial effects of an agent at low (but not homeopathic) doses but with toxicity occurring at higher doses.
Immunotoxicity	The ability to produce an adverse effect on the functioning of organs and cells involved in immune competence. (IEH, 1999b)
IRIS	Integrated Risk Information System. The computerised database of the US EPA, which provides the Agency's adopted hazard and dose-response assessment for chemical and radiological agents. Used as guidance and to provide consistency in the Agency's regulatory decisions designed to reduce risk related to environmental exposures (see abbreviations).
LD₅₀	The quantity of a chemical compound that, when applied directly to test organisms, via inhalation, oral or dermal exposure is estimated to be fatal to 50 per cent of those organisms under the stated conditions of the test. Number of microorganisms of a particular species that are fatal in 50 per cent of the host organisms.
LED₁₀	Lowest Effective Dose. The lower 95 per cent confidence limit on a dose associated with an estimated 10 per cent increased tumour or relevant non-tumour response. (US EPA, 1996)
LOEL	Lowest Observed Effect Level. The lowest concentration or amount of a substance, found by experiment or observation, that causes alterations of morphology, functional capacity, growth, development or life span of target organisms. WHO (1990) define it as the lowest dose of a substance which causes changes distinguishable from those observed in normal (control) animals.
LOAEL	Lowest Observed Adverse Effect Level. The lowest concentration or amount of a substance, found by experiment or observation, that causes adverse alterations of morphology, functional capacity, growth, development or life span of target organisms.
Level of detection	The minimum concentration or mass of analyte that can be detected at a known confidence level
Level of reporting	The value calculated from the instrumentation detection limits and with appropriate scale up factors applied. The scale up factors are affected by the procedures, methods and the size of the sample.

Lifetime	Covering the average life span of an organism (e.g. 70 years for humans).
Metabolite	A substance that is the product of biochemical alteration of the parent compound in an organism.
Model	A mathematical representation of a biological system intended to mimic the behaviour of the real system, allowing description about empirical data and predictions about untested states of the system.
Mutagenicity	The ability to produce a permanent, heritable change in the amount or structure of genetic material of cells or organisms. (IEH, 1999b)
Neurotoxicity	The ability to produce an adverse effect in the central or peripheral nervous system. (IEH, 1999b)
NOAEL	The No Observed Adverse Effect Level is the highest dose of a substance at which no toxic (i.e. adverse) effects are observed. (WHO, 1990) It may also be worded in more detail thus: The NOAEL is defined as the highest exposure at which there is no statistically- or biologically-significant increase in the frequency of an adverse effect when compared to a control group. (National Academy of Sciences/National Research Council, 1994) The definition of NOEL is equivalent, but with the removal of the term, 'adverse'. Often, the difficult issue in the use of the terms NOEL or NOAEL is in deciding whether a compound-related effect noted in a particular study is necessarily an 'adverse' effect. Alterations of morphology, functional capacity, growth, development or life span of the target organism may be detected which are judged not to be adverse.
Nongenotoxic carcinogen	A chemical which induces tumours via a mechanism which does not involve direct damage to DNA (IEH, 1999b).
Physiologically-based pharmacokinetics (PBPK)	Modelling the dose or degree of exposure to a chemical at a target tissue, cell or receptor, by integration of pharmacokinetic data with anatomical, physiological and biochemical data (IEH, 1999b).
NOEL	The 'No Observed Effect Level' or 'No Observable Effect Level' (NOEL) is the highest dose of a substance administered to a group of experimental animals at which there is an absence of observable effects on morphology, functional capacity, growth, development or life span, which are observed or measured at higher dose levels used in the study. Thus, dosing animals at the NOEL should not produce any biologically significant differences between the group of chemically exposed animals and an unexposed control group of animals maintained under identical conditions. The NOEL is expressed in milligrams of chemical per kilogram of body weight per day (mg/kg bw/day) or, in a feeding study, in ppm in food (converted to mg/kg bw of compound intake by measured or estimated food intake over the period of the study) The NOEL has been simply defined as the highest dose of a substance which causes no changes distinguishable from those observed in normal (control) animals (WHO, 1990).
PM₁₀	Particulate Matter 10µm: the fraction of particles passing an inlet with a 50 per cent cut-off efficiency at an aerodynamic diameter of 10µm

PTWI	Provisional Tolerable Weekly Intake. The tolerable intake of a chemical expressed as a weekly amount. The term was established by WHO (1972) for several heavy metals which 'are able to accumulate within the body at a rate and to an extent determined by the level of intake and by the chemical form of the heavy metal present in food.' (WHO, 1989)
Public health	The science and art of preventing disease, prolonging life and promoting health through the organised efforts of society.
Reproductive toxicity	The ability to produce an adverse effect on any aspect of reproductive capacity, function or outcome. It includes effects on the embryo, fetus, neonate and prepubertal organism and on adult reproductive and neuroendocrine systems (IEH 1999b).
R_fD	Reference Dose (R _f D). An estimate (with uncertainty factors spanning perhaps an order of magnitude) of the daily exposure (mg/kg/day) to the general human population (including sensitive sub-groups) that is likely to be without an appreciable risk of deleterious effects during a life time of exposure. It is derived from the NOAEL or the LOAEL by application of uncertainty factors that reflect various types of data used to estimate R _f D and an additional modifying factor, which is based on professional judgement of the entire data base of the chemical. (IRIS, 1996). Usually doses less than the R _f D are not likely to be associated with adverse health risks, and are therefore less likely to be of regulatory concern. As the frequency and/or magnitude of the exposures exceeding the R _f D increase, the probability of adverse effects in a human population increases. However, all doses below the R _f D are not assumed to be 'acceptable' (or risk-free) and nor are all doses that exceed the R _f D necessarily 'unacceptable' (i.e. result in adverse effects) (US EPA)
Risk	The probability that, in a certain timeframe, an adverse outcome will occur in a person, group of people, plants, animals and/or the ecology of a specified area that is exposed to a particular dose or concentration of a hazardous agent, i.e. it depends on both the level of toxicity of the agent and the level of exposure.
Risk assessment	The process of estimating the potential impact of a chemical, physical, microbiological or psychosocial hazard on a specified human population or ecological system under a specific set of conditions and for a certain timeframe
Risk communication	An interactive process involving the exchange among individuals, groups and institutions of information and expert opinion about the nature, severity, and acceptability of risks and the decisions taken to combat them.
Risk management	The process of evaluating alternative actions, selecting options and implementing them in response to risk assessments. The decision making will incorporate scientific, technological, social, economic and political information. The process requires value judgements, e.g. on the tolerability and reasonableness of costs.
Safety factor	See factor. Safety factor usually refers to health-related concerns.
Skin irritancy	A local inflammatory reaction affecting the skin
Stochastic	A random probabilistic phenomenon
Structure activity relationship	The relationship between the biological activity of a chemical or series of chemicals and their structure. The relationships can be described qualitatively and quantitatively.

Systemic dose	Amount of a substance that is eventually distributed in the blood after absorption, distribution and storage.
Teratogenicity	The ability to produce a structural malformation or defect in an embryo or fetus (IEH, 1999b)
Threshold	The lowest dose or exposure level which will produce a toxic effect and below which no toxicity is observed (IEH, 1999b).
Threshold dose	The lowest dose which produces an effect and below which no biological effect occurs. The acceptability and usefulness of the concept of the experimental NOEL/NOAEL depends on the scientific rationale supporting the existence and demonstrability of a threshold for responses produced by biologically active agents. As used here, the term 'threshold' designates that level of a stimulus which comes just within the limits of perception, and below which level a recognisable response is not elicited.
TDI	Tolerable Daily Intake. An estimate of the intake of a substance which can occur over a lifetime without appreciable health risk. It may have different units depending on the route of administration. (WHO, 1994). (Imray and Langley, 1996, p. 18). The term, 'acceptable daily intake' is used for chemicals such as pesticides (herbicides, insecticides, antifungals etc.) which are deliberately used on food crops or food-producing animals and for which some level of residues may be expected to occur in food. The term 'tolerable daily intake' is used when the chemical is a potential food or environmental contaminant. Whilst exposure should not occur, a TDI is an established health limit below which lifetime exposure should not have any adverse health effects. (See also 'Acceptable Daily Intake' and 'Reference Dose')
TWI	Tolerable Weekly Intake. The TI expressed as a weekly amount
Tolerable intake	An estimate of the intake of a substance that over a lifetime is without appreciable health risk. (WHO, 1994). Examples are the ADI, TDI and Reference Dose.
Toxicity	The quality or degree of being poisonous or harmful to plant, animal or human life.
Transformation	The process by which a normal cell acquires the capacity for neoplastic or carcinogenic growth. It is thought to occur in several stages.
Tumour	A mass of abnormal, disorganised cells, arising from pre-existing tissue, which is characterised by excessive and uncoordinated cell proliferation or growth and by abnormal differentiation (specialisation). There are two types of tumours, benign and malignant. Benign tumours morphologically resemble their tissue of origin, grow slowly (may also stop growing) and form encapsulated masses; they do not infiltrate other tissues, they do not metastasise and are rarely fatal. Malignant tumours resemble their parent tissue less closely and are composed of increasingly abnormal cells genetically, morphologically and functionally. Most grow rapidly, spread progressively through adjacent tissues and metastasise to distant tissues.
Tumour initiation	The first step in carcinogenesis whereby a small number of cells (or one cell) are irreversibly changed due to genetic damage.
Tumour progression	The stage in carcinogenesis when tumours acquire the features of malignant growth.

Tumour promotion The process by which initiated cells undergo clonal expansion to form overt tumours.

Uncertainty The lack of knowledge about the correct value, e.g. a specific exposure measure or estimate.

Uncertainty factor A numerical factor applied to the no-effect level to derive an exposure level considered to be without appreciable risk to health (the NEL is divided by the uncertainty factor). The magnitude of the uncertainty factor depends on the nature of the toxicity observed, the quality of the toxicological data available, and whether the effects were observed in humans or animals (IEH, 1999b).

Variability Measurable factors that differ e.g. height is variable across populations. The major types of variability are temporal, spatial and interindividual. They may be discrete (e.g. albinism) or continuous (e.g. body weight). It may be readily identifiable (e.g. presence of albinism) or difficult to identify (e.g. ability to detoxify a particular chemical metabolite)

Volume of distribution (Vd) Is the relationship of plasma chemical concentration and the amount of chemical distributed throughout the body. This is not a real volume in the true sense, but an apparent (mathematical) volume which can be estimated by:

$$Vd = \frac{D}{Cp}$$

where D = dose administered, and Cp = plasma concentration (Gossel and Bricker, 1989).

Background to Risk Assessment

Risk assessment is the process of estimating the potential impact of a chemical, physical, microbiological or psychosocial hazard on a specified human population or ecological system under a specific set of conditions and for a certain timeframe.

Risk assessment is intended 'to provide complete information to risk managers, specifically policymakers and regulators, so that the best possible decisions are made' (Paustenbach, 1989, p. 28). There are uncertainties related to risk assessment and it is important to make the best possible use of available information.

Risk assessment gathers and organises information and enables:

- risks at a point in time (including baseline risks) and changes in risk over time to be estimated and whether action is necessary;
- health Guidance Values to be estimated for environmental hazards that can be used and which will adequately protect public health;
- assessments of new types of risk;
- assessments of different types of risk;
- a comparison of the potential health impacts of various environmental health interventions (thus enabling cost-effectiveness estimates);
- the identification and comparison of different factors that affect the nature and magnitude of the risk;
- risk-based standards setting for regulatory exposure limits, and clean-up standards
- prioritising issues according to their levels of risks;
- questionable theories, methods and data to be challenged and addressed by providing a clearly documented and open process (Covello and Merkhofer, 1993);
- risk-based policy making; and
- consistent, transparent appraisal and recording of public health risks.

Risk assessment may be done as a relatively rapid 'desk top' study for simple issues or may be a large and complex process where there are significant health concerns. There are numerous models of risk assessment to suit the many contexts in which risk assessments are undertaken.

Even limited measures of the level of risk can be valuable for identifying complex cause and effect processes and the most efficient means of addressing the risks.

It is important that assessors, users, regulators and members of the public recognise risk assessment may not always provide a compelling or definitive outcome. There are criticisms of risk assessment some of which are:

- default values and assumptions are not realistic. A series of such unrealistic values or assumptions compounds the inaccuracy so that risks may be seriously overstated or understated if the default values are too conservative or insufficiently conservative, respectively;
- interactions between agents (i.e. mixtures of agents) and the variability of response between individuals may be insufficiently taken into account;
- the use of default values and assumption may become too rigid so that situation-specific data are not applied;
- the nature of the population to whom the risk assessment is to be applied is sometimes poorly defined;
- the uncertainties of risk assessment are often inadequately described e.g. specific point estimates are given which do not recognise uncertainty, or simplistic upper bound estimates of uncertainty are used;
- there is an emphasis on cancer risk to the possible neglect of other adverse effects e.g. reproductive and developmental outcomes;
- in some situations there may be insufficient scientific knowledge to be able to perform credible risk assessments;

- risk assessment can be perceived to be tailored to provide a desired or predetermined outcome (NRC, 1994);
- excessive emphasis is given to the process of risk assessment rather than its content. In the USA, a US\$150 000 risk assessment was undertaken on the results of a single environmental sample;
- the risk assessment process is used as a 'whitewash';
- Tal (1997) indicates that environmental groups identify a number of problems with the way risk assessments have been practised including disempowerment and potential regulatory delays. Risk assessments should be designed and undertaken in ways that minimise these pitfalls; and
- risk assessment is used to justify the continuation or increase of polluting activities.

1.1 When to Undertake Risk Assessment

The Issues Identification phase will determine when to undertake a risk assessment. The need to undertake a risk assessment will be influenced by situation-specific factors. As such, the following list is indicative and not exhaustive. In general risk assessments will be needed for products, processes, situations and activities where there is a plausible increased risk of significant health consequences for the human population.

Examples are:

- new additives to food or potable or recreational waters;
- changes to climate, landform, geography or demography that may impact on disease vectors and parasites;
- situations where environmental standards or guidelines are unavailable;
- environmental changes that will increase traffic flow and may increase the risk of injury or air pollution e.g. new traffic corridors;

- changes where impacts on environmental health factors may be permanent and irreversible;
- changes which may impact on the microbiological or chemical safety of food chains and food supplies;
- situations where there is a high level of public interest in and/or concern about environmental health issues;
- situations where vulnerable populations may be affected by environmental health issues e.g. the placement of schools;
- planning new towns or communities;
- situations involving planning modification or approval;
- legislative changes;
- policy changes;
- designating housing set-backs from industry and transport corridors;
- assessment of existing installations to improve existing risk treatment practices;
- locating new airports;
- locating new power generation plants;
- locating intensive horticulture;
- locating toxic waste disposal plants;
- locating sewage treatment plants;
- designation of watersheds; and
- where Health Impact Assessments are undertaken.

1.2 Types of Risk Assessment

1.2.1 Individual and population risk assessments

Risk assessments may assess individual or population risks. Individual risks may be for the average (i.e. typical) individual or the highly exposed or particularly susceptible individual and the risks may be estimated for various durations of

exposure (e.g. per year or per lifetime) or for different locations. Individual risk can only be assessed for a hypothetical individual with assumed characteristics. Assessing the risk for any real individual will be frustrated by the fact that risk predictions for an individual can never be validated by experience. Any real individual will either experience the negative outcome or will not. Neither of these results can validate any risk prediction other than a probability of one or zero.

Population risk may relate to the number of adverse health effects (e.g. fatalities, cancers, or illnesses) in a population over a specified period of time or the rate of adverse effects for a given location or sub-population (Covello and Merkhofer, 1993).

1.2.2 Qualitative and quantitative risk assessments

The level of risk can be described either qualitatively (i.e. by putting risks into categories such as 'high', 'medium' or 'low') or quantitatively (with a numerical estimate). Current risk assessment methods do not enable accurate quantitative estimates of risk for low levels of exposure to environmental hazards. Numerical estimates of risk will rarely be feasible because of variability in the agent and population and limitations in toxicological and exposure data which will be reflected in the uncertainty assessment, but a degree of quantification may be possible for some components such as data collection and exposure assessment. Further discussion of qualitative and quantitative risk assessment is given in Section 9.3 of 'Risk Characterisation'.

1.3 Assessing Risk Assessment Methods

There are various criteria for assessing risk assessment methods (Covello and Merkhofer, 1993) including:

- the logical soundness of the method (e.g. its justification based on theoretical arguments or scientific knowledge, and the validity of the underlying methodological assumptions);

- completeness (e.g. whether it can address all aspects of the problem and the degree to which it excludes issues because they are hard to accommodate);
- accuracy (e.g. the precision reflected in the confidence level associated with the results; biases resulting from undue weight given to specific interests or considerations; and the sensitivity of results to untested or untestable assumptions);
- acceptability (e.g. compatibility with existing processes; whether it is viewed as rational and fair; the level of understanding for all parties affected by it; and the confidence and familiarity of those who will use it);
- practicality (e.g. the level of expertise, time and input data required); and
- effectiveness (e.g. usefulness of results; range of applicability across different risks and problem areas; the generalisability of the conclusion to other problem areas; and effectiveness and efficiency of linkage with other types of methods).

1.4 Models of Risk Assessment

There are various models available for the environmental health risk assessment. The US National Academy of Sciences (1983) model was published relatively early in the development of risk assessment processes and the model has been particularly influential as a template:

'risk assessment...mean(s) estimating the potential adverse health effects of human exposures to environmental hazards. Risk assessments include several elements: description of the potential adverse health effects based on an evaluation of results of epidemiological, clinical, toxicological, and environmental research [hazard identification]; extrapolation from those results to predict the type and estimate the extent of health effects in humans under given conditions of exposure [dose response assessment]; judgements on the number and characteristics of persons exposed at various intensities and durations [exposure assessment]; and summary judgements on the existence and

overall magnitude of the public health problem [risk characterisation]. Risk assessment also includes characterisation of the uncertainties inherent in the process of inferring risk.’

Several other international models are detailed in Appendix 6 (‘International Models of Risk Assessment’). The models are generally similar although the use of differing definitions of terms such as ‘risk’, ‘hazard’ and ‘assessment’ can be confusing. (The International Programme on Chemical Safety has commenced a process to harmonise definitions and methodologies.)

1.5 Bayesian Tools for Risk Assessment

Bayesian approaches have been proposed for risk assessment. Given that in some risk assessments there will be a considerable element of judgement and different experts will have different prior beliefs, the Bayesian approaches incorporate these in a formalised way into the risk assessment by using simulations with different weightings so that prior knowledge, assumptions and judgements can be formalised and explicitly used in the risk assessment. This approach can be as valid as conventional statistic techniques for estimating probabilities (IEH, 1999b).

1.6 Australian Models of Risk Assessment

There are a variety of models used for risk assessment in Australia by government agencies and consultants (Appendix 5).

This document uses a model of risk assessment that involves five stages. The model follows a review of various models and is based largely on the National Academy of Sciences model (1983) with the addition of a preliminary step, ‘Issue Identification’:

- issue identification;
- hazard identification;
- dose–response assessment;

- exposure assessment for the relevant population; and
- risk characterisation.

These five stages are closely linked and highly dependent on the preceding stages. The model is illustrated in Figure 1, below. The terminology is similar to terminologies used by other major models (See Figure 1, Appendix 6).

1.6.1 Issue identification

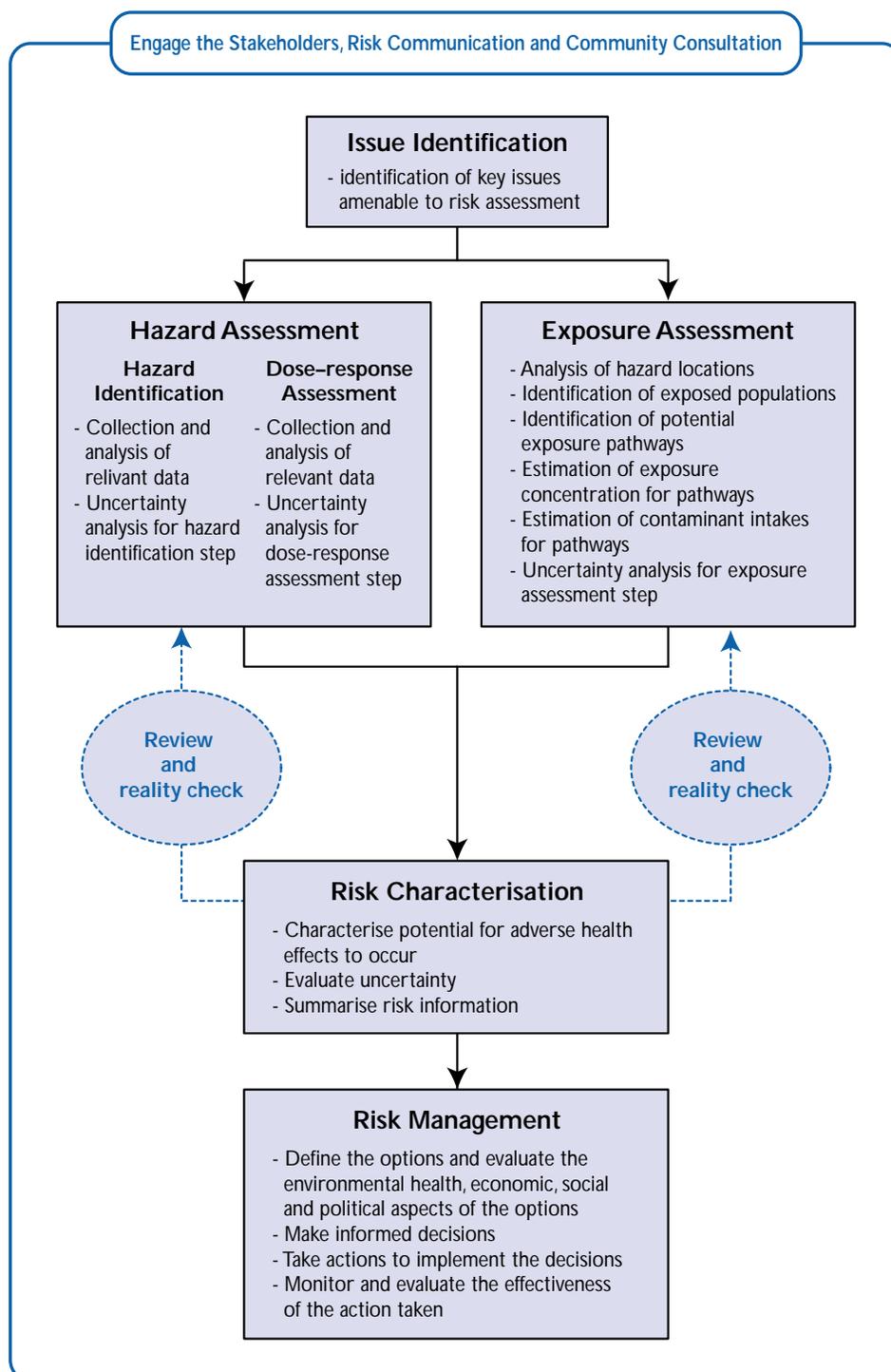
Issue Identification identifies issues amenable to risk assessment and assists in establishing a context for the risk assessment by a process of identifying the problems that the risk assessment needs to address. It includes identifying:

- what is the concern;
- what is causing the identified concern;
- why is the concern an issue;
- how the concern was initially identified;
- how the concerns were raised;
- whether the issue is amenable to risk assessment; and
- whether risk assessment is appropriate.

1.6.2 Hazards vs issues

‘Hazards’ need to be distinguished from ‘issues’. The determination of the issues is necessary to establish a context for the risk assessment and assists the process of risk management. Issues have dimensions related to perceptions, science, economics and social factors. Examples of issues are: community concerns over emissions from a smelter; community outrage over the proposed development of a communications tower; assessment of a new water treatment chemical; and changes to a microbiological food standard. ‘Hazards’ relate to the capacity of a specific agent to produce a particular type of adverse health or environmental effect. Examples of hazards are: the capacity of benzene to cause leukemia; the capacity of solar radiation to cause skin cancer; the capacity of *Salmonella* to cause vomiting and diarrhoea.

Figure 1: Risk assessment model



1.6.3 Hazard assessment

'Hazard Assessment' is comprised of 'Hazard Identification' and 'Dose-Response Assessment'.

1.6.4 Hazard identification

Hazard identification involves determining:

- what types of (adverse) health effects might be caused by the agent; and
- how quickly the adverse health effects might be experienced and their duration (Health Canada, 1999).

The data for hazard identification will come from a range of toxicological, epidemiological, *in vitro* and mechanistic studies. Not only the agent may need to be assessed but, in the case of chemicals, the breakdown products e.g. acrolein as well as butadiene when doing environmental monitoring; the four metabolites of atrazine (desethylatrazine, desisopropylatrazine, diamonochlorotriazine and hydroxyatrazine) when monitoring atrazine contamination of water catchments.

1.6.5 Dose-response assessment

Dose-response assessment considers both qualitative and quantitative toxicity information to determine 'the incidence of adverse effects occurring in humans at different exposure levels' (US EPA, 1989, p. 1.6). Where available, human and animal evidence will be assessed as part of this process. Risk assessment cannot be done without good dose-response information.

Whereas constant doses can be used in animal studies, long term human exposures may be variable. This may be a significant source of uncertainty and there is a need to develop an integrated estimate of long term exposure.

1.6.6 Exposure assessment

Exposure assessment involves the determination of the frequency, extent duration and character of exposures in the past, currently, and in the future. There is also the identification of exposed populations and particularly sensitive sub populations, and potential exposure pathways. Environmental monitoring and predictive models

can be used to determine the levels of exposure at particular points on the exposure pathways. The contaminant intakes from the various pathways under a range of scenarios can then be estimated (US EPA, 1989).

Where the risk assessment is being done as part of a protective and pro-active risk assessment, exposure assessment data may not be available and may have to be estimated. Modelled data may also be used where the data package is limited.

1.6.7 Risk characterisation

Risk characterisation provides a qualitative and/or quantitative estimate, including attendant uncertainties, of the nature, severity and potential incidence of effects in a given population based on the hazard identification, dose-response and exposure assessments.

1.6.8 Follow up

Risk assessment is an iterative process that will be reviewed as the risk assessment progresses. After risk assessment is completed there may be a need to review the situation from time-to-time as new information becomes available or circumstances change to ensure that the risk assessment is still relevant and protective.

1.6.9 Aims of the health risk assessment method

The method is intended to assist risk assessment practitioners and those evaluating risk assessments.

The aims of the method are:

- to identify information needed to make decisions;
- to make the decision-making process more explicit by identifying the specific elements affecting risk so that more objective and scientific decisions can be made;
- to make the decision process more transparent to promote confidence by the community, industry and scientists about decisions and actions taken;

- to increase consistency in risk assessment so that different people assessing similar problems will come to comparable conclusions;
- to have the ability to account for the range of risks that are present or could arise as the result of actions;
- to refine the assessment and management of risk so that better decisions are made and more rigorous risk assessment and management occurs;
- to enable the adoption of future improvements to risk assessment; and
- to enable risk-benefit analysis and the evaluation of the outcomes of risk management decisions about current and possible future risks (ACDP, 1996).

1.7 Risk Assessment and Health Impact Assessment

Health impact assessment is described in the *Health Impact Assessment Guidelines* (enHealth, 2001) as a systematic process to assess the actual or potential, and direct or indirect, effects on the health of individuals, groups or communities arising from environmental conditions or hazards arising from policies, objectives, programs, plans, or activities. It is usually a process undertaken as part of an Environmental Impact Assessment for a significant project and looks at both positive and negative impacts on health. The definition of health is taken to be broader than the mere absence of disease or infirmity but 'a complete state of physical, mental and social wellbeing' (WHO Constitution).

Environmental Health Risk Assessment provides a tool for appraising health risks in the broader process of Health Impact Assessment.

1.8 Principles of Risk Assessment

In conducting risk assessments there are several guiding principles:

- **Risk assessment is to inform the risk management process.**

- **Risk assessors and risk managers should be sensitive to distinctions between risk assessment and risk management.** The assessors should (a) generate a credible, objective, realistic, and scientifically balanced analysis; (b) present information on the separate components of the risk assessment; and (c) explain the confidence in each assessment by clearly delineating strengths, uncertainties and assumptions, along with the impacts of these factors (e.g. confidence limits, use of conservative/non-conservative assumptions) on the overall assessment. The risk assessors do this without considering issues such as cost, feasibility, or how the scientific analysis might influence the regulatory or site-specific decision (US EPA, 1995, p. 2).
- **Risk assessment processes should be coherent and transparent.** It is important that the basis of the decision-making is clearly documented. This formal record should be clear comprehensive and concise and include a summary of the key data which influenced the risk assessment and an appraisal of its quality (ACDP, 1996, p. 5).
- **Risk assessment information is only one of several kinds of information used for decision-making.** The risk management decision will not be determined only by the risk assessment but a range of other factors including 'technical feasibility (e.g. treatability, detection limits), economic, social, political,' and legislation when determining whether to regulate and, if so, to what extent (US EPA, 1995, p. 2).
- **Consultation with the community to identify their concerns.**
- **Scientific judgements and policies must be clearly identified.** Inevitable gaps in knowledge will be filled by scientific judgements and policies. These must be clearly identified so that others may understand the role of judgement in interpreting the evidence.

1.9 Dealing with Uncertainty and Variability

The use of conservatism should be carefully considered. An appropriate level of conservatism is important for policy makers because, in general, underestimating a particular risk is likely to have greater health, environmental, economic and social losses than overestimating the same risk. However, applying conservatism to risk assessment may distort the results particularly where there is layer upon layer of conservative assumptions, the compounding effect of which may be an overly cautious risk assessment. Addressing an excessively cautious risk assessment may have significant opportunity costs on a community i.e. the extra money could be more effectively spent on other health interventions (Covello and Merkhofer, 1993). If unduly conservative risk estimates are misinterpreted as the expected risks, considerable anxiety may be created in the community.

A degree of conservatism is warranted where there are significant uncertainties about exposure or toxicological data or if the variability in populations has not been taken into account. The variability can arise from heterogeneity in factors such as:

- uptake e.g. due to variations in diet and inhalation rates;
- pharmacokinetic heterogeneity resulting in differences in concentration over time in the blood or at the site of action e.g. due to differences in metabolism or excretion;
- response, where there are differences at the site of action (Hattis and Silver, 1994 p. 422); and
- the degree of conservativeness should be made quite clear in the risk assessment so that risk managers are fully aware of the precautions inherent in the risk assessment and do not add unnecessarily further levels of conservatism for the risk management step.

1.10 Risk Assessment and the Precautionary Principle

The Precautionary Principle was first introduced in 1984 at the First International Conference on Protection of the North Sea and has since been integrated into numerous international conventions and agreements. In Australia, the Inter Governmental Agreement on the Environment (May, 1992) describes the principle in the following way:

Where there are threats of serious or irreversible environmental damage, lack of full scientific certainty should not be used as a reason for postponing measures to prevent environmental degradation. In the application of the Precautionary Principle, public and private decisions should be guided by:

- i) careful evaluation to avoid, wherever practicable, serious or irreversible damage to the environment; and
- ii) an assessment of the risk-weighted consequences of various options.

The Precautionary Principle is particularly relevant during the risk management phase. Risk assessment provides a process for applying the Precautionary Principle by providing information about the nature and magnitude of the 'threats of serious or irreversible environmental damage'.

The European Commission (1998) describes the precautionary approach as a risk management tool to be used in the face of scientific uncertainty and where there is a need for action in the case of a potentially serious risk without awaiting the results of scientific research. The European Union has detailed six guidelines (*ibid*) as the basis for the approach:

1. Implementation of an approach based on the precautionary principle should start with an objective risk assessment, identifying at each stage the degree of scientific uncertainty.
2. All the stakeholders should be involved in the decision to study the various management options that may be envisaged once the results of the risk assessment are available and the procedure be as transparent as possible.

3. Measures based on the precautionary principle must be proportionate to the risk which is to be limited or eliminated.
4. Measures based on the precautionary principle must include a cost/benefit assessment (advantages/disadvantages) with an eye to reducing the risk to a level that is acceptable to all the stakeholders.
5. Measures based on the precautionary principle must be able to establish responsibility as to who must furnish the scientific proof needed for a full risk assessment.
6. Measures based on the precautionary principle must always be of a provisional nature, pending the results of scientific research performed to furnish the missing data and perform a more objective risk assessment.

1.10.1 Key factors in risk assessments

Key factors that are to be considered in risk assessments (ACDP, 1996) include:

1. Hazard assessment
 - interactions with other agents in the environment
 - immediate or delayed onset of health effects
 - severity of health effects
 - reversibility of health effects
 - presence of a clear threshold for effects
 - potency of agent
2. Exposure
 - duration of exposure
 - frequency and consistency of exposure
 - patterns of exposure
 - past, current and future exposure
 - timing of exposure

- exposure route (ingestion vs inhalation vs dermal contact) may influence outcome
- intergenerational exposures
- cumulative vs non-cumulative exposures
- failure of exposure controls
- quality of exposure data
- quality of exposure models

3. Population

- genetic variability
- individual host characteristics (e.g. age, gender, body weight, pre-existing poor health, immune status, nutritional status, previous exposures, reproductive status)
- population characteristics (e.g. herd immunity and social behaviours for communicable diseases, social mobility for exposure to air and soil contaminants, recreational patterns for exposure to contaminated recreational waters)

4. Environment

- intervention strategies (e.g. containment of contaminated soil, chlorination of water, pasteurisation of food)
- transport mechanisms (e.g. meteorological factors affecting air pollution, vectors for communicable diseases)
- factors affecting persistence (e.g. photolysis and volatilisation of chemicals, desiccation of microorganisms)
- breakdown of public health measures (e.g. flooding affecting waste control and potable water treatment)

1.11 Risk Assessment and Particular Population Groups

Sensitivity of individuals is likely to be affected by age, sex, nutritional and pregnancy status, and combinations of these (IEH, 1999c).

1.11.1 Risk assessment and children

Children may differ from adults in a range of behavioural and physiological parameters that may need to be taken into account in the risk characterisation phase of risk assessments.

The principal factors causing these potential differences are (Roberts, 1992):

- growth, development and maturational rates;
- children have greater potential future durations of life, which is relevant to the potential for accumulation or exceeding latency periods;
- dietary differences—children can eat much greater quantities of particular foods (particularly dairy products, soft drinks and some fruit and vegetables) than adults on a body weight basis (Rees, 1999);
- exposure factors—the surface area to body mass ratio will change markedly with ageing. In the newborn the ratio is typically 0.067 (m²/kg) decreasing to 0.025 in an adult. While the respiratory volume remains fairly constant at 10 ml/kg/breath, the surface area of the alveoli increases from 3m² in an infant to approximately 75m² in an adult and the respiration rate drops from 40 breaths per minute to 15 breaths per minute (Snodgrass, 1992). Children have unique exposure possibilities e.g. placental transfer and breast milk (Kimmel *et al*, 1992);
- behavioural factors, e.g. children are more likely to indulge in soil eating behaviours;
- available parameters for toxicity assessment, e.g. techniques for assessing dizziness, intelligence and hearing impairment are different between children and adults;
- biochemical and physiological responses—children have a higher metabolic rate, more limited ability to control body temperature, more rapid growth rate, a higher percentage of water in the lean body tissue;
- disposition of the agent within the body, e.g. transit time, pH and enzyme activity in the

gut are different for children as are tissue-chemical bindings;

- liver function related to detoxification matures after birth, as does the renal excretion of foreign compounds;
- differences in gut microflora;
- the immaturity of children's immune systems; and
- differences in the clearance of chemicals—the higher clearance of certain chemicals from the body in children compensates in part for the greater sensitivity for their developing organ systems (Renwick, 1999) but for some other chemicals, clearance may be lower.

The potential impact of these differences highlights the need for agent-by-agent appraisal.

1.11.2 Risk assessment and older persons

For the ageing, there is a lack of functional reserve in the physiological and psychological systems. Distribution of chemical agents is affected by changes in body composition with age: body fat increases and body water decreases with age. The clearance of renally eliminated compounds is reduced because of changes in renal function. Liver function can be reduced in the elderly affecting biotransformation of chemical agents. Increased sensitivity to the central nervous system in the aging population from many drugs has been reported (Crome 1999). Changes will occur to the immunological system often resulting in reduced immunocompetance.

Ageing populations are very heterogeneous in terms of their general health. For those with impaired health, there may be a variety of conditions present.

Cognitive impairment is common in the very old and affects their abilities to recognise, interpret and react to acute and chronic environmental hazards. They are higher consumers of pharmaceuticals and there is a potential interaction with these pharmaceuticals and other agents.

1.11.3 Risk assessment and gender

Gender differences may need to be taken into consideration when identifying potential exposure pathways in the exposure assessment phase and characterising potential adverse health effects in the risk characterisation phase of the risk assessment process.

There are anthropometric (e.g. height, weight, body surface area) and body composition differences (e.g. fat content, muscle mass) between males and females that may affect exposure concentrations of agents from different pathways. These differences may also influence the absorption, distribution, metabolism and elimination of xenobiotics and have a significant influence on toxicity (Silvaggio and Mattison, 1994). Some of the factors which influence these processes are summarised in Tables 1–4.

Men and women also differ in many lifestyle factors (e.g. alcohol drinking and cigarette

smoking) dietary patterns and how they spend their time (American Industrial Health Foundation, 1994; US EPA, 1996) and their occupational exposures. These factors may influence the exposure and effect of an agent on the individual.

For many chemical toxicants there are important differences between males and females in experimental studies. Calabrese (1985) identified 200 toxicants where toxicological data analysis of animal studies suggest there are important differences between males and females in the expression of toxicity.

There have been reports of differences when comparing men and non-pregnant women in their response to toxic levels of lead, beryllium and benzene. Gender differences have also been reported to occur from exposure to ionising radiation, noise and vibration and extreme temperature changes (i.e. heat and cold stress) (Hunt, 1982).

Table 1: Factors influencing the absorption of chemicals

Parameter	Physiological difference	Toxicokinetic impact
Gastric juice pH	M < F < pregnant F	Absorption of acids/bases modified by change in pH
Gastric juice flow	M > F > pregnant F	Absorption modified by decreasing flow
Intestinal motility	M > F > pregnant F	Absorption increases with decreasing motility
Gastric emptying	M > F > pregnant F	Absorption and gastric metabolism increase with decreasing gastric emptying
Dermal hydration	Pregnant F > M, F	Altered absorption in pregnant F
Dermal thickness	M > F	Absorption decreases with increasing dermal thickness
Body surface area	M > pregnant F > F	Absorption increases with increasing body surface area
Skin blood flow	Pregnant F > M, F	Absorption increases with increasing skin blood flow
Pulmonary function	M > pregnant F > F	Pulmonary exposure increases with increasing minute volume
Cardiac output	M > pregnant F > F	Absorption increases with increasing cardiac output

F, female; M, male

Table 2: Factors influencing the distribution of chemicals in the body

Parameter	Physiological difference	Toxicokinetic impact
Plasma volume	Pregnant F > M > F	Concentration decreases with increasing volume
Total body water	M > pregnant F > F	Concentration decreases with increasing body water
Plasma proteins	M, F > pregnant F	Concentration fluctuates with changes in plasma proteins and protein binding
Body fat	Pregnant F > F > M	Body burden of lipid-soluble chemicals increases with increasing body fat
Cardiac output	M > pregnant F > F	Distribution rate increases with increasing cardiac output

F, female; M, male

Table 3: Factors influencing the rate of metabolism of chemicals

Parameter	Physiological difference	Toxicokinetic impact
Hepatic metabolism	Higher BMR in M, fluctuating hepatic metabolism in pregnant F	Metabolism generally increases with BMR
Extra-hepatic metabolism	Metabolism by fetus/placenta	Metabolism fluctuates
Plasma proteins	Decreased in pregnant F	Elimination fluctuates with changes in plasma proteins and protein binding

BMR, basal metabolic rate; F, female; M, male

Table 4: Factors influencing the elimination of chemicals from the body

Parameter	Physiological difference	Toxicokinetic impact
Renal blood flow, GFR	Pregnant F > M > F	Renal elimination increases with increasing GFR
Pulmonary function	M > pregnant F > F	Pulmonary elimination increases with increasing minute volume
Plasma proteins	Decreased in pregnant F	Elimination fluctuates with changes in plasma protein and protein binding

GFR, glomerular filtration rate; F, female; M, male

(tables adapted from Government/Research Councils Initiative on Risk Assessment and Toxicology, 1999)

1.11.4 Risk assessment and reproductive status

The human reproductive system is susceptible to environmental factors that can produce a variety of adverse effects during the production of ova (oocytogenesis) and viable sperm (spermatogenesis); on fertilisation; on implantation within the uterus; and growth and development of the embryo and fetus.

Reproductive status is also influenced by the extent of exposure and adverse effects from occupational and environmental agents. Teratogenesis (abnormal development of the embryo and fetus) is a risk for the fetus that may be exposed to environmental agents. The principal factors that determine an agent's risk of teratogenicity and which need to be considered in risk assessment include (Goldfrank *et al*, 1990):

- the nature of the agent;
- access of the agent to the fetus;
- the onset and duration of exposure;
- the level and duration of dosage; and
- the genetic constitution of the fetus.

Substances that inhibit mitosis, (e.g. antineoplastic agents such as vincristine and vinblastine) are also of a particular risk to pregnant women and exposure to such agents may lead to teratogenicity and embryotoxicity. The female fetus is sensitive to toxins affecting gametogenesis which, in humans, finishes by the seventh month.

Access of an agent to the fetus is determined by its molecular weight. Generally the larger the molecular weight of a substance, the less likely it will cross the placental barrier. Most teratogenic effects are also dose related, that is, the larger the dose, the more likely and severe the effect. High dose exposures to polychlorinated biphenyls (PCBs) have been associated with fetal abnormality.

Timing of exposure is particularly important. The critical period for organogenesis is in the first trimester (between days 18 and 55 of gestation).

This is the time of greatest cell differentiation and environmental agents may have a profound effect on development at this stage. For example, with thalidomide the period of greatest sensitivity appears to be between days 21 and 33 of gestation. The effects of thalidomide on the fetus do not appear to be dose related and teratogenic effects appeared in over 80 per cent of the fetuses exposed during the critical period (American Academy of Pediatrics, 1999)

The extent of the toxicity effect will also depend on the genetically determined detoxification mechanisms (i.e. enzyme systems) of individuals.

Exposure of environmental or occupational agents can also occur at the postnatal stage. The production of milk during nursing and breast-feeding is one pathway for the excretion of contaminants such as lead, mercury, PCBs and organochlorine pesticides (e.g. DDT) stored in other body tissues. Kinetic processes such as absorption, distribution and elimination will influence the passage of agents into breast milk. Milk has a high fat and protein concentration and lipid-soluble or protein-bound contaminants pass readily to milk and are dissolved in or bound to the milk fat and protein. (Hunt, 1982).

1.11.5 Risk assessment and lifestyle factors

Lifestyle factors may have an impact on individual risk assessments and population risk assessments if the activity is widespread. For this reason, the potential influence of lifestyle factors needs to be clearly identified in risk assessments. Specific lifestyle factors that may have an effect on risk assessment include:

- tobacco smoking;
- diet; and
- hobbies.

Tobacco smoking will affect the exposure assessment component of the risk assessment process because there will be an increase in background exposure to substances found in smoke e.g. cadmium, cyanide and polycyclic aromatic hydrocarbons (PAHs).

Tobacco smoking also affects the toxicity assessment component. Maternal cigarette smoking and passive smoking have been associated with respiratory illness, acute toxicity and cardiotoxicity among newborns. Furthermore epidemiological studies have shown evidence of synergistic interaction between human carcinogens and long term cigarette smoking. The best studied interactions have included joint exposure to tobacco and radon and tobacco and asbestos, respectively. Results from epidemiological studies of joint exposure to radon and cigarette smoke have shown an additive or possibly a multiplicative increase in the number of cancers induced and a synergistic decrease in the latency period for tumour induction.

Epidemiological studies have shown that asbestos and tobacco administered together can produce an increased incidence in lung cancer that is greater than from the administration of either agent alone and the interaction is considered to be multiplicative by most investigators (NRC, 1994).

Diet will also influence the stages of the risk assessment process particularly the toxicity and exposure assessment stages. Interactions between toxic metals and essential metals from the diet have been known to affect the risk of toxicity. Absorption of toxic metals from the lung and gastrointestinal tract may be influenced by the presence of an essential metal or trace element if the toxic metal shares the same homeostatic mechanism. Examples are lead and calcium, and cadmium and iron. Other dietary interactions include an inverse relationship between protein content of the diet and cadmium and lead toxicity. Vitamin C in the diet also reduces lead and cadmium absorption.

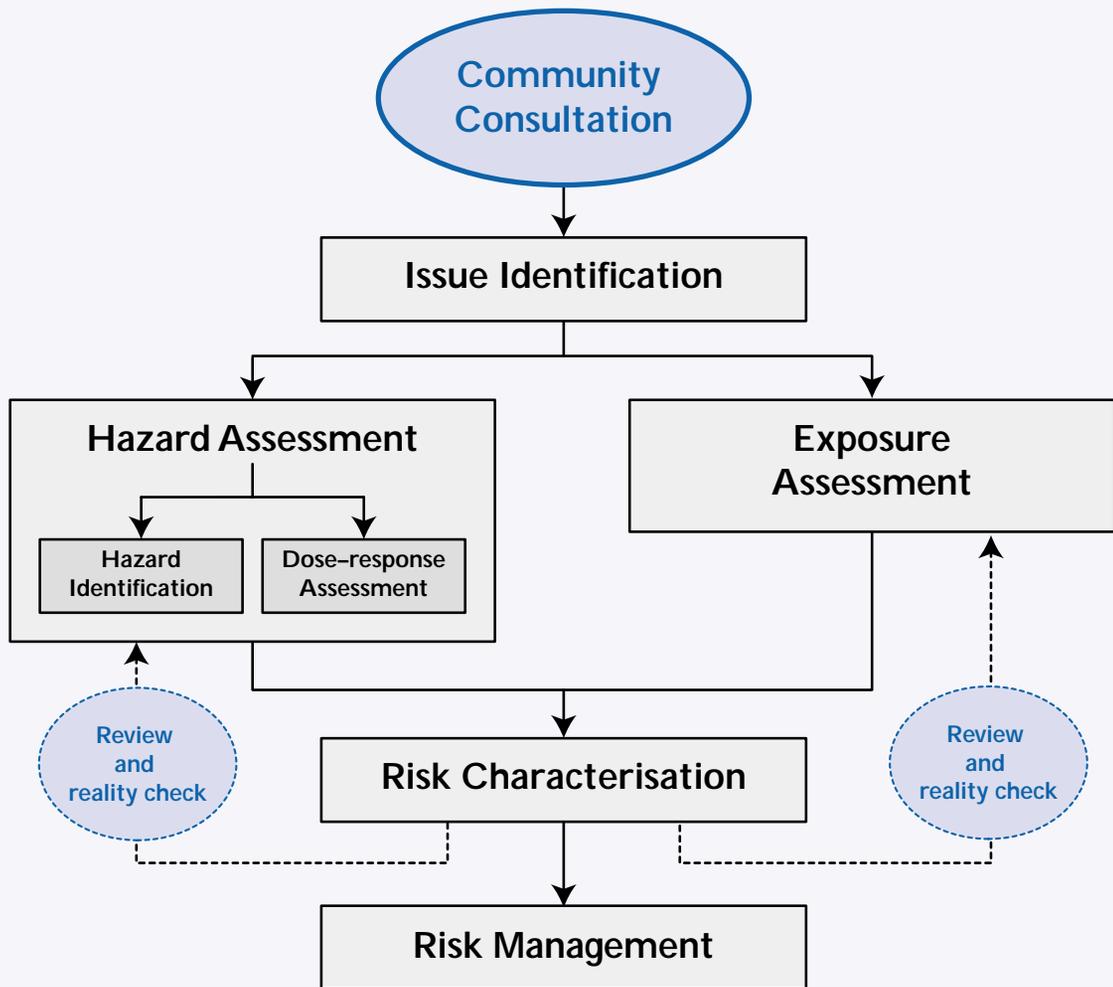
Different types of food will have different amounts of agents and hence cause a range of toxic effects depending on dietary habits. For example the major pathway of exposure to many toxic metals in children is food and children consume more joules per kg of body weight than adults do. Furthermore, children have a higher gastrointestinal absorption of metals, particularly lead.

Alcohol ingestion may influence toxicity indirectly by altering diet and reducing essential mineral intake. The ingestion of alcoholic beverages (ethanol), fats, protein, calories and aflatoxins has been implicated in carcinogenesis. (Klaassen, 1996).

Homegrown produce such as vegetables has been associated with contamination of heavy metals such as lead, arsenic and cadmium. Free-range poultry tissue (e.g. meat, fat, skin) and eggs (egg yolk) have been associated with contamination by organochlorine pesticides such as aldrin, dieldrin and DDT. Hence the consumption of these food types may result in an increased exposure to these agents (Cross and Taylor, 1996).

The type of diet can also influence the risk to exposure to hazardous agents. Individuals who are vegetarians will have a reduced exposure to zinc. Individuals who consume barbecued foods can be exposed to relatively large amounts of PAHs from the charcoal used to cook the food. Populations (e.g. general population and fishermen) who consume seafood may be exposed to heavy metals such as mercury in fish and zinc in shellfish (e.g. oysters).

The exposure to a hazard may also be influenced by lifestyle and hobbies. For example the amount of time spent indoors (e.g. in the home, work environment/office, factory), outdoors or travelling in the car, bus, aeroplane, train will also influence the amount of exposure of agents and the risk to health (e.g. lead, benzene levels in the car, cosmic radiation in aeroplanes etc). Hobbies such as pistol shooting in indoor shooting ranges; antique furniture restoration, lead soldering, boat building and lead lighting can result in an increased exposure to lead (Lead Safe, 1997). House renovating can also result to an increase exposure to hazardous agents such as lead and asbestos. Other hobbies involving paint stripping using methylene chloride can cause exposure to its metabolic breakdown product, carbon monoxide, and car maintenance can also result in an increase in exposure to hydrocarbons and heavy metals.



An Australian Framework for Risk Assessment

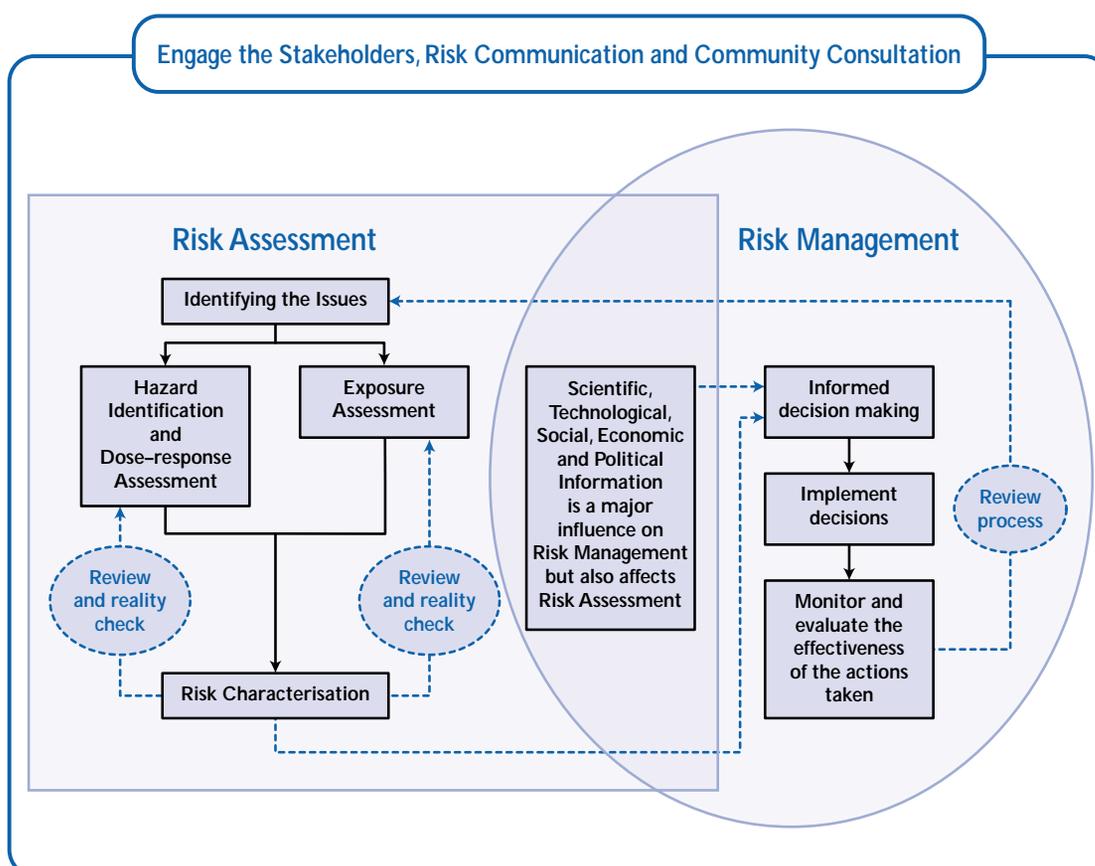
2.1 Context of Risk Assessment

The relationships of environmental health risk assessment, risk management, stakeholder engagement, risk communication and community consultation are detailed in Figure 2 which demonstrates the links between the steps and the overlap with risk management.

2.2 Community Consultation and Involvement

There is a growing awareness of the need for appropriate community consultation and involvement. The process may not lead to consensus, but it is likely to ultimately smooth the passage of a proposal to increase the validity of the risk management process, and to provide information that is useful throughout the risk assessment and management steps.

Figure 2: Relationship of risk assessment and risk management



(adapted from P/CCRARM, 1997; Patton, 1998; NRC, 1983)

A partnership approach is most appropriate and the scope and nature of community involvement should be commensurate with the potential effects on the community. Triggers for community involvement should be identified.

There are usually time, money and resource pressures on a development but urgency to achieve short term goals can ultimately lead to delays (See Box 1).

Risk cannot be managed without addressing human behaviour so that community involvement is essential in the process. Community consultation can provide assistance at each step of the risk assessment process. Examples follow of how it can be used at each stage but it does not need to be tightly compartmentalised.

Issue identification

At first contact community involvement can provide a range of information about the site,

health concerns and potential value conflicts. A communication plan can be prepared at this time. Further matters where information can be exchanged with the community include:

- why the risk assessment is being undertaken;
- what the risk assessment will consider (i.e. what risks deserve attention);
- what information may be available from the community;
- how the risk assessment will be performed (i.e. what process will be used); and
- what will happen to the risk assessment (i.e. how does it fit into the risk management process).

Hazard identification

- To provide information about data gaps, local perceptions of hazards and the applicability of assumptions to the community.

Box 1: Management of scheduled wastes

By the late 1980s Australia had accumulated a substantial store of waste organic pollutants such as the organochlorine pesticides (e.g. DDT, aldrin and heptachlor), hexachlorobenzene and PCBs. These wastes were called 'intractable wastes' as they were persistent and difficult to destroy. In an attempt to dispose of them a decision was made by the Australian Government to develop high temperature incinerators and to locate them in New South Wales, Victoria, Western Australia or the Northern Territory. There were at least twelve attempts to establish a high temperature incinerator (HTI) for scheduled wastes. These attempts to site a HTI failed as the communities were unwilling to accept the risks associated with toxic waste incineration.)

In July 1992, after the final proposal to establish a HTI had failed, the Australian and New Zealand Environment and Conservation Council (ANZECC), acting on the advice of an independent panel, decided to abandon the proposal to establish a centralised high temperature waste disposal facility.

The rejection of the HTI created significant problems for the disposal of the scheduled wastes in Australia but also created significant opportunities as alternative methods of destruction had to be investigated and established. While in some cases these technologies were more expensive to establish, as pollution control requirements for HTIs expanded, the price differentiation decreased.

In response to this situation two committees were established; the Scheduled Wastes Management Group (SWMG) and the National Advisory Body (NAB). The SWMG was made up of senior officers of the State, Territory and Commonwealth environment departments. The NAB comprised stakeholders from industry, government, unions and environmental groups. Ultimately, through a process of negotiation and broad community consultation, a series of national management plans were developed that were agreed to by the members of the advisory body. These plans have been endorsed by ANZECC and are currently being adopted into State legislation and implemented.

Dose–response relationships

- The community’s attitudes towards the range and type of technical data and the assumptions made in the interpretation of the data.

Exposure assessment

- Information about: the community’s attitudes to biological monitoring, and health monitoring; local knowledge of the range and nature of exposures; relevant exposure settings; the community’s attitudes to sampling design and environmental monitoring and to the uncertainties and assumptions in the exposure assessment phase.

Risk characterisation

- Information of the community’s concepts of risk and safety

Evaluating the actions taken

- Community involvement will affect how environmental monitoring may be undertaken to ensure that the best decisions are made.

Risk management

- Information of the community’s concepts of acceptable risk and safety. Community consultation is an integral part of risk management.

The objectives for each stage of the risk assessment process should be examined to determine the nature of the community consultation.

At a legislative and administrative level the requirements for, and practise of, community consultation vary. For example, there is limited community consultation required for certain aspects of the approval of therapeutics.

2.3 Risk Perception and Risk Communication

Ideally ‘actual’, ‘estimated’ and ‘perceived’ risks should be closely aligned. This presents an immediate problem as actual risks are unquantifiable and unknowable. The aim of risk

assessment should be to achieve the alignment of actual and estimated risk and the aim of good risk communication should be the alignment of perceived and actual risk.

All parties, both expert and non-expert will have perceptions of risks. Experts and non-experts alike are influenced by emotion, beliefs and their views of the world (Thomas and Hrudey, 1997).

A simple numerical estimate of risk portrayed as the ‘real risk’ ignores the subjectivity and multiple dimensions of risks (Thomas and Hrudey, 1997). People see risk as multi-dimensional and not represented by a numerical value and will judge it according to its characteristics and context. For example trauma or death as the result of an involuntary catastrophic reaction is likely to be dreaded more than the situation where the adverse consequences are the result of a situation where the risk is assumed voluntarily and the person feels some degree of control (e.g. motor vehicle crashes).

Concerns about risk will be heightened by risks that are:

- involuntary or imposed on the community;
- man made rather than natural;
- inescapable;
- controlled by parties outside the community;
- have little or no benefit to the community;
- unfairly distributed;
- related to an untrusted source;
- exotic or unfamiliar;
- affect children or pregnant women;
- affect identifiable rather than anonymous people;
- the cause of insidious and irreversible damage;
- the cause of dreaded health effects such as cancer;
- poorly understood by science; and

- subject to contradictory statements from responsible sources (or, even worse, from the same source) (DOH, 1998).

Concerns about risk will be lessened when:

- the risks are voluntarily assumed;
- the risks have a natural origin;
- individuals or the community feel able to exert some control over the risks;
- there are clear benefits from the risks;
- the risks are fairly distributed;
- the risks are associated with a trusted source;
- the risks are familiar;
- the risks only affect adults;
- the risks are understood; and
- the process of how the risks are determined is understood.

Risk communication is often seen as a one-way process aimed at rectifying incongruities between the community's perceptions and the opinions of regulators. However it should be recognised that all parties will have perceptions about a situation and the ultimate aim is to draw these perceptions about risk, the estimated levels of risks, and the actual levels of risks as closely together as possible.

Risk communication should not be seen as a retrospective form of community involvement and consultation. It is an interactive process involving the exchange among individuals groups and institutions of information and expert opinions about the nature, severity and acceptability of risks and the decisions taken to combat them.

Good risk communication and consultation results in an outcome where there is a high level of agreement between the affected parties. It also entails knowing how to respond to public concern and is a genuine process conducted with the community's interest in mind. Good risk communication and community involvement will enable government and industry to better understand public perceptions and to more readily anticipate community responses. It will increase

the effectiveness of risk management decisions and reduce unwarranted tension. It will explain risks more effectively and constructively inform communities.

Information about risks needs to take into account their complexities and uncertainties and be constructed so that they can result in meaningful interpretation by all parties. People's responses to risk will be strongly influenced by their wider values so that isolated facts about risks may have limited impact on their acceptability (DOH, 1991) especially when they are perceived to have little benefit.

The communication process need not always be to reduce concern about risks. Many public health interventions are intended to increase public concerns about risks such as smoking or excessive alcohol consumption. In communities with regional lead contamination (e.g. Port Pirie or Broken Hill), public health activities have been designed to increase concerns about what are often subtle effects and to provide information about specific activities that can be undertaken to protect children.

Some of the key principles of effective risk communication are:

- accepting and involving the public as a partner and stakeholder;
- carefully planning and evaluating the nature and content of the risk communication undertaken so that it is relevant and understandable;
- listening to the public's specific concerns. Trust, credibility, competence, fairness and empathy are often as important to the community as statistics and scientific details. Trust and credibility are very difficult to regain if lost. Experts do not command automatic trust;
- being honest, realistic and open;
- appreciating that intentional communication is often only a minor part of the message actually conveyed. The manner of delivery and its tone may be more important than its content;

- ensuring that information is accurate, consistent between agencies, and not speculative;
- effectively communicating with the media;
- acknowledging the public concerns and the effects on the community; and
- focusing on issues and processes rather than people and behaviours.

(adapted from US EPA 1988, DOH 1998)

Even with good community consultation and risk communication there may be disagreement between parties.

In designing community consultation and risk communication programs the following issues should be addressed:

- What is the purpose of the consultation? Is it to gain information, ideas and options? Is it to build credibility? Is it to meet regulatory requirements? Is it to provide maximum opportunity for public involvement?
- Who is the audience? Anybody who perceives themselves to be affected should be able to participate in the process. 'The community' is diverse, with different groups regarding risk in different ways. They may need a range of messages and styles of delivery;
- How will industry be involved?
- What does the community want to know? Local community leaders, environmental groups, and environmental health officers may often be able to provide broader information about particular concerns (See Box 2);
- How will communication occur? Smaller, informal meetings are often more effective than large impersonal meetings. At large meetings some members of the community may feel apprehensive about asking questions or expressing opinions. There is a need to avoid partisan Chairs for meetings and written materials may have more credibility

than the spoken word. Materials need to be pre-tested before they are printed and distributed and evaluated afterwards. There is a need to determine how industry and government will listen to concerns and how information about concerns will be sought. If the community is not listened to, it will cease to listen;

- Do not seek more feedback than you are able to use as this will lead to community disillusion and loss of trust (adapted from Chess and Hance, 1994); and
- Seeking grudging approval from the community will be far less productive than genuinely seeking feedback that will be used, asking for comments in a situation where plans can be changed.

Avoid problems by anticipating issues such as:

- lack of communication skills (by any of the parties);
- limited resources and time and staffing (by any of the parties);
- confusion between the 'risk assessment' and 'risk management' phases;
- cultural differences;
- legal considerations;
- external politics, hidden agendas and political pressures;
- conflicting interests within the varying parties concerned;
- impacts from the media; and
- evaluation of the consultation. Evaluation is a continuous process designed to avoid mid course corrections and repeating failures. Evaluation may cover: whether the communication was timely; whether the communication was sufficient; whether the public was empowered; and whether the credibility and trust of the organisation was enhanced (adapted from Chess and Hance, 1994).

Box 2: Aluminium smelting and the community

Public consultation and commitment to an independent study resulted in a successful resolution of public health concerns in the Portland community.

In 1994, Portland Aluminium sought approval to increase sulfur dioxide emissions by nearly 30 per cent so that it could increase production at its aluminium smelter in Portland.

Members of the community were opposed to any increase in emissions with the central issue being the effect of sulfur dioxide on health. There was a widespread belief that asthma levels were high in the Portland area. There were also similar concerns about the levels of sore and itchy eyes and skin irritations, as well as odours and acid smells.

Portland Aluminium stated that, with increased emissions, the use of taller stacks would improve air quality at ground level by allowing sulfur dioxide to disperse higher into the atmosphere.

Many residents had concerns about the reliability of air monitoring within the Portland area and believed they were not given complete information about the potential health effects associated with aluminium production.

In response to these concerns, the Victorian Department of Human Services established a Health Professionals Advisory Committee which included local health professionals, a respiratory physician and Department representatives.

The role of the committee was to organise and oversee an independent health study to assess the potential for any adverse health effects from the proposed increase in sulfur dioxide emissions from the smelter.

A proactive program of community consultation was established and local residents were interviewed and given the opportunity to raise key areas of concern. The committee then ensured that these concerns were addressed in the study's terms of reference.

The Victorian EPA then granted Portland Aluminium approval to replace the low stacks at the smelter with six tall stacks and to monitor their emissions for 12 weeks. The findings of the health study and the results of monitoring of emissions from the old stacks and new, tall stacks were to be evaluated before the application to increase sulfur dioxide emissions was granted.

The health study involved a literature review and a health survey. To determine whether there was an increase in asthma and itchy eyes in Portland, the consultants surveyed residents of Portland and Warrnambool (a similar population) using a questionnaire which covered a range of health symptoms.

The study also reviewed the measurements of ground level concentrations of sulfur dioxide that resulted from emissions from the older low stacks and the new tall stacks, after they were built.

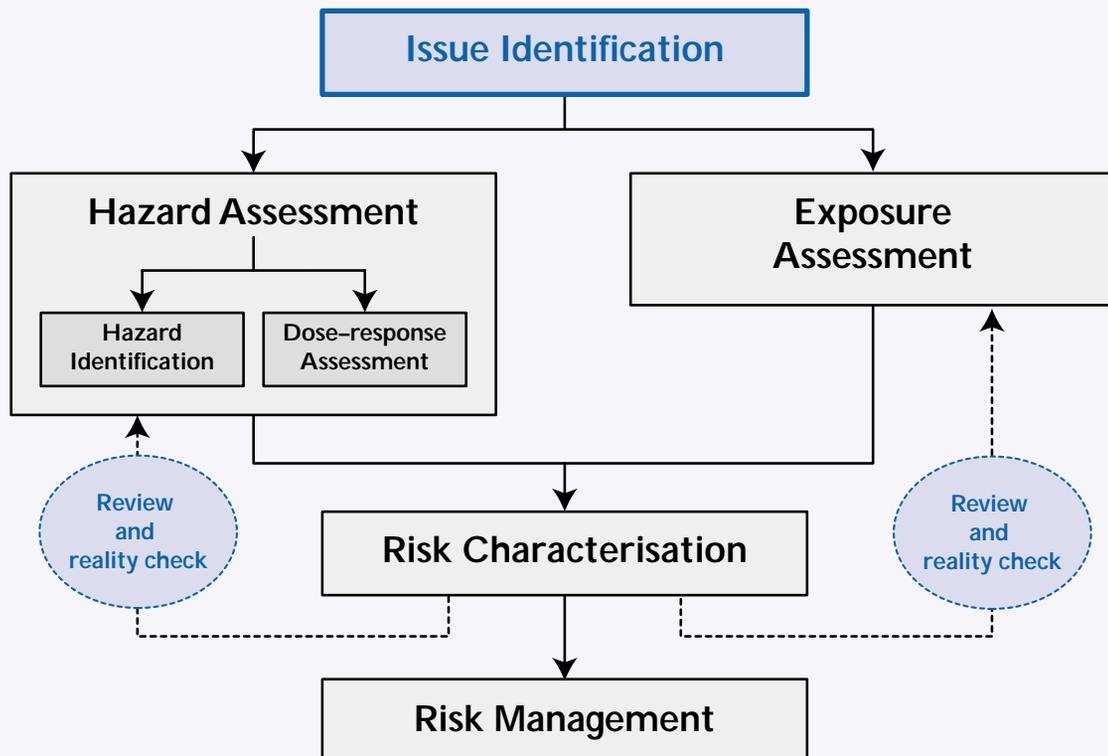
The literature review found that there was no evidence that sulfur dioxide caused people to become asthmatic but it did cause symptoms such as wheeze to occur more often. The survey showed that other health symptoms such as itchy eyes, cough, stuffy nose, sore throat and skin rash were more common in Portland but there was no significant difference in the proportion of people with asthma and wheeze, although both cities had high rates.

Monitoring data for 1995, 1996 and 1997 showed that the one-hour 'acceptable level' for sulfur dioxide at ground level was exceeded four times over this period. However, monitoring of emissions from the new tall stacks showed much lower levels.

The monitoring results were used to predict the ground level concentrations of sulfur dioxide that would occur with the proposed 30 per cent increase in smelter emissions. The levels in Portland and surrounding areas were predicted to be well below the standard.

The results of the study were discussed with the community at a public meeting and a report of the study was circulated. The study concluded that there was no evidence that the proposed increase in sulfur dioxide emissions from the taller stacks would be detrimental to health.

The report was well received by the community. Portland Aluminium was given EPA approval to increase sulfur dioxide emissions from the smelter and ongoing monitoring of air pollutants would be a condition of the licence.



Issue Identification

3.1 Introduction

Issue identification identifies issues for which risk assessment is useful and establishes a context for the risk assessment by a process of identifying the concerns that the risk assessment needs to address. Issue Identification draws on all relevant lines of information.

Issue Identification comprises several phases:

1. identification of environmental health issues (or an individual issue) and determining whether there are hazards amenable to risk assessment. This will involve demarcating 'hazards' from 'issues' and may require environmental sampling (See Section 8.5);
2. putting the hazards into their environmental health context (clarification and prioritising of problems and hazards);
3. identification of potential interactions between agents; and
4. stating clearly why risk assessment is needed and the scope and objectives of the risk assessment. This will involve identifying problems for which information is, or can be, available to undertake adequate risk assessments and problems which risk assessment cannot assist (ACDP, 1996; P/CCRARM, 1997).

At this stage it often becomes apparent that the setting for the risk assessment is a situation where:

- there are multiple, interacting hazards rather than an isolated hazard;
- there are concerns about a range of potential health effects from various hazards;
- there is variable and often superficial information on exposure and the level of health problems; and
- there is an environment of public anxiety, anger and impatience.

A consideration of conflicts will assist in providing a context for effective risk assessment, risk management, risk communication and community consultation. Examples of these value conflicts are:

- economic activity (e.g. jobs, property values) vs conservation and health protection;
- personal experiences and perceptions vs so-called 'objective' evidence;
- quality of life and aesthetics vs defined disease problems;
- local control and involvement vs external control structures;
- local concerns vs national/statewide/regional concerns;
- monitoring and health data vs personal experience;
- personal experience vs scientific literature in making causal inferences;
- broad community concerns vs narrow interest groups;
- urgency vs priority determination;
- political activism vs incremental, scientific analysis; and
- voluntary exposure hazards vs involuntary exposure hazards.

Communication and consultation is important so that these conflicts are resolved.

When issues have been identified, a preliminary qualitative risk assessment may be carried out to prioritise issues for more detailed study. This will consider the likelihood of exposure and the possible consequences taking into account things such as biological plausibility, evidence of exposure and community concerns.

3.2 Identification of Environmental Health Hazards

Environmental health hazards may be caused by physical, chemical, biological or social factors in the environment.

Physical factors include heat, cold, noise, mechanical hazards, solar radiation, ionising radiation (e.g. X-rays) and non-ionising radiation (e.g. microwaves), noise and vibration.

Chemical factors include synthetic and naturally occurring substances.

Biological factors include viruses, prions, bacteria, parasites and vermin.

Social factors include poverty and unemployment.

Hazardous agents may be identified from range of data sources including:

- environmental monitoring (e.g. of food, air, water and soil);
- emissions inventories (e.g. the National Pollutant Inventory);
- biological monitoring (e.g. of children's blood lead levels or Ross River Virus antibody levels);
- disease surveillance (e.g. of *Salmonella* types for food poisoning, skin cancer rates, pregnancy outcomes);
- health monitoring (e.g. of lung function testing to detect the onset of environmentally-caused asthma);
- epidemiological studies (e.g. of particular disease rates in certain populations such as workers) to identify previously unknown hazards; and
- information about analogous hazards.

3.3 Environmental Sampling and Analysis

Environmental sampling and analysis is a key factor in identifying the agents that may be present, their concentrations and distributions. The results of initial environmental sampling and analysis will assist in identifying issues and will influence the direction of the risk assessment.

It will be particularly important in the Exposure Assessment phase and detailed information is provided in Section 8.

3.4 Putting the Hazards into their Environmental Health Context

This entails a consideration of:

- **Whether the hazard has a single or multiple sources** (e.g. atrazine contamination of a drinking water supply from a chemical spill vs particulates in ambient air arising from diesel engines, wood stoves and environmental tobacco smoke);
- **Whether the contaminant affects multiple environmental media** (e.g. lead smelter emissions contaminating soil, air, water and food);
- **How do stakeholders perceive the problem? Do different groups have different perceptions?** A stakeholder group comprised of workers at a smelter who are also nearby residents may have complex perceptions; and
- **How do the hazards compare to other environmental hazards affecting the community?** This component of the appraisal will be affected by objective data (e.g. of different disease rates) and subjective perceptions by the stakeholders (P/CCRARM, 1997). It enables the priority order of risk assessment to be determined.

There may be multiple iterations of hazard appraisal as the risk assessment proceeds and new information and perspectives emerge.

3.5 Identification of Potential Interactions between Agents

There may be interactions between the physical, chemical, biological and social hazards that need to be identified and considered as part of the risk assessment. For example malnutrition may increase the absorption of cadmium and hence the risk of renal dysfunction. A high zinc intake may reduce the gastrointestinal absorption of cadmium reducing the risk from high environmental levels. People who carry the sickle cell anaemia gene have a reduced risk of malaria, while people with the genetic condition of Wilson Disease will have a greatly increased risk from environmental copper.

There are several potential types of interaction between hazardous agents:

- **Additive** where the combined effect of two or more agents is equal to the sum of the individual effects e.g. $2+3=5$. An example is cholinesterase inhibition from simultaneous exposure to two organophosphorus insecticides;
- **Synergistic** where the combined effect of two or more agents is much greater than the sum of the individual effects e.g. $2+2=20$. Examples are risk of lung cancer from asbestos and smoking and the hepatotoxicity of carbon tetrachloride and ethanol;
- **Potentiation** where one agent alone does not have a toxic effect but, when given with another agent, results in a much greater toxic effect from the other agent e.g. $3+0=8$. An example is risk of cancer from an initiator and a promoter (tobacco smoke contains both); and
- **Antagonistic** where the combined effect of two or more agents is less than the sum of the individual effects (Hodgson *et al*, 1998). An example is risk of cyanide toxicity from cyanide after receiving an antidote such as Kelocyanor (Klaassen, 1996).

The potential hazards from interactions between chemicals are widely discussed but there are no generally accepted methods for predictive appraisal of interactions as part of the risk assessment process (See Section 6.9).

3.6 Stating Why Risk Assessment is Needed

In some instances the hazard and need for action will be so obvious to all stakeholders that risk assessment will be undertaken only to determine the effect and cost-effectiveness of the various management options. In this situation, the opportunity costs of undertaking a risk assessment to determine whether action is necessary are considerable. In other instances risk assessment will be inappropriate as the solutions to the problem will not be based on addressing

risk but on addressing other factors such as social and political concerns.

In deciding to undertake a risk assessment the following matters must be clear:

- what is the concern?
- why is it a concern?
- how urgent is the concern?
- how do stakeholders perceive the concern? (P/CCRARM, 1997)

Risk assessment is inappropriate when it is a ritual rather than a meaningful process and should not be undertaken when:

- there is no data or an insufficient amount of data;
- there is an inability to take action or it is too late to take action;
- there are insufficient resources; and
- it is politically or socially unacceptable.

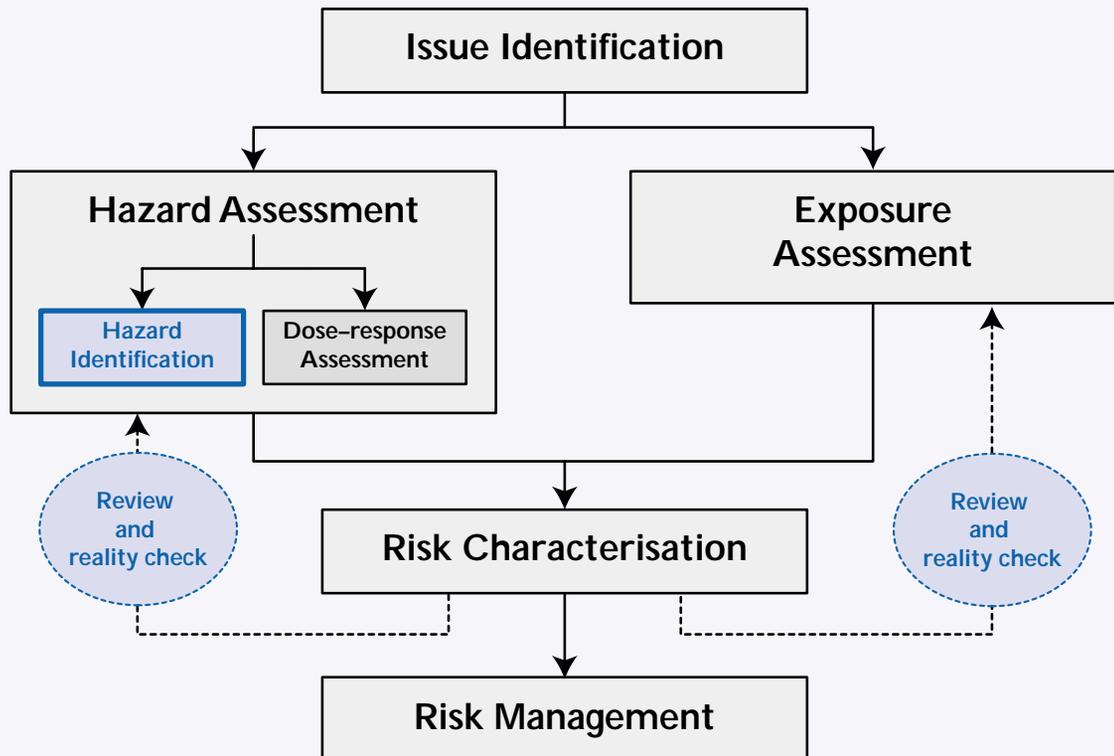
Of relevance to risk assessment is Bardwell's reference (1991) to a study that indicates that 'about 90 per cent of real world problem solving is spent:

- solving the wrong problem;
- stating the question so that it cannot be answered;
- solving a solution;
- stating questions too generically; or
- trying to get agreement on the answer before there is agreement on the question' (Bardwell, 1991 cited in Thornton and Paulsen, 1998, p. 799).

3.7 Limitations and Uncertainties

At this stage it may become apparent that there are limitations to the proposed risk assessment such as:

- information gaps e.g. effects of mixtures, low level and variable exposures over time; relative contributions of 'lifestyle' factors vs other environmental hazards; variations in sensitivity;
- poor exposure information e.g. complex mixtures of hazards with complex behaviours in the environment; limited knowledge about the actual or potential population and sensitive sub populations; geographic variations in exposure;
- limitations of toxicological and epidemiological research e.g. small populations, limited exposure information; multifactorial causes of many diseases; 'background noise' affecting research into common diseases or symptoms; population heterogeneity; expensive and time consuming;
- complexity e.g. large number of combinations of hazards, exposures and health states;
- complex causality for many health conditions;
- confidentiality of health and commercial information;
- charged atmosphere of fear, antagonism and distrust; and
- value conflicts.



Hazard Assessment— Part 1:

Hazard Identification—Toxicology

4.1 Introduction

There are two elements to the toxicological assessment: hazard identification and dose–response assessment.

Hazard identification examines the capacity of an agent to cause adverse health effects in humans and other animals (US EPA, 1995). It is a qualitative description based on the type and quality of the data, complementary information (e.g. structure–activity analysis, genetic toxicity, pharmacokinetic), and the weight of evidence from these various sources (*ibid*). Key issues include (*ibid*):

- nature, reliability and consistency of human and animal studies;
- the availability of information about the mechanistic basis for activity; and
- the relevance of the animal studies to humans.

The dose–response assessment examines the quantitative relationships between exposure and the effects of concern. ‘The determination of whether there is a hazard is often dependent on whether a dose–response relationship is present’ (*ibid*). Important issues include:

- the relationship between the extrapolation models selected and available information on biological mechanisms;
- how appropriate data sets were selected from those that show the range of possible potencies both in laboratory animals and humans;
- the basis for selecting interspecies scaling factors to account for scaling doses from experimental animals to humans’;
- relevance of the exposure routes used in the studies to a particular assessment and the interrelationships of potential effects from different exposure routes;
- environmental conditions (pH, organic matter, clay content, temperature);

- the relevance to the assessment of ‘the expected duration of exposure and the exposure durations in the studies forming the basis of the dose–response assessment’; and
- ‘the potential for differing susceptibilities in population subgroups’ (*ibid*)

Both qualitative and quantitative toxicity information is evaluated in assessing ‘the incidence of adverse effects occurring in humans at different exposure levels’ (US EPA, 1989, p. 1.6).

Hazard identification uses:

- **Animal data.** This is usually assessed by toxicological methods.
- **Human data.** This is usually assessed by epidemiological methods when groups of people are involved, or by toxicological methods when using case studies and acute chamber studies.
- **Other data.** This includes data such as structure–activity data or *in vitro* data assessed by toxicologists.

The data may come from a range of sources such as: ad hoc data, anecdotal data, case-report data and data collected from epidemiological registries (such as cancer or pregnancy outcome data). In each instance the quality of the study design and methodology and the resulting data will need to be rigorously assessed.

This chapter on toxicological evaluation is based in part on the draft OECD Monograph, *Guidance Notes for the Analysis and Evaluation of Repeat-Dose Toxicity Studies*, prepared for the OECD by the Chemicals Unit, Department of Health and Ageing, Canberra, Australia, in cooperation with the US EPA and the Canadian Pest Management Regulatory Agency (PMRA).

This chapter focuses on chemical hazards and in particular on some of the problems and pitfalls which may arise during an assessment of possible compound-related changes in parameters measured in toxicology studies conducted on a chemical or substance. It is intended to provide guidance on the process of hazard identification and assessment.

Toxicology studies have been designed to permit determination of toxic effects associated with exposure to chemical hazards. Such studies can provide information relating to toxic effects and potential health hazards likely to arise from single or repeated exposures, in terms of predicting potentially important toxicity end points and identifying potential target organs or systems. It is important to note that, over time, the scientific community will gain a better understanding of the mechanisms of toxicity and this may lead to changes in both methodology and interpretation of hazard data; analysis and evaluation of toxicity studies should reflect scientific consensus at the time the data are reviewed.

4.2 Toxicity Testing— Major *in vivo* Study Types

Hazard identification mostly relies on the results of *in vivo* toxicity studies conducted according to standard protocols e.g. OECD Test Guidelines (OECD, 1998). The following types of studies are defined:

- **Acute toxicity studies** are studies which investigate the effects of single doses of a substance. The LD₅₀ test, or medium lethal dose test (OECD test Guideline 401) which records gross toxicity and mortality data over a 14 day post-dosing period, has been commonly employed, but newer tests ('limit' tests and 'up-and-down' dosing methods) are now favoured as they reduce the numbers of animals required and reduce the suffering seen in the classical LD₅₀ test. OECD Test Guideline 420 covers acute oral toxicity determination by the 'Fixed Dose Method', TG 423 by the 'Acute Toxic Class Method', and TG 425 by the 'Up-and-Down Procedure'.

The standard acute toxicity studies include tests for: acute oral, dermal and inhalational toxicity, eye irritation, skin irritation and skin sensitisation. Such studies may serve as the basis for classification and labelling of a particular chemical or mixture, and serve as an initial guide to possible toxic modes of

action and in establishing a dosing regimen in sub-chronic toxicity studies.

- **Sub-chronic toxicity studies** are short term repeat-dose studies. A short-term study has been defined (WHO, 1990) as 'having a duration lasting up to 10 per cent of the animal's lifespan, 90 days in rats and mice, or 1 year in dogs', although the US EPA considers a 1 year dog study to be a chronic study. The main purpose of sub-chronic testing is to identify any target organs and to establish dose levels for chronic exposure studies.
- **Chronic toxicity studies**, or long-term studies, are defined as studies lasting for the greater part of the lifespan of the test animals, usually 18 months in mice, 2 years in rats (WHO, 1987; 1990). The protocol for these studies may cover the investigation of chronic toxicity or carcinogenicity, or both.
- **Reproductive toxicity studies** are studies designed to provide general information about the effects of a test substance on reproductive performance in both male and female animals, such as effects on mating behaviour, gonadal function, oestrous cycling, conception, implantation, parturition, lactation, weaning and neonatal mortality. These studies may also provide some information about developmental or teratogenic effects of the test substance. The conduct of and the results from these studies are very important to assess with care, since the reproductive process is critical for perpetuation of the species and factors or agents that alter or disrupt this process can have devastating consequences, both in fact and in public perception (Korach, 1998). For information on study design, refer to OECD Test Guideline 415, One-Generation Reproduction Toxicity Study; and 416, Two-Generation Reproduction Toxicity Study: (OECD, 1998)
- **Developmental toxicity studies** are studies which examine the spectrum of possible in utero outcomes for the conceptus, including death, malformations, functional deficits and

developmental delays (Tyl and Marr, 1997). Exposure during sensitive periods may alter normal development resulting in immediate effects, or may subsequently compromise normal physiological or behavioural functioning later in life. Since some developmental processes can occur peri- or postnatally, protocols for developmental studies are being reviewed with the possibility of extending the dosing period in developmental toxicity studies from the period covering major organogenesis to cover the perinatal and early postnatal period.

- **Genotoxicity studies** are designed to determine whether test chemicals can perturb genetic material to cause gene or chromosomal mutations. A large number of assay systems, especially *in vitro* systems, have been devised to detect the genotoxic or mutagenic potential of agents. Most authorities consider that a minimum set of data is required to define a mutagen/non-mutagen. These data usually consist of gene mutations in bacteria and mammalian cells and *in vitro* and *in vivo* cytogenetics. Newer assays which could provide additional information include the Comet assay, mutations in transgenic animals, fluorescent in situ hybridisation and cell transformation (IARC, 1999).

4.3 Important Issues in Toxicity Testing and Assessment

4.3.1 Study protocol and design

Dosing regimen

The purpose of toxicity studies is the detection of valid biological evidence for any toxic and/or oncogenic potential of the substance being investigated. Therefore, protocols should maximise the sensitivity of the test without significantly altering the accuracy and interpretability of the biological data obtained. The dose regimen has an extremely important bearing on these two critical elements.

Since the determination of dose responses for any observed effects is one of the objectives of repeat-

dose studies, at least 3 dose levels are normally required, as well as controls. US EPA guidelines allow a limit dose of 1000 mg/kg in chronic and sub-chronic studies; if this dose produces no observable toxic effects and if toxicity is not expected, based upon data on structurally-related compounds, then a full study using three dose levels might not be considered necessary. Ideally, the dose selection should maximise the detection of potential dose-response relationships and facilitate the extrapolation of these to potential hazards for other species including humans. The largest administered dose should not compromise biological interpretability of the observed responses. For example, it is generally considered that the upper dose should not:

- a) cause a body weight decrement from concurrent control values of greater than 10–12 per cent;
- b) in a dietary study, exceed 5 per cent of the total diet because of potential nutritional imbalances caused at higher levels or;
- c) produce severe toxic, pharmacological or physiological effects that might shorten duration of the study or otherwise compromise the study results;
- d) in a carcinogenicity study, alter survival in a significant manner due to effects other than tumour production.

The International Life Sciences Institute (ILSI) 'Risk Sciences Working Group on Dose Selection' has published its deliberations on the selection of doses in chronic rodent bioassays (Foran JA and the ILSI Risk Sciences Working Group on Dose Selection, 1997).

Although it has been argued that responses observed at doses far in excess of levels experienced under real or potential exposure conditions legitimately fall within the classical dose-response concept, there are valid scientific concerns that such doses introduce a further layer of uncertainty into the already difficult task of evaluating animal dose responses and the assessment of their relevance to human hazard identification and risk (Paynter, 1984). High

doses which overwhelm normal mechanisms for metabolism, detoxification and/or excretion, or produce severe tissue damage (i.e. necrosis, demyelination) can make interpretation difficult or lead to inappropriate conclusions about the extent of the hazard.

With respect to the selection of the low dose, it is commonly accepted that the lowest dose should not produce any evidence of toxicity (i.e. allows the establishment of an NOAEL).

Dosing route

For repeat-dose studies, the most convenient route of administration is by dietary admixture. However, depending on the possible route of exposure of the public or occupationally exposed workers to a chemical or an environmental contaminant, it may need to be investigated by the dermal and/or inhalational route.

For dermal exposure the material, in a suitable vehicle, is applied to the clipped skin of rats, rabbits or guinea-pigs; OECD test guidelines (no. 410) recommend even application to an area representing about 10 per cent of the total body surface area. The site is generally occluded with polyethylene sheeting and gauze patches, or semi-occluded, in order to prevent dislodgment of material and oral ingestion, which could affect the validity or usefulness of the study. For volatile or semi-volatile materials, application and covering procedures should minimise the possibility of evaporation. Useful chapters or sections on dermal toxicity testing may be found in textbooks on toxicology e.g. Derelanko and Hollinger (1995) and Hayes (1994).

The surface area of the respiratory membrane is large, estimated at approximately 50–100 square metres in the normal adult compared with the estimated area of the small intestine at 250 square metres (Guyton, 1991) and much more air (about 5000 times, by volume) is inhaled each day than food or water is ingested (McClellan and Henderson, 1989). Thus, exposure to airborne material is potentially greater than via dermal or oral exposure. Airborne material can be gases or vapours, liquid droplets or solutions, aerosols

(solid and vapour components), or dry fibres or powders. As a consequence, to conduct inhalational toxicity studies, mechanisms needed to deliver chemicals to a test chamber in a form that can be inhaled are quite complex, particularly when coupled with the need to include measuring devices which can establish particle size, concentration and form of the material in the exposure chamber. Furthermore, many factors can influence the inhalation, deposition and retention of inhaled materials in the respiratory tract. Thus, the conduct of inhalational studies is considerably more complex than equivalent studies by the dietary or dermal routes.

Of critical importance, in both the conduct and assessment of such studies, is the need to establish what portion of the material delivered to the exposure chamber was in a respirable form. In addition to standard toxicology texts, some useful specific references on inhalation toxicology include McClellan and Henderson (1989), Mohr *et al* (1988) and Salem (1987).

Study findings—Physiological, pharmacological, or toxic?

In conducting an hazard assessment, the evaluator needs to determine whether effects seen in studies are physiological, pharmacological or toxic.

Responses produced by chemicals in humans and experimental animals may differ according to the quantity of the substance received and the duration and frequency of exposure e.g. responses to acute exposures (a single exposure or multiple exposures occurring within twenty four hours or less) may be different from those produced by sub-chronic and chronic exposures. Not all observed responses within a study, irrespective of exposure duration or frequency, will represent toxicity *per se*. They may encompass a range of effects from physiological through pharmacological and toxic manifestations. Although it sometimes may be difficult to make a clear distinction between these responses, an attempt to do so should be made. If an evaluator is uncertain of the type or the biological significance of a response, he/she should not hesitate to obtain competent advice for resolving

the uncertainty. It is essential that all relevant toxicity end points (statistically and/or biologically significant) be identified for consideration when evaluating data for the presence or absence of non-toxic levels.

Physiological responses vary within limits which are in accord with the normal functioning of a living organism; examples of such response are the usual respiratory and pulse rate increases associated with increased physical activity, systemic changes associated with normal pregnancy, and those associated with homeostatic mechanisms. These variable factors are not important toxicity end points in sub-chronic and chronic exposure studies unless their fluctuations are abnormally altered by a dose regimen. If such alterations occur at a particular dose or are part of a dose–response relationship, they should be correlated with other toxicity end points which may be present.

Pharmacological responses are altered physiological functions arising from interaction of a substance with a cellular receptor site, are reversible, and are usually of limited duration following removal of the stimulus. Whilst some of these responses may be undesirable under certain circumstances, they are distinguished from toxic (adverse) responses by generally not causing injury. An example of this type of response is the increased activity of the hepatic cytochrome P-450 containing mono-oxygenase systems (enzyme induction) caused by exposure to many pesticides, industrial chemicals, and drugs (noting, however, that while not a direct adverse effect, a cytochrome P-450 inducer can, for example, alter hormonal homeostasis and effect tumour promotion, or increase an organism's susceptibility to other chemical exposures).

Toxic responses may be reversible or irreversible but are distinguished from other types of responses by being injurious and therefore adverse and harmful to living organisms or tissues. A chemical which causes a physiological or pharmacological effect may produce a toxic response if the exposure is prolonged and/or if the dose is increased beyond a certain level.

The reversibility or otherwise of such responses may also depend on these two factors. The reversibility or irreversibility of a histopathological change will depend on the ability of the injured organ or tissue to regenerate. For example, liver has a relatively great ability to regenerate and many types of injury to this organ are reversible. By contrast, differentiated cells of the central nervous system are not replaced and many injuries to the CNS are irreversible.

4.4 Assessment of the Quality of the Data Characterising the Hazard

The following considerations address the acceptability of experimental studies and the documentation provided.

1. The adequacy of the experimental design and other experimental parameters, including: the appropriateness of the observational and experimental methods; frequency and duration of exposure; appropriateness of the species, strain, sex and age of the animals used; the numbers of animals used per dosage group; justification of dose, route and frequency of dosing; and the conditions under which the substance was tested.
2. There are many guidelines to the generation of scientifically valid data which concern good experimental design, laboratory practice and reporting e.g. OECD and US EPA guidelines, and accepted codes of Good Laboratory Practice, or GLP (OECD, 1982; US EPA, 1983). They can be useful as aids in determining report and data acceptability. However, the evaluator needs to make a judgement about how well the study, *in toto*, facilitates the identification of potential adverse effects, or lack thereof, of the substance being evaluated, rather than how precisely it fits a prescribed test guideline or 'recipe'. The experience of senior evaluators can be helpful in resolving concerns about acceptability of study conduct and/or reporting.

3. The competency and completeness of the conduct and reporting of the study.
4. The effects of modifying factors which may result in major inequalities between control and test animals.

This qualitative consideration has more to do with the evaluation and interpretation of data than with acceptability of documentation. It is placed here because determination of the factors which may have a major influence on toxicological data needs to be made prior to the analysis of the data. There are many factors influencing the responses of experimental animals to experimental treatment; some of these are discussed by Doull (1980). Some influences may be quite subtle, as exemplified by studies performed by Thompson *et al* (1982), in which it was noted that the onset of acute pulmonary oedema in rats being used in immune hypersensitivity studies was sudden and seasonal. Circadian rhythms and seasonal physiological variations can subtly influence experimental results. Such factors influencing animal responses can be troublesome when their effects are confused with or misinterpreted as toxic responses to treatment. For further discussion of environmental effects on experimental parameters see Herrington and Nelbach (1942).

The acceptability of reports and other technical information is primarily a scientific judgement. Therefore, the rationale for rejecting a hazard assessment study should be succinctly stated in the evaluation document.

4.5 Analysis and Evaluation of Toxicity Studies

Useful guidance documents for evaluating data and conducting assessments include the IPCS Environmental Health Criteria (EHC) monographs viz. EHC 6, 70, 104 and 141 (WHO, 1978; 1987; 1990; 1992).

4.6 Analysis and Evaluation of Major Study Parameters

Not all observed effects of test substances are toxic effects. Rather, they may be adaptive (e.g. liver enzyme induction leading to some hepatic enlargement) or may be a manifestation of a pharmacological effect (e.g. in an animal colony suffering from various low-grade infections, an antibiotic will lower leucocyte counts in treated animals relative to controls; obviously it is not appropriate to describe this as a leukopaenic effect of the chemical).

Concurrent control groups should always be used; notwithstanding the value of historical control ranges in tumorigenicity studies. It is generally not appropriate to rely on statistical comparisons with historical controls since the incidence of spontaneous lesions can vary significantly over time (and even between concurrent randomised control groups). Controls must be age-matched because some forms of toxicity represent no more than acceleration and/or enhancement of age-related changes. Examples of pathological changes in aged rats which may be affected by compound administration include chronic progressive glomerulonephropathy, peripheral nerve degeneration, amyloidosis and various neoplasms.

The use of non-treated and vehicle-control groups aids assessment of effects due to vehicle or excipients. When a vehicle is used to deliver the doses of the agent under study (e.g. a lipophilic agent delivered in corn oil), the need for vehicle-treated controls is paramount. Since some parameters can be affected by animal handling (e.g. serum ALT was raised in mice which were grasped around the body compared with unhandled or tail-handled mice; Swaim *et al*, 1985), control animals should be treated in the same way as test animals.

Control animals must receive as much attention during the analysis and evaluation process as do the treated ones. Any untreated animal or group may exhibit some signs of abnormality or drift from the norm for that species or strain. Because of the possibility that statistically significant

differences between treated and control groups are the result of abnormal values among the controls, such differences should usually be dose-related and should delineate a trend away from the norm for that stock of animals, if they are to be indicative of a true compound-related effect.

Historical control data may be useful when evaluating the acceptability of the 'normal' data obtained from control groups (Haseman *et al*, 1984; Paynter, 1984; Sumi *et al*, 1976; Tarone, 1982). Any departure from the norm by the control groups should be taken into consideration, especially during the conduct of any statistical analysis. The finding of consistent departures from the norm in control groups may necessitate investigation of the source of the animals.

Ideally, historical control data should be taken from the same laboratory, utilising the same strain, age and sex of animals obtained from the same supplier, and only include those studies conducted within a 2 to 3-year span on either side of the study under review, with identification of study methodology (e.g. pre-sampling conditions such as fasting or non-fasting, assay methodology for study parameters, histopathological criteria for lesion identification, time of terminal sacrifice etc.) which could have affected the results.

Weil and McCollister (1963) analysed toxicity end points, other than oncogenicity, from short- and long-term tests and concluded that only a relatively small number of end points were effective in delineating the lowest dosage producing an effect in such tests. Body weight, liver weight, kidney weight, and liver pathology delineated this dosage level in 92 per cent of test chemicals in short-term (sub-chronic) studies and 100 per cent in long-term (chronic) studies. To reach 100 per cent efficiency in short-term studies, renal and testicular histopathology had to be included. Heywood (1981) surveyed the toxicological profiles of fifty compounds in rodent and non-rodent species and confirmed these observations.

4.6.1 Mortality/survival

Reasonable efforts should be made to determine the cause or likely cause of individual deaths. The evaluation of pathological lesions or morphological changes in belatedly-observed deaths are frequently complicated by post-mortem autolysis. The separation of deaths caused by factors unrelated to exposure to the test agent (e.g. acute or chronic infections, age or disease-related degenerative processes, anatomical abnormalities, negligent handling or accident) from toxicity-induced deaths is important. All data relating to moribund or dead animals during their study life, as well as the results of post-mortem examinations, should be scrutinised in an attempt to make this distinction. Note that US EPA guidelines state that the highest dose used in sub-chronic studies with non-rodents should not produce an incidence of fatalities which would prevent meaningful evaluation.

Analysis of mortality requires more than a statistical treatment of incidence at termination of a study. Survival/mortality data can be influenced by factors other than the test substance. Changes in the protocol during the course of a study can complicate the analysis e.g. alterations in dosage levels can produce a confusing mortality pattern.

Any unusual mortality pattern should be explained by the test laboratory on biological or toxicological grounds. If overall mortality is high (i.e. significantly greater than expected for the particular colony and strain) for any repeat-dose study, or for a particular group within a study, a credible explanation should be provided.

An evaluation of mortality patterns within each group is important. Such patterns may indicate that mortality is clustered early or late in the course of the study, is intermittent and scattered throughout the duration of the study, or has a higher incidence in one sex than in the other. The analysis of the cause of individual deaths will aid in determining the toxicological significance of these various patterns. Early deaths within treated groups may just reflect deaths of the more susceptible animals in the test population. Alternatively, it may indicate changes in

compound intake per unit body weight, in those experiments in which the quantity of test substance in the diet is kept constant. Relative to body weight, young rats ingest more food than older rats and hence, young rats ingest relatively more of the test substance than do older rats. Early deaths may therefore be the result of the higher exposure, on a mg/kg/d basis, of young animals compared to older animals.

Deaths which are clustered at a specific time period may reflect a spontaneous epidemic disease situation of limited duration. High mortality associated with infectious agents in treated groups, in the absence of such evidence in the concurrent control group, could indicate an immunosuppressive action of the chemical being tested.

The effect of dietary intake on mortality needs to be considered. A compound administered in the diet may make the laboratory chow more or less palatable, may have a pharmacological stimulant or depressant effect on appetite, or may affect the partitioning of the nutrients in the food. Likewise, decreased water consumption (e.g. in the case of an unpalatable compound administered in the water) will lead to reduced food consumption. These effects may significantly influence longevity since it has been clearly shown in animal species that long-term dietary restriction very significantly increases lifespan (e.g. Tucker, 1979). Conversely, excessive *ad libitum* intake of highly nutritious diets can reduce lifespan compared with the expected average lifespan for an animal species/strain. To date, regulatory authorities have not come to any decision on recommending restricted diets vs. *ad libitum* feeding in toxicity study guidelines; some useful references on this topic include Keenan (1998; see also other related articles by this author), Klinger *et al* (1996), Masoro (1992), and Thurman *et al* (1995).

4.6.2 Clinical observations

Adverse clinical signs (gross observations) noted during the exposure period may correlate with toxicity end points or disease processes. These can be used as supportive evidence for dose-response relationships and may play a role in the

determination of the NOEL/NOAEL. However, not all adverse clinical signs will correlate with pathological or morphological changes in organs or tissues. Some will be caused by biochemical or physiological effects i.e. incoordination, muscle twitching, tremor, or diarrhoea may indicate acetylcholinesterase inhibition without any morphological changes being evident in nervous tissue.

Many of these qualitative signs can be counted, scored for intensity, and tabulated as incidences. However, statistical analysis is of limited value. The evaluator must rely on the number of individuals per group exhibiting signs of a particular type, as well as the intensity of the responses, to gain an impression of a dose-response relationship.

Clinical observations such as palpable tumours or those which might be associated with neoplasia (e.g. haematuria, abdominal distension, or impaired respiration) may be useful in defining the time a tumour was first suspected as being present. Such signs might aid in the evaluation of decreased tumour latency in long-term rodent studies. They may also aid in determining cause of death. A statement of the correlations, or the lack thereof, between clinical signs and specific toxicity end points should be made in the evaluation.

Useful information on gross behavioural observations in laboratory animals and abnormal behaviour patterns can be found in Bayne (1996).

The revised OECD test guidelines for 90-day oral toxicity studies in rodents and non-rodents (Test Guidelines 408 and 409; adopted 21 September 1998) have placed additional emphasis on neurological end-points i.e. studies should allow for the identification of chemicals with the potential to cause neurotoxic effects, which may warrant further in-depth investigation. The reader is referred to the references cited in Test Guideline 408 relating to neurotoxicity assessment, including sensory reactivity to stimuli of different types (auditory, visula, proprioceptive), grip strength, and motor activity.

4.6.3 Body weight changes, food and water consumption

Body weight changes (gains or losses) for individual animals and groups of animals when compared to concurrent control changes during the course of a study are a criterion of some importance (Heywood, 1981; Roubicek *et al*, 1964; Weil and McCollister, 1963). Such changes are usually related to food intake, and analysis of one without an analysis of the other is of limited value. Weight decrement may not always be related to toxicity *per se* (Seefeld and Petersen, 1984). Occasionally the incorporation of the test substance into the diet will reduce the palatability of the diet to many individuals in all treatment groups or to the majority of individuals in the higher dietary level groups. Food spillage needs to be considered in the evaluation of food palatability and compound intake. The same considerations apply if the compound is administered in drinking water.

This effect is often evidenced during the first two or three weeks of the study. Sometimes animals in the affected groups(s) are able to accommodate to the diet and a gradual increase in group weight gain will occur (Nolen, 1972). In sub-chronic studies, the lag in group weight gain may persist, even though the individual animal gains per gram of food consumed (food utilisation efficiency) are favourable after the accommodation, and produce a statistically significant difference between the affected group and the concurrent controls which is not related to toxicity of the test substance (McLean and McLean, 1969). Sometimes the addition of the test substance will interact with one or more essential nutritional elements in the diet thereby producing weight gain decrements or alterations of toxic responses (Casterline and Williams, 1969; Conner and Newbern, 1984; Rogers *et al*, 1974). This phenomenon may be encountered in sub-chronic studies and when identified, can usually be overcome by acceptable means before a chronic study is initiated. Infrequently, control values for weight gain (at one or more time points) can be low, causing the other value to appear unusually high.

Diet composition, food and water consumption, and body weight gains *per se* can also have an important influence on many aspects of animal responses including shifts in metabolic, hormonal, and homeostatic mechanisms (Kennedy, 1969) as well as disease processes (Berg and Simms, 1960; Paynter, 1984; Ross and Bras, 1965; Tannenbaum, 1940) and maturation (Innami *et al*, 1973), and should be considered when unusual effects are observed in the absence of any indication of injury to organs and other vital systems.

The evaluation of body weight changes and attendant effects is significantly aided by the graphical presentation of group mean body weights and food consumption vs compound consumption (on a mg/kg body weight basis). This allows quick identification of any unusual or sudden changes in gain or loss by any group.

4.6.4 Haematological, clinical chemistry, and urinary measurements

Regulatory guidelines generally suggest that haematological, clinical chemistry, and urinary parameters be routinely measured in sub-chronic and chronic toxicity studies.

Normal biological variation in inter-animal values and their alteration in response to a variety of inputs means that evaluators will have to contend with much 'noise' in this area, and will frequently be presented with scattered, statistically significant effects, in the absence of any evidence of clinically significant relationships to specific toxicity end points. To deal with 'noise' there is a need to examine whether the effect noted is within the normal range of variation (concurrent and historical controls). Note that some of these parameters can vary significantly with no clinical manifestations but others (e.g. serum potassium) have a very narrow normal clinical range and small differences can be important.

Frequently these data show apparently 'random' changes in individual group(s) or, less commonly, non dose-related trends in changes across several groups. If using historical control data as an aid to evaluation, only values produced by the identical

methods from the same laboratory are valid in such comparisons. Literature values for normal ranges which do not specify the method by which they were obtained should be used with caution.

A good review of factors (physiological, environmental etc.) which can complicate the interpretation of findings in a toxicity study may be found in the Handbook of Toxicologic Pathology (Bucci, 1991).

To gain maximum information from enzyme determinations it is important to consider the most appropriate enzymes. It is important that organ distribution and location of the enzyme in the cell is known. ALT (Alanine aminotransferase) is found in greatest concentration in the liver in rats, even more so in dogs. AP (Alkaline phosphatase, ALP) is virtually absent from the liver in these two species, being mainly confined to the kidney, intestine and bone. CPK (Creatine phosphokinase, CK) is mainly located in skeletal and heart muscle, whilst AST (Aspartate aminotransferase) is found in various concentrations in most organs. It is clear that CPK is the most appropriate enzyme to detect muscle damage, while changes in ALT would probably reflect some liver necrosis. Although AST is not organ-specific, it serves to confirm organ damage, especially for muscle and liver, if its activity changes in parallel with other enzymes. In dogs, AP is a sensitive test for biliary function but in the rat it is of little diagnostic value since it is absent from the liver and principally derived from the intestines. For hepatocellular evaluation, ALT, AST, SDH (Sorbitol dehydrogenase) and GLDH (Glutamate dehydrogenase) are the most appropriate, while for hepatobiliary evaluation, AP, 5'-nucleotidase, GGT (Gamma glutamyl transferase) and total bilirubin are the most appropriate measurements. It is important to understand that many of these types of serum enzyme tests and urinalysis fail to detect minor injury or may reflect only transient or reversible changes. Therefore, evaluation and interpretation of the test results must be performed carefully and correlated with more specific, sensitive, and reliable histopathological findings.

Sensitivity and specificity of the enzyme changes as diagnostic of organ pathology are greatly influenced by the species selected for testing (see e.g. Clampitt, 1978; Tyson and Sawhney, 1985). For example, in mammalian species, aspartate transaminase is not specific to any tissue and thereby elevated plasma AST activity may suggest damage to any one of many tissues. In contrast, alanine transaminase is relatively specific to the liver in the cat, dog, ferret, mouse, and rat, whereas in primates, ALT is present in heart, skeletal muscle, and liver. Plasma alkaline phosphatase measurement has been less useful in detecting liver cell necrosis in the dog, sheep, cow, and rat but may be indicative of other types of liver damage, particularly those of a cholestatic nature in a number of species. It is evident that species differences are of great importance when specific clinical chemistries are selected for inclusion in toxicity studies.

When analysis and evaluation of clinical data indicate a dose response relationship or a biologically important drift from concurrent control values, the effects observed should be correlated with other manifestations of toxicity. The evaluator should indicate that a correlation could not be made, if that is the situation.

Standard veterinary (e.g. Bush, 1991; Duncan *et al*, 1994; Evans, 1996; Fox *et al*, 1984; Jain, 1993) and human clinical manuals (e.g. Fischbach, 1996; Henry, 1984; Tyson and Sawhney, 1985; Walach, 1996) should be consulted for information about laboratory diagnostic tests and to assist in the evaluation of potential correlations between clinical chemistry, haematological, urinary data, and adverse effects.

The deliberations of a joint international committee, established to provide advice for clinical pathology testing of laboratory animal species used in regulated toxicity and safety studies, has published its recommendations, including those parameters which should be measured (Weingand *et al*, 1996). Whilst these recommendations have not been formally incorporated into national or international guidelines at this stage, they are noted, as follows:

For repeated-dose studies in rodent species, clinical pathology testing is necessary at study termination. Interim study testing may not be necessary in long-duration studies provided that it has been done in short-duration studies using dose levels not substantially lower than those used in the long-duration studies. For repeated-dose studies in non-rodent species, clinical pathology testing is recommended at study termination and at least once at an earlier interval. For studies of 2 to 6 weeks in duration in non-rodent species, testing is also recommended within 7 days of initiation of dosing, unless it compromises the health of the animals. If a study contains recovery groups, clinical pathology testing at study termination is recommended.

The core haematology tests recommended are total leukocyte (white blood cell) count, absolute differential leukocyte count, erythrocyte (red blood cell) count, evaluation of red blood cell morphology, platelet (thrombocyte) count, haemoglobin concentration, haematocrit (or packed cell volume), mean corpuscular volume, mean corpuscular haemoglobin, and mean corpuscular haemoglobin concentration. In the absence of automated reticulocyte counting capabilities, blood smears from each animal should be prepared for reticulocyte counts. Bone marrow cytology slides should be prepared from each animal at termination. Prothrombin time and activated partial thromboplastin time (or appropriate alternatives) and platelet count are the minimum recommended laboratory tests of haemostasis. The core clinical chemistry tests recommended are glucose, urea nitrogen, creatinine, total protein, albumin, calculated globulin, calcium, sodium, potassium, total cholesterol, and appropriate hepatocellular and hepatobiliary tests. For hepatocellular evaluation, measurement of a minimum of two scientifically appropriate blood tests is recommended, e.g. alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, glutamate dehydrogenase, or total bile acids. For hepatobiliary evaluation, measurement of a minimum of two appropriate blood tests is recommended, e.g. alkaline phosphatase, gamma-glutamyltransferase, 5'-nucleotidase, total

bilirubin, or total bile acids. Urinalysis should be conducted at least once during a study. For routine urinalysis, an overnight collection (approximately 16 h) is recommended. It is recommended that the core tests should include an assessment of urine appearance (colour and turbidity), volume, specific gravity or osmolality, pH, and either the quantitative or semi-quantitative determination of total protein and glucose. For carcinogenicity studies, only blood smears should be made from unscheduled sacrifices (decedents) and at study termination, to aid in the identification and differentiation of haematopoietic neoplasia.

4.6.5 Absolute and relative organ weights

It is generally considered that histopathology is more sensitive for establishing the lowest dose producing an effect than are organ or body weight changes. Organ weights are usually reported as absolute organ weights and as relative organ weights (relative to body weight and/or brain weight). Relative organ weight comparisons are used since body weights are often affected by compound administration.

Experimentally controllable and uncontrollable factors (i.e. circadian rhythms, food intake, dehydration, nature of the diet, age of animals, organ workload, stress, and method of killing) have an influence on organ and body weights and the variability of such data. A review of this subject by Weil (1970) should be consulted. The most important influencing factor appears to be the method of killing and the timing of necropsy. The killing method used not only affects the appearance of the tissue, important in describing gross necropsy observations, but also, in conjunction with the timing of necropsies, may cause postmortem shifts in organ weights (Boyd and Knight, 1963; Pfeiffer and Muller, 1967).

A not uncommon problem in interpretation of study findings is the misinterpretation of relative organ weight changes e.g. there is no sense in reporting an increase in relative brain weight in a toxicity study in which the chemical is having a significant effect in causing bodyweight loss or

reducing body weight gain because the brain will be spared under conditions leading to reduced bodyweight, the relative brain weight will obviously increase. Similarly, other organs may change in relative weight in a manner dependent upon body weight rather than as a result of a specific compound effect: useful Tables of the relationship of relative organs weights to various levels of reduced bodyweights (produced by dietary restriction) may be found for rats in Sharer (1977). When growth is markedly affected in a toxicity experiment, alterations of organ weight:body weight ratios have to be expected as a physiological response of the organism to decreased nutrient intake; such changes must be differentiated from organ weight changes resulting from primary toxic effects of the compound being tested.

The interpretation of organ weight changes must not be made solely on the determination of a statistically significant difference between the concurrent control value and a treatment group value. A proper evaluation will also include consideration of any correlation between organ weights (absolute and relative), histopathological and metabolic/pharmacodynamic data.

4.6.6 Post mortem observation

Although much progress has been made in the standardisation of nomenclature, to minimise any difficulties in this area, an experienced pathologist will describe each significant lesion type, at least once, in such detail that another competent pathologist can perceive a mental picture of the lesion and form a judgement as to its relevance to the histopathology induced by the chemical being tested.

To assist in the uniform description of pathologies, a series of articles on pathology nomenclature have been published, under the title Standardized System of Nomenclature and Diagnostic Criteria Guides for Toxicologic Pathology by the US Society of Toxicologic Pathologists (STP), in cooperation with the Armed Forces Institute of Pathology (AFIP) and the American Registry of Pathology (ARP).

Age-associated, especially geriatric, changes can have an extremely important effect on histopathology, as well as clinical chemistry, metabolic and pharmacokinetic parameters (Grice and Burek, 1983; Mohr *et al*, 1992; 1994; 1996) and therefore, important overt, and frequently subtle, influences on observed physiological, pharmacological, and toxic responses during the latter part of any long-term study. It is essential in all cases where spontaneous and/or age associated lesions are present, to differentiate between such lesions and treatment induced lesions. References such as Grice and Burek (1983) and Benirschke *et al* (1978) (containing detailed descriptions of potential histopathological changes caused by toxic substances, spontaneous or degenerative and other diseases, and their incidences in experimental animals) are very helpful in this respect, as is advice from a competent and experienced pathologist.

An overview of factors (physiological, environmental etc.) which can complicate the interpretation of morphological findings in a toxicity study may be found in the Handbook of Toxicologic Pathology (Bucci, 1991).

4.6.7 Analysis and evaluation of study parameters in acute, developmental, reproductive and special toxicity studies

Acute toxicity studies

Important end-points in acute toxicity studies are clinical signs, gross necropsy signs, and mortality; each of these end-points are discussed in detail at Sections 4.6.1, 4.6.6 and 4.6.2 respectively. Since the purpose of acute toxicity studies has moved away from the establishment of a strict, quantitative number for the median lethal dose to an estimate of the likely toxicity range, the emphasis is more on clinical signs and gross organ pathology than on mortality.

Reproductive toxicity studies

Sections 4.6.1–4.6.6 describe the major study parameters to be considered in repeat-dose toxicity studies and these end-points may also

apply to the sires and dams in developmental toxicity studies. However, the critical end-points relate to potential toxic effects on reproductive parameters, including effects on mating behaviour (both sexes), on fertility (both sexes), the implantation of blastocysts, embryonic and fetal development and survival, parturition, lactation, and postnatal survival and development. Thus, a plethora of reproductive parameters need to be assessed in one or more generations, depending on whether the study is a one-generation (OECD Test Guideline 415), two-generation (TG 416) or three-generation test. Important end-points to assess within each generation include: time after pairing to mating; mating behaviour; percentage of females pregnant; number of pregnancies going to full term; litter size; number of live births; number of stillborns; pup viability and weight at parturition, and postnatal days 4, 7, 14 and 21 days of age; the fertility index (percentage of matings resulting in pregnancy); gestation index (percentage of pregnancies resulting in live litters); viability index (percentage of pups that survive 4 or more days); and lactation index (percentage of pups alive at 4 days that survived to day 21 i.e. weaning); gross necropsy and histopathology on some parents (sires and dams), with attention paid to the reproductive organs; and gross necropsy on weanlings. It is beyond the scope of this guidance to go into detail about the procedures for the assessment of these end-points, but guidelines and procedures are well documented e.g. Korach (1998).

Developmental toxicity studies

The critical end-points in developmental toxicity studies relate to potential developmental effects in utero, including death, malformations, functional deficits and developmental delays in fetuses. Thus the following parameters need to be assessed; no. of live litters; no. of live fetuses/litter (total and by sex); sex ratio of fetuses; fetal body weights; litter weights; no. and percentage of fetuses with malformations; no. and percentage of litters with malformations; no. and percentage of fetuses with variations; no. and percentage of litters with variations; no. and percentage of fetuses/litter with malformations; no. and percentage of fetuses/litter with variations; and types of malformations and

variations. It is beyond the scope of this guidance to go into detail about the procedures for the assessment of malformations and deviations but guidelines and procedures for soft tissue and skeletal examination are well documented e.g. Tyl and Marr (1997). In addition to the above developmental parameters, it is appropriate to investigate other reproductive parameters, including the following; number of females pregnant; number of corpora lutea/dam; number of implants/dam; and number and percentage of pre-implantation loss/litter. Whilst the dosing period in a standard teratology study commences after mating, conception and commencement of implantation, it is appropriate to check these parameters to see that the study has not been compromised by factors other than the compound under test. OECD Test Guideline 414 outlines the protocol for a standard developmental or 'teratology' study.

Special studies

Different classes of chemicals may require special toxicology studies which are not part of the 'standard' package of studies. For example, it is common to test organophosphate (OP) pesticides for their ability to cause delayed neuropathy by conducting tests in hens (OECD Test Guideline 419), since this species is especially sensitive to inhibition of neuropathy target esterase (NTE) by OPs. Furthermore, sponsors of particular chemicals may conduct further *in vitro* and *in vivo* studies to attempt to resolve possible mechanisms for toxic effects seen in the standard toxicology test battery. Because of the wide range of types of studies which may be classified in this category, it is not possible to comment on the assessment of particular end-points, but the evaluator should apply sound scientific judgement in reviewing these studies.

Toxicokinetic and metabolism data

Toxicokinetic (absorption, distribution and elimination) and metabolic data on the handling of the substance in the test species, can be very useful in the evaluation and interpretation of sub-chronic and chronic exposure study data, as discussed by Paynter (1984) and references cited therein.

References in this paper also discuss dose-dependent effects in the absorption process and in biotransformation interactions (Levy, 1968), the potential difficulties presented by impurities, the overloading of detoxification mechanisms (Munro, 1977) and other important experimental considerations (Dayton and Sanders, 1983).

A number of toxicology textbooks include chapters on pharmacokinetics and toxicology assessment e.g. Sharma and Coulombe (1996). The publication, Science and Judgement in Risk Assessment (National Academy of Sciences (NAS)/National Research Council (NRC), 1994), has useful sections on the impact of pharmacokinetic information in risk assessment.

4.6.8 Interspecies scaling of doses

(from NHMRC, 1999)

Where animal bioassays are the source of data, an estimate or measure of the human equivalent dose is required for assessing the health risks posed by environmental agents. To derive a human equivalent dose from animal data, the preferred option is to use toxicokinetic data which provides biologically equivalent doses.

In the absence of such data, the recommended procedure is to scale the daily applied dose in proportion to body weight. That is, milligrams per kilogram of body weight of the experimental animal in the bioassay would be equivalent to milligrams per kilogram body weight in humans.

Where oral doses are expressed in parts per million (ppm) in the diet or drinking water, the dosage needs to be converted to mg/kg body weight using appropriate estimates of food or water consumption and body weights (see WHO, 1987; Faustman and Omenn, 1996).

4.6.9 Route-to-route scaling

(from NHMRC, 1999)

Often the toxicological data are not available for the most appropriate route of exposure for humans. For example, only oral carcinogenicity data may be available, whereas exposure to soil

contaminants by oral, dermal and inhalational routes may be important. Thus, extrapolation from one route of exposure to another may be necessary; this needs to be assessed on a case-by-case basis depending on the available data.

One important consideration in route-to-route extrapolation is determining whether the adverse health effects are localised to the exposure site or whether they are a consequence of systemic distribution. If the effects are localised at the exposure site and not a consequence of the systemic distribution of the agent, then it may be inappropriate to extrapolate the dose to a different route of exposure. If the effects are consequent to absorption and systemic distribution of the agent, then dose scaling between routes of exposure needs to account for the bioavailability of the agent by the different routes.

Therefore, bioavailability is an important consideration when extrapolating the applied dose to different routes of exposure. However, additional factors may need to be considered, such as physiological differences between species when extrapolating, for example, from inhalational exposure in animals to oral exposure in humans or *vice versa*. The assessor should include information about the bioavailability of the chemical agent in the experimental studies in the final report.

In cases where bioavailability data are not available, important clues may be gained from the physical and chemical properties and physical state of the agent (e.g. liquid, solid or gas).

4.6.10 Other factors in scaling of doses

(from NHMRC, 1999)

For inhalational exposure, doses expressed as mg/m³ or ppm must be converted to mg/kg body weight in the test species by calculations based on the physical properties of the agent and minute volumes and respiration rates of the animal (Kennedy and Valentine, 1994). The procedure for deriving a human equivalent dose for inhaled particles and gases is as described by Di Marco and Buckett (1996).

4.6.11 Extrapolating occupational data to the general public

Occupational data is often derived from a relatively homogeneous group: usually male, aged between 20 and 65 years and relatively healthy. When applying this data to the general population the differences between the exposed populations should be taken into account as the general population will contain females, and people who are not in the workforce because of their age (young or old) or poor health.

4.6.12 Statistical tests

The objective of a toxicology study is to demonstrate responses of biological importance. Where statistical analyses are used in the judgement process, an awareness of the validity of the test and the degree of certainty (confidence) pertaining within the context of the study should be demonstrated.

There are limitations associated with the use of statistics in toxicology (Gad and Weil, 1986):

1. statistics cannot make poor data better;
2. statistical significance may not imply biological significance;
3. an effect that may have biological significance may not be statistically significant;
4. the lack of statistical significance does not prove safety.

The importance and relevance of any effect observed in a study must be assessed within the limitations imposed by the study design and the species being studied (See also Section 5; 'Hazard Assessment Part 2: Hazard Identification—Epidemiology').

If statistical tests have not been used, if inappropriate tests appear to have been used, or if tests not commonly employed have been used, then this should be noted and action taken e.g. data re-analysis.

A number of textbooks and papers on the application of statistics in experimental toxicology and the life sciences are available; these include

Dickens and Robinson (1996), Gad and Weil (1986), Gad and Weil (1989), Lee (1993), Salsburg (1986), Tallarida and Murray (1987) and Waner (1992).

4.6.13 General comments

Detailed comments about the analysis and evaluation of toxicology studies have been made above. The following further general comments may be made.

If possible, compound-related changes in biochemical, haematological or urinalysis parameters should be linked with organ weight, gross pathology and/or histopathological changes.

The following points also should be noted in evaluating repeat-dose toxicity data:

Findings should be considered on the basis of both statistical significance and likely biological significance. The variability of biological data must be remembered in assessing a statistically-significant result. Conversely, a finding that is not statistically significant may have biological significance when considered in the light of the likely toxicological or pharmacological action of the compound, or when combined with results from other studies. Thus, evaluators should note trends or transient changes in parameters if there is an indication that these may be related to dosing with the compound in some way. This information may be useful when comparing results across studies and in the consideration of the overall significance or relevance of an observed effect i.e. in one study an effect may be only a trend whilst in another study it may be very clearly treatment-related.

A difficult problem for evaluators is the fact that some studies producing either clearly positive or negative results may have to be considered as flawed. In any long-term study there may be questionable components of the study and the experienced toxicologist must learn to recognise what is useful and discard what is not. The use of a seriously flawed negative study may provide only a false sense of security. On the other hand, a flawed positive study may be entitled to some weight; how much is a matter of judgement (Task Force of Past Presidents, 1982).

Data obtained from studies carried out many years ago should not be dismissed out-of-hand simply because they do not meet today's standards; they may provide some useful information. Again, this is a matter for scientific interpretation and judgement on a case-by-case basis.

4.6.14 Completion of hazard analysis

At this point the assessor should have formulated judgements and supporting rationale concerning:

- a) the acceptability of the study and its database;
- b) the existence of biologically important adverse effects;
- c) the relevance of any factors noted during the evaluation which might have had some bearing on the outcome of the study and modified the findings in some way; and
- d) the likelihood that any of the observed effects were induced by the administered substance.

The evaluator should succinctly summarise the critical toxicokinetic and toxicological data, together with any modifying factors for the study under review. The lowest, or most appropriate NOEL/NOAEL, or the absence thereof, should be stated, with a clear indication of the effect(s) on which it was based (i.e. the lowest-observed effect level or LOEL should be apparent). It is important to correlate findings seen in different studies; whilst this is done within the final summary of all toxicity studies, it will often be appropriate to make some mention of cross-study correlations (or the unexpected/unexplained absence of them) within individual study summaries. Possible or proven mechanisms of toxicity should also be discussed and included in the summary.

4.7 Evaluation of the Weight-of-Evidence and Consideration of the Toxicology Database *in toto*

The essential purpose of toxicity studies is the detection of valid biological evidence of the hazard potential of the substance being investigated. In this document, the evaluation of the weight of evidence¹ produced by toxicity studies is that process which considers the cumulative data pertinent to arriving at a level of concern about the potential adverse effects of a substance. It is composed of a series of judgements concerning the adequacy, validity, and appropriateness of the methods used to produce the data base, and those judgements which bring into causal, complementary, parallel, or reciprocal relationships, all the data considered. Because our knowledge about mechanisms of toxicity is still developing, because good epidemiological evidence is seldom available, and because animal studies are not always conclusive, the information available at a given time may provide only 'persuasive' rather than 'hard' evidence of a defensible presumption, one way or the other, about the potential health effects of a substance under given conditions of exposure. Therefore, it is necessary to succinctly discuss the rationale for judgements and conclusions contained in risk assessments together with any associated uncertainties. This becomes important when new data or new scientific knowledge requires re-evaluation of the database or a change in a previous risk assessment or regulatory action.

At present, there is no acceptable substitute for informed judgement, based on sound scientific principles, in the analysis, evaluation, interpretation, and weighting of biological and toxicological data derived from animal toxicity studies conducted according to currently available protocols.

1 'Strength of evidence' is commonly taken to mean the degree of conviction regarding the outcome of an experiment eg NTP's 'clear evidence', 'some evidence', 'equivocal evidence' and 'no evidence' of carcinogenicity. 'Weight of evidence' involves integration of all available data, not just one study.

It is also accepted practice to apply safety or uncertainty factors to the NOEL/NOAEL derived from animal studies when estimating an ADI (or TDI) as an aid in evaluating the acceptability of actual or potential human exposures. For a further discussion on this, see Sections 11.2 and 11.3 (also Dourson and Stara, 1983; Paynter and Schmitt, 1979; Weil, 1972).

In addition to identifying toxic effects and the doses at which these effects do or do not occur, toxicity studies may yield insight into the mode- or mechanism of action of a chemical toxicant. The evaluator may be able to combine information from a number of studies within the database (e.g. metabolic/toxicokinetic, acute, short-term repeat-dose, subchronic, chronic/carcinogenicity, developmental, reproductive, and genotoxicity studies), to adduce information about the mode or mechanism of toxic action of the substance.

It is at the point of overviewing the entire toxicology database the WHO/IPCS Conceptual Framework for Cancer Risk Assessment (see Appendix 7) is intended to be applied. This 'Framework' is an analytical tool providing a logical, structured approach to the assessment of the overall weight of evidence for a postulated mode of carcinogenic action. Use of the Framework should increase the transparency of the analysis by ensuring that the facts and reasoning have been documented clearly, including any inconsistencies and uncertainties in the available data.

Note that although the Conceptual Framework has been developed to assist in the assessment of carcinogenic end-points, the principles upon which it is based are broad, and should enable its use in analysing modes of action of non-neoplastic effects of chemicals. Irrespective of the nature of the disease process, characterising the mode of action will facilitate subsequent judgements about the human relevance of the toxicological findings, the possible need for further data, risk quantification, and setting appropriate regulatory standards for the chemical.

4.8 Methods for the Hazard Identification of Carcinogens

4.8.1 Evaluation of carcinogens

A variety of risk assessment methods has been used elsewhere, for example by the United States Environmental Protection Agency (US EPA, 1986), and the World Health Organization (WHO, 1993a).

Advances in biological knowledge are enabling mechanistic data, pharmacokinetic data and other relevant data to be increasingly taken into account in classifying and assessing the risks of carcinogens.

Existing methodologies have difficulties in conveying the broad range of health implications of exposure to environmental pollutants. This, combined with a high 'dread factor' for cancer, has resulted in many cases in a disproportionate regulatory, political and public focus on cancer as compared to other-than-cancer health effects.

Australia uses a variety of methods for classifying carcinogens including the International Agency for Research on Cancer's method for the classification of carcinogens (IARC, 1978).

The International Agency for Research on Cancer (IARC) developed the first system for qualitatively categorising chemical carcinogens (IARC, 1978). Initially, the approach was to adopt a strength-of-evidence scheme to decide whether, for humans and experimental animals separately, there was sufficient or limited evidence of carcinogenicity for a substance, mixture, or exposure circumstance, or whether data were inadequate for classification (prior IARC monographs essentially only summarised existing tumourigenicity studies). Since then, the scheme has evolved whereby now all data, including human, animal and *in vitro* studies are assessed for an overall weight-of-evidence evaluation of human carcinogenicity (Vainio and Wilbourn, 1992).

A major contributor to this evolution was the decision that 'in the absence of adequate data on humans, it is reasonable, for practical purposes [it is biologically plausible and prudent (IARC,

1987)], to regard chemicals for which there is sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk to humans' (IARC, 1983; IARC, 1987). Thus considerable weight is given to the animal cancer bioassays, though some researchers are not convinced of the validity of this philosophy.

Another recent decision by IARC was to incorporate information on the mechanism of action of chemicals in the evaluation process (Vainio *et al*, 1992). For example, in practical terms, this means that category Group 1 (sufficient evidence for carcinogenicity in humans) 'could be extended to include agents for which the evidence of carcinogenicity in humans is less than sufficient but for which there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenesis' (Vainio *et al*, 1992). This aspect of the evaluation process will become increasingly important as the understanding of mechanistic pathways improves; great advances are being made, especially with the advent of sophisticated laboratory molecular techniques. Essentially four descriptive dimensions of mechanistic data are proposed:

1. evidence of genotoxicity (i.e. structural change at the level of the gene);
2. evidence of effects on the expression of relevant genes (i.e. functional changes at the intracellular level);
3. evidence of relevant effects on cell behaviour; and
4. evidence of time and dose relationships of carcinogenic effects and interactions between agents. (Fitzgerald 1993, p. 51)

4.9 The Hazard Identification Report: Structure and Format

The hazard assessment component is likely to be based on a number of studies, conducted in different species within each toxicology study type e.g. acute, chronic, developmental, or reproductive toxicity. The report must be transparent, accountable and defensible. The quality of the Hazard Identification report often determines whether the Hazard Identification stands or falls.

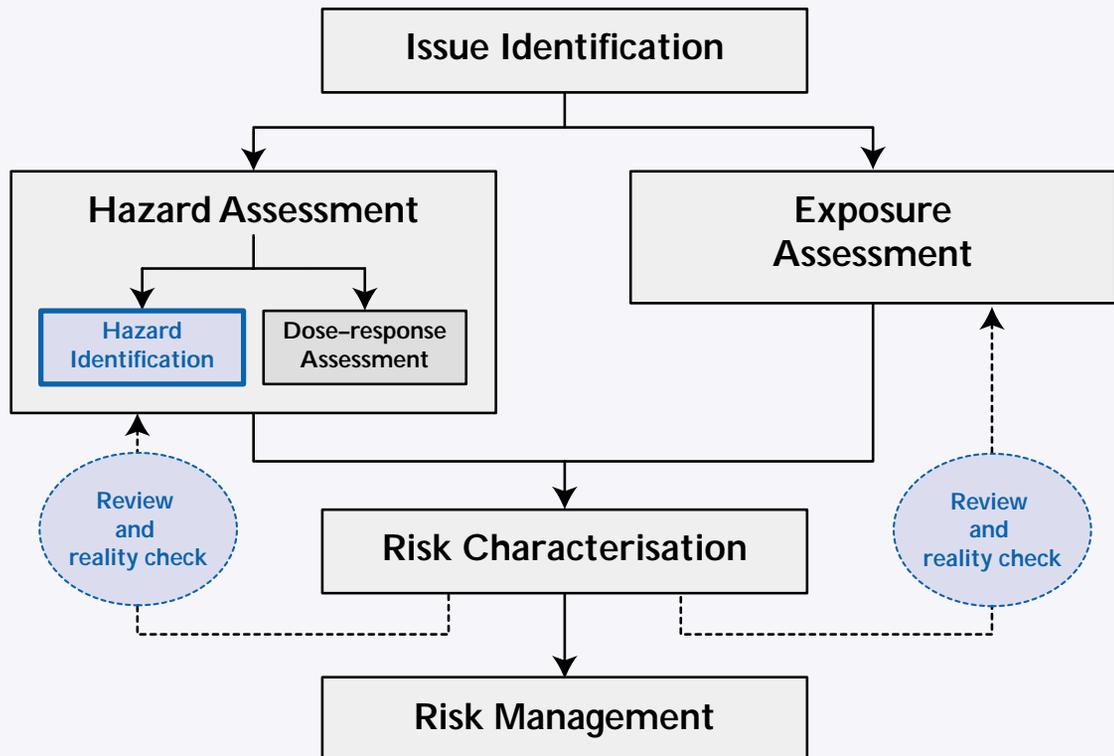
4.9.1 Study identification

The toxicity studies [or review(s)/monograph(s)] on which the hazard identification and assessment are based should be clearly identified in the risk assessment report. This information is important for the identification of the basic data [or review(s)/monograph(s)] on which the risk assessment is based.

4.9.2 Layout and formatting

The report should be structured to allow for ready access to all significant and relevant points arising from the assessment.

Reports should be as concise and precise as possible, consistent with adequate and transparent reporting.



Hazard Assessment—Part 2:

Hazard Identification—Epidemiology

5.1 Introduction

Epidemiology and toxicology are complementary in risk assessment. Epidemiology is the direct human evidence component and, if based on sound epidemiological methods, can provide the most important evidence in characterising risk. Epidemiology is the principal driver in microbiological risk assessment.

Epidemiology is ‘the study of the distribution and determinants of health related states or events in specified populations, and the application of the study to the control of health problems’ (Last, 1988).

An excellent introductory text is:

- Beaglehole R, Bonita R, Kjellstrom T (1993). *Basic epidemiology*. World Health Organization: Geneva.

Epidemiological methods are used to investigate the cause of adverse health effects; the natural history of health conditions; the description of the health status of populations; and to evaluate health related interventions (Beaglehole *et al*, 1993). In the context of environmental health, epidemiological methods may also be used to characterise population exposures, investigate perceived clusters of disease, to develop health surveillance programs to establish a baseline, and to monitor the consequences of risk management activities.

Epidemiology can assist risk assessment in several of its stages, including:

- hazard identification;
- dose response assessment; and
- exposure assessment.

At the same time, there are often unrealistic expectations of what an epidemiological study may be able to achieve.

The purpose of this chapter is to provide a basis for understanding the strengths and weaknesses of Epidemiology in supporting risk assessment. As Mundt *et al* (1998) noted, if the limitations of epidemiological studies are not understood by the

risk assessment team, the validity of an assessment might be compromised by including inappropriate, possibly misleading, epidemiological data. The systematic appraisal of epidemiological studies is intended to answer the question ‘Is there any other way of explaining the set of facts before us [i.e. the study results], is there any other answer equally, or more, likely than cause and effect?’ (Hill 1965 in WHO 2000). Alternative explanations may result from chance, bias and confounding (WHO 2000).

5.2 Bias and Confounding: Key Concepts in Environmental Epidemiology

There are many ways in which error can be introduced into epidemiological studies. Error may be random (due to chance alone, and potentially reduced by improving sample size), or systematic (and not reduced by increasing sample size). Whilst this section does not attempt to deal with the subject of systematic error in any depth, the two key concepts of bias and confounding must be highlighted. The size of the statistical confidence intervals will provide an indication of the potential for random sampling error, but statistical confidence intervals do not represent uncertainty arising from bias or confounding.

Bias occurs if there is a systematic tendency by a study to produce results that diverge from the truth. There are many sources and varieties of bias, but the most important include selection bias and measurement (or classification) bias. The reader is referred to Beaglehole *et al* (1993) for a succinct account of bias. It may be difficult to precisely estimate the effect bias has in a study, but it is vital for risk assessors to look for and attempt to identify the potential size and direction of bias in interpreting a study’s findings.

Confounding is the distortion of the effect of the agent of interest by an extraneous factor (Moolgavkar *et al*, 1999). This may occur if another exposure exists in the study population that is associated with both the disease

(or outcome) and the exposure being studied e.g. a third factor ('confounding variable') that independently affects the risk of developing the disease.

There are specific approaches for the control of confounding that can be used in both the design and analysis of analytic studies providing that the confounding variables have been identified and measured.

5.3 Types of Epidemiological Study—An Overview

Broadly speaking, epidemiological activity can be either 'descriptive' (reporting and describing the distribution of exposure and effect) or 'analytical' (designed to analyse and understand the degree of association between exposure and effect).

Descriptive studies include case reports, case series and cross-sectional surveys. Cross-sectional surveys measure exposure and effect in an individual at the same point in time and thus are unable to support causal inference.

In practical terms in environmental epidemiology there are four main categories of analytical study:

- cohort (longitudinal) studies;
- case-control studies;
- cross-sectional studies; and
- ecological studies (including a special subgroup known as time-series studies).
(from Moolgavkar *et al*, 1999)

Cohort, cross-sectional and case control studies differ from ecological studies in that information on exposure and disease is available on an individual basis. With ecological studies this information is only available on a group basis, so the community or region is the unit of analysis.

In case-control studies, exposure and other attributes of cases of the disease under investigation are compared with those from a suitable control or comparison group of persons unaffected by the disease, and analysed to yield effect estimates. The selection of appropriate controls to avoid bias is a significant challenge

with case-control studies. They are relatively inexpensive, ideal for studying rare diseases and useful for investigating multiple, different exposures (Gregg, 1996).

Cross-sectional studies measure the prevalence of disease and measure exposure and effect at the same time. They are relatively easy and economical to conduct and are particularly useful for measuring fixed characteristics of individuals such as socioeconomic status (Beaglehole *et al*, 1993).

Cohort studies follow cohorts or groups of individuals, defined in terms of their exposures, over time to see if there are differences in the development of new cases of the disease of interest (or other health outcome) between the groups with and without exposure. Such studies can be carried out by either reviewing past records (retrospective) or by tracking people into the future (prospective cohort). The essential feature of these longitudinal studies is that for each individual prior exposure information can be related to subsequent disease experience (Breslow and Day 1987).

Ecological studies involve the investigation of a group of people such as those living within a geographical area such as a region or state. For example, place and time of residence may be used to create surrogate measures of the real exposure of interest (Elliott *et al*, 1992). Rates of disease and average exposure levels to a particular agent are determined independently, and on a group basis. This may give rise to spurious apparent correlation, called the ecological fallacy. Because it is not ascertained whether individuals who have been exposed to the agent are the same individuals who developed the disease, statements about causal associations are inappropriate. However ecological studies are relatively inexpensive for linking available health data sets and environmental information and are useful for hypothesis-generation (Yassi *et al*, in press). Examples of ecological studies are the assessments of the relationship between tobacco sales in different countries and lung cancer rates, and fluoride in water supplies and dental caries.

A subset of ecological studies, known as time series studies, is regarded as very helpful in understanding the influence of short-term fluctuations in air pollutants on day-to-day changes in population morbidity and mortality after controlling for factors such as season and air temperature. However disentangling the effects of individual pollutants as measured in a mixture such as urban air pollution can be quite difficult.

To strengthen the design of ecological studies, Nurminen (1995) recommended the selection of areas with populations that:

- are homogeneously exposed (to minimise within-area exposure variation);
- represent different extremes of exposure distribution (to maximise between-area exposure variations);
- are comparable with respect to co-variate distributions (e.g. socio-economic status, demography); and
- use the smallest possible sampling units for ecological analysis.

The largest number of environmental epidemiology studies found in the literature are of the ecological or cross-sectional type, because they

are easier to carry out and cost less (Thomas and Hrudey 1997). However, as noted above and discussed further below in relation to assessment of causality, such studies may be useful for identifying potential hazards or hypothesis generation, but they cannot determine cause and effect.

Characteristics of the various study types are summarised in Table 5: Epidemiological studies are rarely definitive and a single epidemiological study cannot establish causality. A 'weight of evidence' approach is generally required, involving the interpretation of integrated information.

Unfortunately experimental interventions such as randomised controlled trials are rarely available to assist environmental health risk assessment. An example of an experimental intervention is a randomised trial of lead abatement procedures undertaken in Broken Hill (S. Corbett, personal communication)

Epidemiological studies, depending on their design, may serve two purposes; hypothesis-generation or assessment of a causal relationship. Their ability to evaluate a causal relationship may be limited by a lack of control of potential confounders or a lack of power (which is usually the result of limited sample sizes) (Samet *et al*, 1998).

Table 5: Study designs in environmental epidemiology that use the individual as the unit of analysis

Study Design	Population	Exposure	Health Effect	Confounders	Problems	Advantages
Case reports, case series and other descriptive studies	Community or various sub-populations	Records of past measurements	Mortality and morbidity statistics; case registers; other reports	Difficult to sort out	Hard to establish exposure-effect relationships	Cheap, useful to formulate hypotheses
Cross-sectional study	Communities or special groups; exposed vs non-exposed	Current	Current	Usually	Current exposure may be irrelevant to current disease	Can be done quickly; can use large populations; can estimate prevalence
Case-control study	Diseased (cases) vs non-diseased (controls)	Records or interview	Known at start of study	If confounders can be identified and measured they may be addressed	Difficult to generalise; may incorporate biases; cannot derive rates	Relatively cheap and quick; particularly useful for studying rare diseases
Time-series study	Large community (several million people); susceptible groups such as asthmatics	Current e.g. daily changes in exposure	Current e.g. daily variations in mortality	Often difficult to sort out, e.g. effects of influenza	Many confounding factors, often difficult to measure	Useful for studies on acute effects
Historical (retrospective) cohort study	Special groups e.g. workers, patients, insured persons	Records of past measurement	Records of past or current diagnosis	Often difficult because of retrospective nature; depends on availability of previously obtained data	Need to rely on records that may not be accurate	Less expensive and quicker than prospective study; can be used to study exposures that no longer exist
Prospective cohort study	Community or special groups; exposed vs non-exposed	Defined at outset of study (can change during study)	To be determined during study	Usually easy to measure	Expensive, time consuming; exposure categories can change; high dropout rate possible	Can estimate incidence and relative risk; can study many diseases in one study; can describe associations that suggest cause effect relationships
Experimental (intervention study)	Community or special groups	Controlled/known already	To be measured during study	Can be controlled by randomisation of subject	Expensive ethical considerations; study subjects compliance required	Well accepted results; strong evidence for causality or efficacy of intervention

(adapted from WHO, 1991)

5.3.1 Observational studies

Different observational study designs have different applications, advantages and disadvantages (see Table 6 and 7). These comparisons assume the different types of studies

are equally well designed. Even so, design variations may affect their performance and provide exceptions. See Beaglehole *et al* (1993) for a more detailed description.

Table 6: Applications of different observational study designs

	Ecological	Cross-sectional	Case-control	Cohort
Investigation of rare disease	+++	-	++++	-
Investigation of rare cause	++	-	-	++++
Testing multiple effects of cause	+	++	-	++++
Study of multiple exposures and determinants	++	++	++++	++
Measurement of time relationship	++	-	+ ^a	++++
Direct measurement of incidence	-	-	+ ^b	++++
Investigation of long latent periods	-	-	+++	+ ^c /-

Key: +...+ indicates the degree of suitability

- not suitable

^a If prospective

^b If population-based

^c If retrospective or historical cohort study

(adapted from Beaglehole *et al*, 1993)

Table 7: Advantages and disadvantages of different observational study designs

	Ecological	Cross-sectional	Case-control	Cohort
Probability of:				
selection bias	N/A	Medium	High	Low
recall bias	N/A	High	High	Low
loss to follow-up	N/A	N/A	Low	High
Confounding	High	Medium	Medium	Low
Time required	Low	Medium	Medium	High
Cost	Low	Medium	Medium	High

(from Beaglehole *et al*, 1993)

5.4 Assessing the Relationship between a Possible Cause and an Outcome

A cause is 'an event, condition, characteristic or a combination of these factors which plays an important role in producing the disease' (Beaglehole *et al*, 1993, p. 76).

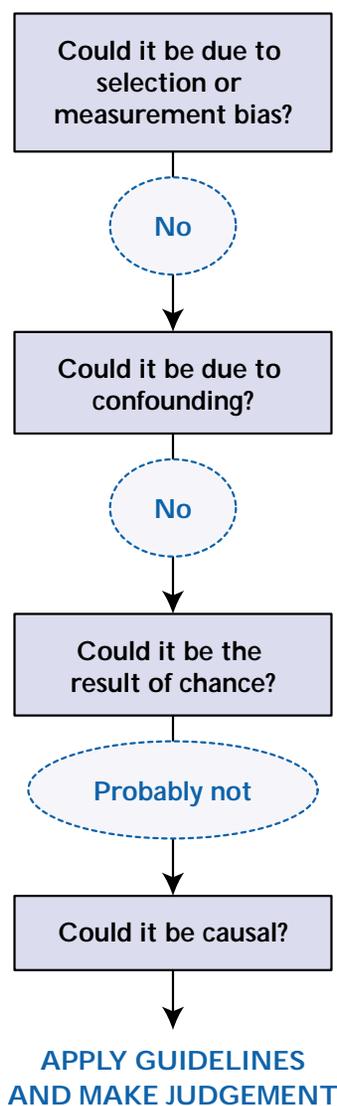
Causation of adverse health effects is affected by four types of factor:

- *predisposing factors* such as immune deficiencies, gender and previous illness;
- *enabling factors* such as poor nutrition and bad housing may favour the development of disease;
- *precipitating factors* such as the exposure to a specific disease agent; and
- *reinforcing factors* such as repeated exposure may aggravate an established disease or state (Beaglehole *et al*, 1993).

The term 'risk factor' is commonly used to describe factors that are positively associated with the risk of development of a disease but that are not sufficient in themselves to cause the disease. A 'sufficient' cause is one which inevitably produces or initiates a disease and a 'necessary' cause is one for which a disease cannot develop in its absence (Beaglehole *et al* 1993). In the biological sciences there is often a constellation of components acting in concert for a cause to create an effect, and many of the components of a 'sufficient cause' may be unknown (Rothman and Greenland 1997). At the low levels of exposure commonly encountered in the environment and where there may be a range of contributory factors present, it may be difficult or inappropriate to assign this nomenclature to an agent even though the agent is accepted as causing a specific effect with high exposures.

As with other scientific disciplines, epidemiology has attempted to define a set of causal criteria to help distinguish causal from non-causal associations. In the first place other explanations for a potentially causal association must be excluded (such as chance, selection or measurement bias, or confounding, as mentioned in Section 5.2). Particularly rigorous scrutiny should be given to studies giving a positive but not statistically significant result. Figure 3 illustrates this process.

Figure 3: Assessing the relationship between a possible cause and an outcome when an association is observed



(from Beaglehole *et al*, 1993)

If alternative explanations such as bias and confounding can be excluded, it is then useful to systematically apply Beaglehole *et al*'s (1993) guidelines for assessing causation as shown in Table 8 below. The concepts in these guidelines derive from work by Hill (1965) and others. However, as Rothman and Greenland (1997) note, apart from temporality (whereby a putative cause must precede the effect) there are no necessary and sufficient criterion for determining whether an observed association is causal. Thus the term 'guidelines' is more appropriate than the slightly more absolute 'criteria'; and there is not necessarily an easy epidemiological road-map to finally determine causation.

The guidelines are similar in some respects to Koch's postulates for determining whether an organism is causal of a particular disease. He required that the putative organism was to be found in every case of the disease and that it could be isolated and grown from cases of the disease. Further the isolate should produce a like disease in a new host and that in turn the organism could be recovered from that case. Modern microbiology is now finding instances where these postulates cannot be fully complied with, e.g. the organism can be detected using

molecular methods, but cannot be isolated, or grown in the laboratory. Notwithstanding this, causality may be imputed by the strength and consistency of evidence.

With environmental health in particular, much decision-making rests on a 'weight of evidence' approach rather than definitive proof of cause, which is commonly not available—hence the final concept, 'Judging the evidence' in Table 8, is particularly relevant.

These guidelines are ordered in a logical sequence for making judgements on causality. They are not weighted equally, and their relative contribution to a final judgement will vary from one situation to another (Thomas and Hrudey, 1997)

Consistency can be demonstrated if several studies give the same result, especially if a variety of designs is used in different settings since this reduces the likelihood that all studies are making the same mistake. However other factors such as different exposure levels or study conditions may need to be taken into account, and the best-designed studies should be given the greatest weight. It is important to note that in environmental epidemiology, reliance on a single pivotal study is the exception rather than the rule.

Table 8: Guidelines for the assessment of causation

Temporal relation:	Does the cause precede the effect (essential)
Plausibility:	Is the association consistent with other knowledge? (mechanism of action; evidence from experimental animals)
Consistency:	Have similar results been shown in other studies?
Strength:	What is the strength of the association between the cause and the effect? (In general, relative risks greater than 2 can be considered strong)
Dose–response Relationship:	Is increased exposure to the possible cause associated with increased effect?
Reversibility:	Does the removal of a possible cause lead to reduction of disease risk?
Study design:	Is the evidence based on a strong study design?
Judging the Evidence:	How many lines of evidence lead to the conclusion?

(adapted from Beaglehole *et al*, 1993, p. 76)

The technique of meta-analysis grew out of the need to reduce random error in clinical trials. Meta-analysis in the context of systematic reviews can be used to pool the data from well-designed studies, each of which may deal with a relatively small sample size, in order to obtain a better overall estimate of effect. Meta-analysis has pitfalls if poor quality studies are included, and needs to be applied with caution to observational studies - which are less able to control for confounding than randomised trials. Standard methods for conducting and reporting systematic reviews have been published (Greenhalgh, 1997). The reader is also referred to an excellent resource published by NHMRC (2000), 'How to review the evidence: systematic identification and review of the scientific literature'.

The strongest evidence comes from well-designed and competently conducted randomised controlled trials. The National Health and Medical Research Council (1999) places strongest emphasis on evidence obtained from systematic reviews of all relevant (and well-conducted) randomised controlled trials ('level I').²

However there are relatively few such trials available for environmental health hazards, that could form the basis for a systematic review. Most apply to the effects of treatment or prevention campaigns. A rare example is the Melbourne

Water Quality Study which was a blinded study involving real and sham domestic reverse osmosis water filters and an assessment of acute gastrointestinal disease (Hellard, 1999).

In practice, most evidence comes from observational studies (e.g. nearly all the evidence on the health effects of smoking). In well-conducted cohort studies bias is minimised. Case control studies are subject to several forms of bias and weaknesses related to time-sequence but, if well designed, may still provide useful evidence for the causal nature of an association. Cross-sectional studies are weaker as they provide no direct evidence on the time sequence of events.

Ecological studies are the least satisfactory because of the dangers of incorrect extrapolation to individuals from data derived from regions or countries. However where certain exposures cannot normally be measured individually (e.g. air pollution, pesticides residues in food, fluoride in drinking water) evidence from ecological studies may be important in environmental health decision making (Beaglehole *et al*, 1993). Time-series studies demonstrating health outcomes associated with fluctuating air pollutant levels may be one particularly useful example.

The above principles about strength of evidence obtained from various study types are summarised in Table 9.

Table 9: Relative ability of different types of study to 'prove' causation

Type of study	Ability to 'prove' causation
Randomised controlled trials	Strong
Cohort studies	Moderate
Case-control studies	Weak/Moderate
Cross-sectional studies	Weak
Ecological studies	Weak

(adapted from Beaglehole *et al*, 1993)

² The NHMRC document referred to is oriented towards clinical interventions and clinical practice guideline development. At present there are no comparable endorsed 'levels of evidence' to guide assessment of epidemiological evidence for environmental health practice, although the National Public Health Partnership with input from NHMRC is constructing a similar approach to public health interventions.

The ranking in this Table assumes that studies are well designed and well conducted in each case. Even the presence of a strong ability to ‘prove’ causation should be supplemented by mechanistic knowledge to be confident of causation.

5.5 The Strengths and Limitations of Observational Epidemiology versus Experimental Toxicology

Epidemiological studies are crucial for assessing effects directly in humans and estimating population attributable risks. However their power of resolution is limited, mainly because of the difficulties in estimating exposure precisely and in controlling bias. Toxicological studies are necessary for elucidating causal mechanisms, which may be important for determining dose–response relations and extrapolating to low doses in risk assessment. On the other hand, direct generalisations to humans based on animal data are often uncertain (Pershagen, 1999).

Epidemiological studies are often given increased weighting because they come from humans but, compared to toxicological studies of animals, may be more costly and time consuming and more likely to result in ambiguous findings (Samet *et al*, 1998). However substantive findings have been obtained at times through opportunistic study of highly exposed groups - such as occupational cohorts or communities that have been inadvertently exposed to contaminants e.g. via food or water. These can be either observational epidemiological studies, or what Lilienfield (1980) called ‘natural experiments’.

5.5.1 Hazard identification

Epidemiology has a number of potential advantages over animal toxicology in the area of hazard identification:

- it directly assesses human health risk;
- absorption, metabolism, detoxification and excretion may vary between humans and the animal species studied does not need to be taken into account in epidemiological studies;

- sample sizes for human studies may be much larger than those available for animal studies;
- genetic diversity may be broad in humans compared to selected animal strains used in toxicological studies;
- epidemiological studies may include different groups (e.g. the young, old and susceptible) that may not be included in the usually relatively homogeneous groups used in toxicological studies; and
- effects on some aspects of mental function or behaviour, and more subjective effects such as nausea or headache, can be better assessed in human studies.

Differences in hazard identification based on epidemiological and toxicological data may be seen in the matter of ‘site concordance’. The epidemiological data may suggest lung cancer is of concern whereas the toxicological data may suggest liver cancer. Similar conflicts can arise where there are suggestions of a problem from epidemiological data unsupported by toxicological evidence (Samet *et al*, 1998).

5.5.2 Dose–response assessment

Epidemiological data may assist in assessing dose–response relationships. Advantages of epidemiology over animal studies may include:

- reduced uncertainty about interspecies variability in metabolism, lifespan, and genetic diversity;
- complex temporal patterns of exposure and doses in situations requiring risk assessment may be impossible to replicate in animal studies; whereas some epidemiological studies may be more useful for understanding these complex dose–response relationships; and
- the ability to assess large numbers of people exposed to low levels of an agent. The doses from exposure to a hazardous agent in epidemiological studies are often considerably less than in toxicological studies. This may have the advantage of providing information about the exposure range of interest although,

if they are the result of (prolonged) adult occupational exposures, the exposures are likely to be considerably more than those experienced by people in the general population. With appropriate tools small differences in relative risk in large populations may be able to be assessed. (Roseman, 1998; Samet *et al*, 1998)

However, epidemiological studies are often limited by the amount of data available on dose and tend to address exposure–response relationships (i.e. they are based on whether or not exposure occurred) rather than dose–response relationships. Doses are usually discontinuous and variable in epidemiological studies compared to controlled toxicological experiments. An integrated measure of exposure may need to be developed to represent the non-uniform doses.

Quantitative description of dose–response relationships may be hampered by incomplete information on exposure (especially for biologically relevant time windows), by exposure or dose misclassification, or by the use of surrogate markers of exposure. Incorrect information about the exposure may bias the description of the exposure–response relationship. If there are wide confidence intervals around the results there can be substantially different policy endpoints depending on whether the upper bound, the lower bound or the midpoint has been chosen for policy making (Samet *et al*, 1998).

Commonly too there are insufficient epidemiological data to discriminate between alternative models that could describe the dose–response relationship. This is particularly important at very low exposure levels and this is where both epidemiological and toxicological data are often limited. Surrogate measures of outcome (e.g. nerve conduction or tremor) and a relationship between the surrogate measures and health outcomes may need to be established in order to interpret the significance of a study, although care needs to be taken that the surrogate outcomes do relate to clinically meaningful outcomes.

The reviewer or risk assessor should answer the basic question of whether the epidemiologic data, in an individual study or cumulatively, are adequate for use in dose–response evaluation. There is no formula or quantitative weighting scheme prescribed for making this judgement.

If epidemiologic data adequate for dose–response evaluation are not available, and a risk assessment is being developed for use in making an important regulatory decision, and if it is feasible to develop new epidemiologic data, or to extract new data from existing studies, an effort should be made to develop and provide good epidemiologic dose–response data that can be used together with, or in preference to, high-dose animal data.

The following ‘London Principles’ (Federal Focus, 1996) may be used to guide the choice of studies in this critical area:

- **Principle 1.** Dose–response assessment should include a range of reasonable dose measures, an explanation why any were rejected, and provide a rationale if any particular dose metric is preferred. In evaluations of both human and animal data, several different measures of dose should be evaluated (if possible).
- **Principle 2.** In the selection of a dose–response model, the greatest weight should be given to models that fit the observed animal and human data and are consistent with the biologically relevant mode(s) of action (genotoxic, non-genotoxic, unclassified). When mechanistic knowledge is uncertain or limited, several plausible dose–response models should be considered and the most plausible ones, based on available data and professional judgement, should generally be used in dose–response evaluation.
- **Principle 3.** When extrapolating cancer risk to exposure levels below the observable range, mechanistic data should be used to characterise the shape of the dose–response function.

- **Principle 4.** When the available epidemiologic data are not adequate to perform dose–response analyses, causing low-dose estimates of risk to be derived exclusively from animal data, every effort should still be made to use the available human data in assessing the validity of low-dose risk estimates. To the extent feasible, heterogeneity in the human population should be accounted for. Whenever feasible, human data on metabolic biomarkers and other biological measures should be employed to adjust the risk estimates for known differences between species and between high and low doses. If possible, data on susceptibility should be included.
- **Principle 5.** When epidemiologic studies are selected for dose response assessment, higher quality studies should be given preference, especially those with precise and accurate exposure information. The availability of information with respect to timing of exposure and response (time/age of first exposure, intensity of exposure, time to tumour), adjustment for confounding variables, and potential interaction with other effect modifiers is particularly important.
- **Principle 6.** A properly conducted meta-analysis, or preferably an analysis based on the raw data in the original studies, may be used in hazard identification and dose–response evaluation when such combination includes an evaluation of individual studies and an assessment of heterogeneity. The combined results ought to provide, more than any single study, precise risk estimates over a wider range of doses. Before using these tools, the gains should be judged sufficient to justify potential errors in inference resulting from combining studies of dissimilar design and quality.
- **Principle 7.** When epidemiological data are used in dose–response assessment, a quantitative sensitivity analysis should be conducted to determine the potential effects on risk estimates of confounders, measurement error, and other sources of uncontrolled bias in study design.

- **Principle 8.** Scientific understanding of differentials in human susceptibility to disease (racial/ethnic/gender/genetic differences, genetic polymorphisms, etc.) should be used to refine the low-dose extrapolation procedures when such phenomena are adequately understood.

5.5.3 Exposure assessment

A lack of good exposure data is a common pitfall of environmental epidemiological studies, to the extent that such studies tend only to be as good as their exposure data. The association of particular health effects and specific patterns of exposure, if in keeping with knowledge of pathophysiology, can provide strong support for causal interpretations (WHO, 2000).

Illustrating this problem, Saunders *et al* (1997) reviewed 14 key relevant studies selected from a short list of 43 analytical studies assessing human health effects in relation to hazardous waste sites, and found that poor exposure measurement was a major factor in the overall lack of convincing evidence of causation from these studies. It is often the case that only a broad indication of the level or nature of exposure may be deduced from epidemiological studies.

Experimental toxicological studies on the other hand generally have the advantage of control and accurate measurement of exposures. Nevertheless, at times environmental epidemiological studies may be the only way of determining the distribution of ‘real-life’ exposures in terms of:

- magnitude;
- duration;
- temporal patterns;
- routes;
- size of exposed population; and
- nature of exposed population.

Future studies should be designed in such a way as to better capture such information.

5.5.4 Risk characterisation

The term 'risk' tends to be used in a subtly different and more specific way in epidemiology than in risk assessment. In epidemiology, risk describes the 'frequency of occurrence of a disease in one population compared with another, either as a difference in rates (attributable risk) or as a ratio of rates (relative risk)' (ACDP, 1996, p. 20). The feature distinguishing the two populations by its presence or distribution is referred to as a 'risk factor'. The reliance on comparisons of disease rates between populations creates substantial limitations for the sensitivity of relative risk determination for common diseases (Thomas and Hrudey 1997, p. 206).

In risk assessment, the characterisation of 'risk' may be arrived at by a wider variety of means than in epidemiology.

5.6 Critical Evaluation of Published Research

The following section is reprinted, with minor adaptation, from 'Introduction to research in the health sciences' by Polgar S and Thomas SA (1991), p. 302–306 by permission of the publisher Churchill Livingstone. Italicised questions are from Riegelman 1981, p. 73 and British Medical Journal 1988, p. 50 (with minor amendments).

5.6.1 Critical evaluation of the introduction

The Introduction of a paper essentially reflects the planning of the research. Inadequacies in this section might signal that the research project was erroneously conceived, or poorly planned. The following issues are essential for evaluating this section:

- *Adequacy of the literature review.* The literature review must be sufficiently complete so as to reflect the current state of knowledge in the area. Key papers should not be omitted, particularly when their results could have direct consequences for the research hypotheses or aims. Researchers must be unbiased in presenting evidence which is unfavourable to their points of view;

- *Clearly defined aims or hypotheses.* The aims or hypotheses of an investigation should be clearly and operationally stated. If this is lacking, then how the evidence obtained in the investigation is to be used for conceptual advances in the area, will be ambiguous;
- *Selection of an appropriate research strategy.* In formulating the aims of the investigation, the researcher must have taken into account the appropriate research strategy. For instance, if the demonstration of causal effects is required, a survey may be inappropriate for satisfying the aims of the research; and
- *Selection of appropriate variables.* The operational definition of the variables being investigated calls for selecting appropriate measurement strategies. If the selection of the variables is inappropriate to the constructs being investigated, then the investigation will not produce useful results.

5.6.2 Critical evaluation of the methods section

A well-documented Methods section is a necessary condition for understanding, evaluating and perhaps replicating a research project. In general, the critical evaluation of this section will reveal the overall internal and external validity of the investigation.

Subjects

The section shows if the sample was representative of the target population and the adequacy of the sampling model used.

- *Sampling model used.* A number of sampling models can be employed to optimise the representativeness of a sample. If the sampling model is inappropriate, then the sample might be biased, raising questions concerning the external validity of the research findings.
- *Sample size.* Use of a small sample is not necessarily a refutation of an investigation, if the sample is representative. However, given a highly variable, heterogeneous population, a small sample will not be adequate to ensure

representativeness. Also, a small sample size could decrease the power of the statistical analysis.

- *Description of the sample. Was there a power-based assessment of adequacy of sample size?* A clear description of key sample variables (for example, age, sex, type and severity of condition) should be provided. When necessary and possible, demographic information concerning the population should be provided. *Was the population of adequate composition to answer the study questions?* If not, the reader cannot judge the representativeness of the sample. Also, the readers might not be able to decide if the findings are applicable to the specific groups of patients being treated.

Instruments/apparatus

The validity and reliability of observations and measurements are fundamental characteristics of good research. In this section, the investigator must demonstrate the adequacy of the equipment used for the data collection.

- *Validity and reliability.* The investigator should use standardised apparatus, or establish the validity and reliability of new apparatus used. The lack of proven validity and reliability will raise questions about the adequacy of the empirical findings.
- *Description of instrumentation.* Full description of the structure and use of novel instrumentation should be presented so that the instrument can be replicated by independent parties.

Procedures

Full description of how the investigation was carried out is necessary for both replication and for the evaluation of its internal and external validity.

- *Adequacy of the design.* A good design should control for alternative interpretations of the data. That is, a poor design will result in uncontrolled influences by extraneous variables, negating the unequivocal evaluation of causal effects. A variety of threats to internal validity must be considered when critically evaluating an investigation.
- *Control groups.* A specific way of controlling for extraneous effects is the use of control groups. If no control groups are employed, then the internal validity of the investigation might be questioned. Also, if placebo or untreated groups are not present, the size of the effects due to the treatments might be difficult to estimate.
- *Subject assignment.* When using an experimental design, care must be taken in the assignment of subjects so as to avoid significant initial differences between exposure groups. Even when quasi-experimental or natural comparison strategies are used, care must be taken to establish the equivalence of the groups.
- *Was there a satisfactory statement given of the source of subjects?*
- *Was a satisfactory response rate achieved?*
- *Was the assignment of people to study and control groups appropriate?*
- *Could selection bias have occurred?*
- *If the study was experimental, were random and blind assignment maintained?*
- *Regardless of the study type, were the study and control groups comparable with respect to characteristics other than the study factors(s)?*
- *Exposure parameters.* Was exposure adequately defined? It is important to describe all the exposures experienced by the different groups. If the exposures differ in intensity or in the quality of the administering personnel, then the internal validity of the project is threatened.

- *Rosenthal and Hawthorne effects.* Whenever possible, studies should be double or single blind. If the subjects, experimenters or observers are aware of the aims and predicted outcomes of the investigation, then the validity of the investigation will be threatened through bias and expectancy effects.
- *Settings.* The setting in which a study is carried out has implications for external (ecological) validity. An adequate description of the setting is necessary for evaluating the generalisability of the findings.
- *Times of exposures and observations.* The sequence of exposures and observations must be clearly indicated, such the issues such as series effects and confounding can be detected. Identification of variability in treatment and observation times can influence the internal validity of experimental, quasi-experimental or n=1 designs, resulting in, for instance, internal validity problems.
- *Were the results adjusted to take into account the effect of possible confounding variables? Common confounders are age and sex, regional differences, socio-economic differentials, smoking, occupation, ethnic differences.*
- *Was a significance test properly performed to assess the probability that the difference was due to chance?*
- *Was a proper measure of the size of the difference presented?*
- *Was a proper measure of the degree of overlap of the differences presented?*
- *Were the confidence intervals given for the main results?*

Motulsky (1995) provides a useful checklist of common pitfalls to bear in mind when reading research papers that include statistical analysis, which has been adapted as follows:

5.6.3 Assessment of outcome

- *Was the assessment of outcome properly performed in the study and the control groups?*
- *Was the measure of outcome appropriate to the study aims?*
- *Was the measure of outcome precise?*
- *Was the measure of outcome complete?*
- *Did the process of observation affect the outcome?*

5.6.4 Critical evaluation of statistical analysis

- *Was there a statement adequately describing or referencing all statistical procedures used?*
- *Were the statistical analyses used appropriate?*
- *Was the presentation of statistical material satisfactory?*
- *Did the analysis properly compare the outcomes in the study and the control groups?*
- *Look at the data*—summary statistics may result in the loss of useful information;
- *Beware of very large and very small samples*—large samples may generate statistically significant but unimportant findings; small samples have little power to detect important differences;
- *Beware of multiple comparisons*—when analysing random data, on average 1 out of 20 comparisons will be statistically significant ($p < 0.05$) by chance;
- *Don't focus on averages alone:* variability may reflect real biological diversity, and outliers may be more important;
- *'Garbage in, Garbage Out'*—statistical tests do not tell whether the study was conducted properly;
- *Confidence limits are as informative as p values* (and may be more so, particularly when dealing with hazards);
- *Statistical significance does not necessarily indicate biological importance;*

- *p* < 0.05 is not sacred—it is an arbitrary cutoff value; and
- Correlation or association does not imply causation.

Section 3.7.12 also provides information on the statistical analysis of data.

5.6.5 Critical evaluation of the results

The ways in which epidemiological data are properly presented and analysed goes beyond the scope of this document in terms of complexity and depth, and reference should be made to standard texts. However, the following general points can be made.

The results should represent a statistically correct summary and analysis of the data. Inadequacies in this section could indicate that inferences drawn by the investigator were erroneous.

- *Tables and graphs.* Data should be correctly tabulated or drawn and adequately labelled for interpretation. Complete summaries of all the relevant findings should be presented.
- *Selection of statistics.* Both descriptive and inferential statistics must be selected appropriately. The selection of inappropriate statistics could distort the findings and lead to inappropriate inferences.
- *Calculation of statistics.* Both descriptive and inferential statistics must be correctly calculated. The use of computers generally ensures this, although some attention must be paid to gross errors when evaluating the data.

5.6.6 Critical evaluation of the discussion

In the discussion, the investigator draws inferences from the data in relation to the initial aims or hypotheses of the investigation. Unless the inferences are correctly made, the conclusion drawn might lead to useless and dangerous treatments being offered to clients.

- *Drawing correct inferences from the data.* The inferences from the data must take account of the limitations of descriptive and inferential statistics. Correlations do not necessarily imply causation, or that a lack of significance in the analysis could imply a Type II error (see below).
- *Logically correct interpretations of the findings.* Interpretation of the findings must follow from the statistical inferences, without extraneous evidence being introduced. For instance, if the investigation used a n=1 design, the conclusions should not claim that a procedure is generally useful.
- *Protocol deviations.* In interpreting the data, the investigator must indicate and take into account unexpected deviations from the intended design. For instance, a placebo/active treatment code might be broken, or 'contamination' between control and experimental groups might be discovered. If such deviations are discovered by investigators, they are obliged to report these, so that the implications on the results might be taken into account.
- *Generalisation from the findings.* Strictly speaking, the data obtained from a given sample are generalisable only to the population from which the sample was drawn. This point is sometimes ignored by investigators, and the findings are generalised to subjects or situations which were not considered in the original sampling.
- *Statistical and practical significance.* Statistical significance does not necessarily imply that the results of an investigation are applicable in practical terms. In deciding on practical significance factors such as the size of effect, side effects, cost effectiveness, as well as value judgements concerning outcome must be considered.
- *Theoretical significance.* It is necessary to relate the results of an investigation to previous related findings, as identified in the literature

review. Unless the results are logically related to the literature, the theoretical significance of the investigation remains unclear. The processes involved in comparing the findings of a set or related papers are introduced in the next sub-section.

- *Was a valid interpretation drawn from the comparisons made between the study and control groups during analysis?*
- *Did the investigators properly reject or fail to reject the null hypothesis?*
- *Did the investigators consider the possibility of Type I and Type II errors in interpreting the meaning of the significance test? (Type I errors are the result of chance and are the rejection of the null hypothesis when no true difference exists in the larger population. Type II errors result from chance or too small a sample size and are the failure to reject the null hypothesis when a true difference exists in the larger population.)*
- *Were the size of the differences and the degree of overlap taken into consideration in the conclusions reached about the meaning of observed differences?*
- *In interpreting the meaning of any relationship, was the concept of cause and effect (causation) properly applied?*
- *Were the extrapolations to individuals not included in the study properly performed?*
- *Did the investigators stay within the limits of the data when extrapolating the results?*
- *If the investigators extrapolated from population data to individual data, was this appropriate and correct?*
- *Did the researchers take into consideration differences between the study population and the population to which they extrapolated their data?*

5.7 Evaluation of Meta-Analyses

Meta-analysis is the process of undertaking a quantitative review of the literature, seeking consistent patterns among, and sources of discrepancies between, studies (WHO, 2000). An assessment should consider the homogeneity of the studies examined and whether summary effects estimates will be calculated and by what methods (*ibid*).

WHO (2000) has recommended that the following features be considered when conducting, or assessing the findings of, a meta-analysis:

- establishing or noting a protocol specifying the objectives of the review and the methods to be employed;
- having inclusion criteria that are more inclusive than exclusive, so enabling sensitivity analysis using different levels on inclusion to be undertaken;
- avoiding a single quality score of studies and presenting, instead, an assessment of a range of characteristics;
- weighting according to the precision of the study;
- assessing and addressing the impact of publication bias;
- systematically quantifying the heterogeneity of the studies which can enable the identification of sources of variability in the results of studies from factors such as the choice of methodology, and the inclusion of susceptible subgroups or unusual exposure conditions;
- using sensitivity analyses of factors such as different analytic approaches, different methods of extracting results from the studies or the inclusion or exclusion of particular studies or types of studies; and
- appraising methods used to obtain qualitative and quantitative summary estimates from a collection of studies.

5.8 Common Omissions and Errors in Published Research

Rushton (2000, p. 2) provides a report on some of the most serious omissions and errors in papers presented in recent years to the journal, 'Occupational and Environmental Medicine'. These are:

Design

- Authors unclear about type of epidemiological study;
- Adequacy of sample size not considered;
- Bias in selection of subjects;

Execution

- Data collection problems and missing data not adequately reported;
- Non-respondents not investigated;
- Sample selection and exclusions inadequately justified;

Analysis

- Parametric tests carried out on obviously skewed data;
- Use of multiple paired tests;
- Inappropriate analysis of repeated measures or longitudinal data;
- Incorrect analysis of matched case-control studies;

- Modelling incorrect—e.g. inadequate adjustment for confounders, interaction terms not included, only significant variables from preliminary analyses included;

Presentation

- Inadequate description of the methodology and statistical procedures;
- Inappropriate summary statistics for non-normal data;
- No presentation of risk estimates—e.g. odds ratios—and confidence intervals;

Interpretation

- Potential bias due to sample selection, no or poor response, missing values, exclusions;
- Lack of statistical power not considered;
- No allowance made for multiple testing; and
- Misunderstanding and misinterpretation of results from models.

Table 10 summarises some of the potential problems and their implications which might emerge in the context evaluation of an investigation. A point which must be kept in mind is that even where an investigation is flawed, some useful knowledge might be drawn from it. The aim of critical analysis is not to discredit or tear down published work, but to ensure that the reader understands its implications and limitations.

Table 10: Checklist for evaluating published research

Problems which might be identified in a research article	Possible implications
1. Inadequate literature review	Misrepresentation of the conceptual basis for the research
2. Vague aims or hypothesis	Research might lack direction; interpretation of evidence might be ambiguous
3. Inappropriate research strategy	Findings might not be relevant to the problem being investigated
4. Inappropriate sampling method	Measurements might not be related to concepts being investigated
5. Inadequate sampling method	Sample might be biased, investigation could lack external validity
6. Inadequate sample size	Sample might be biased; statistical analysis might lack power
7. Inadequate description of sample	Application of findings to specific groups or individuals might be difficult
8. Instruments lack validity or reliability	Findings might represent measurement errors
9. Inadequate design	Investigation might lack internal validity; i.e. outcomes might be due to uncontrolled extraneous variables
10. Lack of adequate control groups	Investigation might lack internal validity; size of the effect difficult to estimate
11. Biased subject assignment	Investigation might lack internal validity
12. Variations or lack of control of treatment parameters	Investigation might lack internal validity
13. Observer bias not controlled (Rosenthal effects)	Investigation might lack internal and external validity
14. Subject expectations not controlled (Hawthorne effects)	Investigations might lack internal and external validity
15. Research carried out in inappropriate setting	Investigation might lack ecological validity
16. Confounding of times at which observations and interventions are carried out	Possible series effects; investigation might lack internal validity
17. Inadequate presentation of descriptive statistics	The nature of the empirical findings might not be comprehensible
18. Inappropriate statistics used to describe and/or analyse data	Distortion of data; false inferences might be drawn
19. Erroneous calculation of statistics	False inferences might be drawn
20. Drawing incorrect inferences from the data	False conclusions might be made concerning the outcome of an investigation
21. Protocol deviations	Investigation might lack external or internal validity
22. Over-generalisation of finding	External validity might be threatened
23. Confusing statistical and clinical significance	Treatments lacking clinical usefulness might be encouraged
24. Findings not logically related to previous research findings	Theoretical significance of the investigation remains doubtful

(adapted from Polgar and Thomas, 1991)

5.9 Undertaking Health Studies

The material in the following sections is adapted from ATSDR (1996).

In some situations there will be a need to undertake health studies as part of a risk assessment. A risk assessment may have been prompted by health studies undertaken by the community. The design of health studies should be underpinned by epidemiological principles. A range of factors need to be considered before embarking on a health study.

- **Public health significance**
Public health significance is a key factor in considering the merits of a proposed health study. Issues for consideration include: the toxicity of the agent; the pathways of human exposure; severity and biological plausibility of the health outcome; need for new information (beyond what is already known or what has already been done); size and susceptibility of the population affected; ability to prevent or mitigate exposure or health outcomes; and relevance to other situations with similar agents and exposure pathways.
- **Community perspective and involvement**
Community involvement is critical to the success of any proposed health study. Various community involvement methods can be used for health studies. Issues for consideration include: an ability to involve key community stakeholders; an understanding of community health concerns; an understanding of the approach and limitations of proposed activities; and community support for the study being conducted.
- **Scientific importance**
Scientific importance is closely related to public health significance. Issues for consideration include: the ability to provide new knowledge or information about an exposure–outcome relationship; to address specific exposures or outcomes that have not

been adequately studied; to allow new laboratory tests or study methods to be used or evaluated; to generalise to other situations or populations; and provide confirmation or additional support to a preliminary hypothesis or theory.

- **Ability to provide definitive results**
Since health studies may end up with inconclusive findings, it is important to consider how definitive the study might be in providing scientifically useful results related to specific exposure–outcome relationships. Issues for consideration include the ability to: obtain appropriate measurements of exposure and to document health outcomes and exposures; use adequate control or comparison populations; obtain community support to ensure an adequate participation rate; state clearly the study objectives and specific hypothesis to be tested; have sufficient statistical power to detect predicted effects, obtain data on important potential confounders, and evaluate a dose–response relationship or gradients of exposure.
- **Resources**
Resources are critical to the support, conduct, and completion of any proposed health study. Issues for consideration include: the availability of qualified personnel and technical support; an ability to obtain necessary data and health information; and the availability of appropriate project timelines and resources;
- **Authority and support**
It is critically important that local, state, and federal health agencies be involved early in discussions about potential health studies. Issues for consideration include: the ability to support or provide technical assistance requested by the local or state health agency; the ability of local and state health agencies to address the community problem and health concerns; and the involvement of appropriate agencies with legislative and regulatory backing.

5.10 Nature of the Health Study

When the decision to conduct a health study is being considered, several criteria are used to determine the type of health study. These relate to whether the relevant research hypothesis requires:

- the characterisation of environmental contaminants by type, media, and concentration levels;
- documented evidence of human exposure at a level of concern;
- level of current knowledge about the relationship between exposure and specific adverse health outcomes; and/or
- documented excess of an adverse health outcome, when known.

The health studies can be grouped into Type 1 and Type 2 studies.

5.10.1 Type-1 health studies

Type-1 health studies explore or generate hypotheses about exposure-outcome associations and address specific exposures, community health concerns, or specific information needs. Examples of Type-1 health studies follow.

- *Cross-sectional studies*. These are surveys of a sample of residents to obtain information about current and past health or environmental exposures, or both. These studies can include comparison populations with demographics similar to those of the exposed (target) population.
- *Pilot investigations* collect additional information to assess the feasibility and value of conducting a full-scale health study. The investigation might include; assessments of data completeness and quality; the level of documentation of exposures or health outcomes; methods to identify and track individuals, study size and statistical power issues; and the availability of a control population or comparison.
- *Cluster investigations* evaluate the reported occurrence of a specific disease or condition is above the expected number for a given

geographic location and time period. These investigations can be conducted to confirm case reports, determine an unusual disease occurrence, and explore potential risk factors.

- *Comprehensive case reviews* are medical or epidemiological evaluations of the medical status of one or more individuals through medical record reviews, interviews or biomedical testing to determine additional information about their health status or potential for exposure.
- *Situation-specific surveillance* is designed to assess the specific occurrence of one or more defined health conditions among a specific population potentially exposed to hazardous agents in the environment. Data collection might include using existing records of health events or records from relevant health care providers.
- *Health statistics reviews* use available health and demographic information to assess the occurrence of specific health effects in defined geographic areas and determine if the rates are elevated compared to similar populations elsewhere. Available information might include: death certificate, birth certificate, and census data; tumour or disease registry data; and health surveillance or disease notification data. A health statistics review may be performed in response to a reported cluster of specific diseases or conditions.
- *Exposure investigations* use environmental or biological testing, or both, for the hazardous agent(s) of interest. The biological test might measure the level of the hazardous agent, a metabolite of a hazardous substance or another marker of exposure in human body fluids or tissues. The purpose of this investigation is to assess individual exposure levels to a specific agent associated with the situation. The levels identified should be compared with that of a relevant reference group or with a known standard reference level. Depending on the hazardous agent, the investigation can be used to explore for evidence of past or current exposure.

- *Disease and symptom prevalence surveys* are used to measure and compare the occurrence of self-reported diseases, in some instances using medical records or physical examinations to validate adverse health conditions. Addressing potential health concerns raised by the community, the survey compares an exposed population (target area) with an unexposed population (control area) with similar demographic characteristics. The purpose is to determine the need for further health studies in the target area, provided there are statistically significant excesses that are clinically important. Depending on the contaminants and circumstances, biological testing of exposure or effect, or both, might also be collected as part of the survey.

When a Type-1 health study is considered appropriate, there are several attributes that are considered necessary in order to ensure the quality of the study effort:

- a reasonable ability to document and characterise exposure in the target area;
- an adequate study size for the type of study recommended;
- an ability to identify and locate subjects and records;
- appropriate comparisons for rates of occurrence or levels of exposure; and
- an ability to control confounding factors and biases (when possible).

5.10.2 Type-2 health studies

Type-2 health studies are specifically designed to test scientific hypotheses about the associations between adverse health outcomes and exposure to hazardous substances in the environment.

Examples of Type-2 health studies follow:

- *Case-control studies* are designed to collect information and compare differences in exposures and other risk factors in two groups of people: persons with specific illnesses or conditions (cases) and persons without the illnesses or conditions (controls). The controls

are selected to represent the population from which the cases were identified. Usually the cases and controls are identified first, and then information is collected about past exposures and other risk factors.

- *Cohort studies* are designed to collect information from a group of people followed over a period of time, and information on the occurrence of specific illnesses or conditions is collected. Cohort studies can be prospective, meaning that individuals involved in the study are followed into the future, or cohorts can be retrospective, meaning that the cohort is reconstructed from historical records and then followed over a specified time period. They are expensive, require long periods of time, and large numbers of people must be followed for rarer outcomes to provide enough cases for analysis.
- *Nested case-control studies* are another approach that uses both of the study designs previously mentioned. The nested case-control study uses cohort individuals who have developed a specific illness or condition (case) and persons sampled from the cohort who have not developed the illness or condition (control). The case-control method is then used to collect additional information and analyse the differences between these two groups.

There are several attributes of Type-2 health studies that are considered necessary in order to ensure valid scientific findings including:

- an ability to reasonably estimate or document individual exposures;
- an ability to document or validate human health outcomes;
- an adequate study size and statistical power;
- an ability to identify and locate subjects and records;
- availability of an appropriate control or comparison population;

- an ability to control confounding factors and minimise biases; and
- an ability to determine influence of environmental, behavioural, or other factors.

5.11 Ensuring the Quality of a Health Study

To ensure a useful and appropriate outcome the following factors should be met:

- The group conducting the health study must be capable and fully responsible for conducting the health study;
- Personnel conducting the health study must be identified and have appropriate training and experience;
- The facilities and resources must be appropriate for the successful completion of the health study;
- Contractors for a health study must follow written and approved work plans and their work must be carefully reviewed by the sponsoring group;
- For complex studies, a detailed study protocol should be written and undergo scientific peer review;
- Ethical issues relating to the protection of human subjects, consent, and data confidentiality procedures must be addressed;
- Reports of complex health studies may need to undergo scientific peer review prior to any public release of information;
- Community involvement and knowledge of the health study are necessary: the involvement process will assist in ensuring that the community understands and supports the study focus and design, and its limitations.
- Depending on the community involvement approach, public meetings might be held to present and discuss the study methods and findings. However, final study methods must be scientifically valid before proceeding;

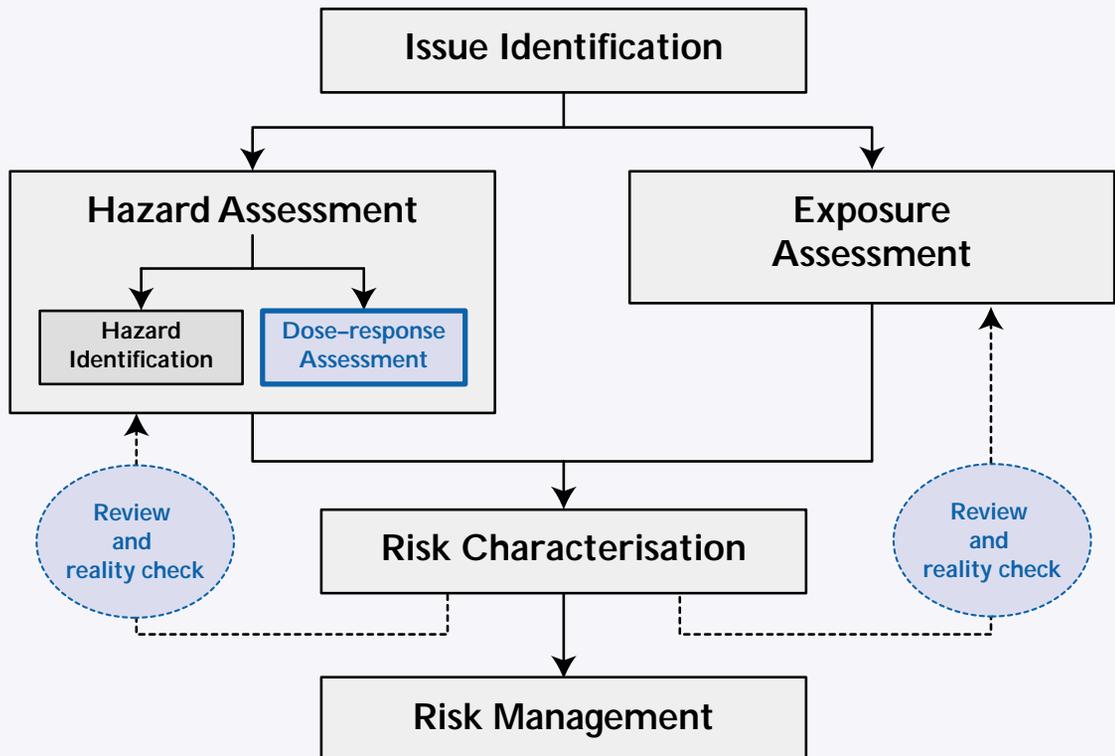
- All study reports, data files and related documentation should be kept in the official records; and
- Any environmental sampling or biological testing must follow existing standards for collection, handling, chain of custody, storage, analysis, and reporting by an approved laboratory(ies): all standard quality control and quality assurance procedures must be followed and documented.

5.12 Contents of a Health Study Protocol

The following components should be considered in drafting a report. Protocols for health studies might not need to contain all of the items within this outline. The listing is more comprehensive in order to cover the wide variety of study approaches.

1. Title and identification page
2. Introduction and overview
3. Background
 - Situation description
 - Demographics
 - Contaminants and pathways
 - Community health concerns
 - Literature review
4. Purpose
5. Study objectives
6. Methods
 - Rationale for study design
 - Study description
 - Eligibility criteria
 - Selection of target area and population
 - Selection of comparison area and population
 - Sample size and statistical power estimates

- Participant selection and definitions
 - Enrollment procedures
 - Location(s) of data and specimen collection
 - Informed consent procedure
 - Questionnaire procedures
 - Interviewer training and methods
 - Methods for measurement of exposure
 - Collection of biological specimens
 - Additional data collection or sources
 - Chain of custody and shipping
 - Laboratory methods and quality control
 - Privacy protection
 - Findings of immediate significance
 - Follow-up of abnormal lab results
 - Data analysis
 - Data entry, editing, and management
 - Data transformation
- 7. Data analysis plan and methods
 - 8. Study timelines
 - Key activities or milestones
 - 9. Community involvement and notification
 - 10. Interpretation of results
 - 11. Limitations of the study
 - 12. References
 - 13. Tables and figures
 - 14. Attachments
 - Data collection forms and questionnaire
 - Study letters of notifications and consent form
 - 15. Specimen collection and shipping protocols



Hazard Assessment—Part 3:

Dose–Response Assessment

6.1 Introduction

The following section uses material from the NHMRC's Toxicity Assessment Guidelines for Carcinogenic Soil Contaminants (1999) and Klaassen (1996).

There are different ways of characterising dose response relationships including:

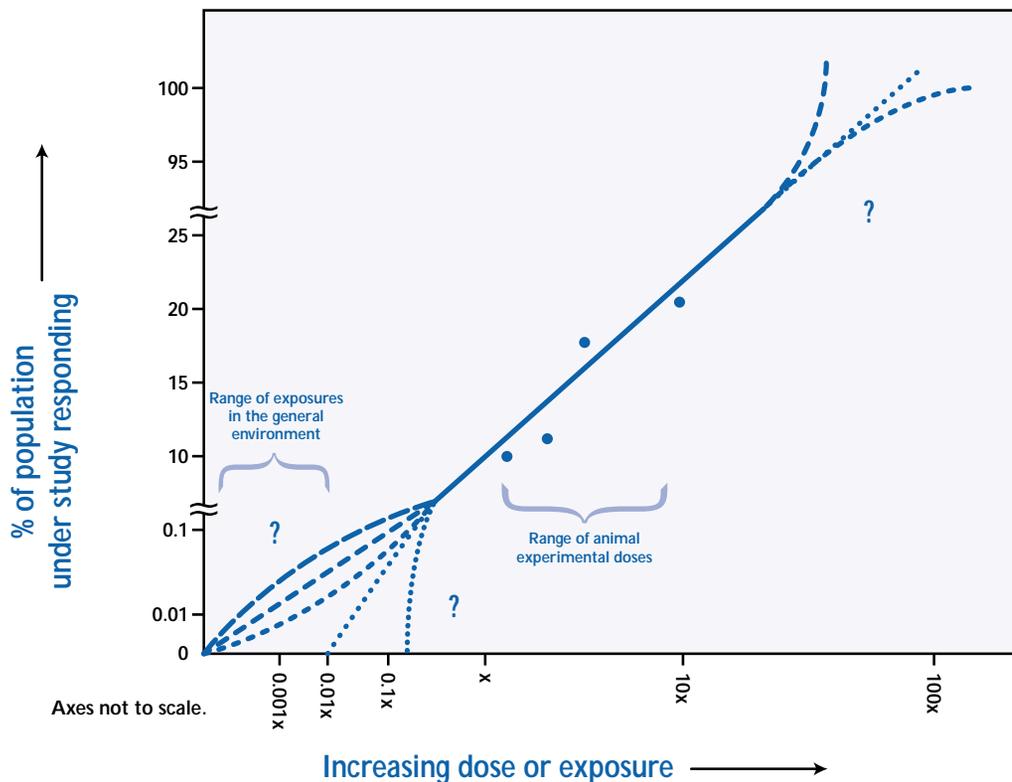
- effect levels (e.g. LD₅₀, LC₅₀, ED₁₀) and no observed adverse effect levels (NOAELs);
- margins of safety;
- therapeutic indices; and

- models to interpolate high dose experimental data to the low doses likely to be experienced in the environment (Klaassen, 1996).

There are often limited human exposure data and animal bio-assay data are most often used for dose response assessment. The use of these data requires extrapolations from animals to humans and interpolations from high doses to low doses (*ibid*).

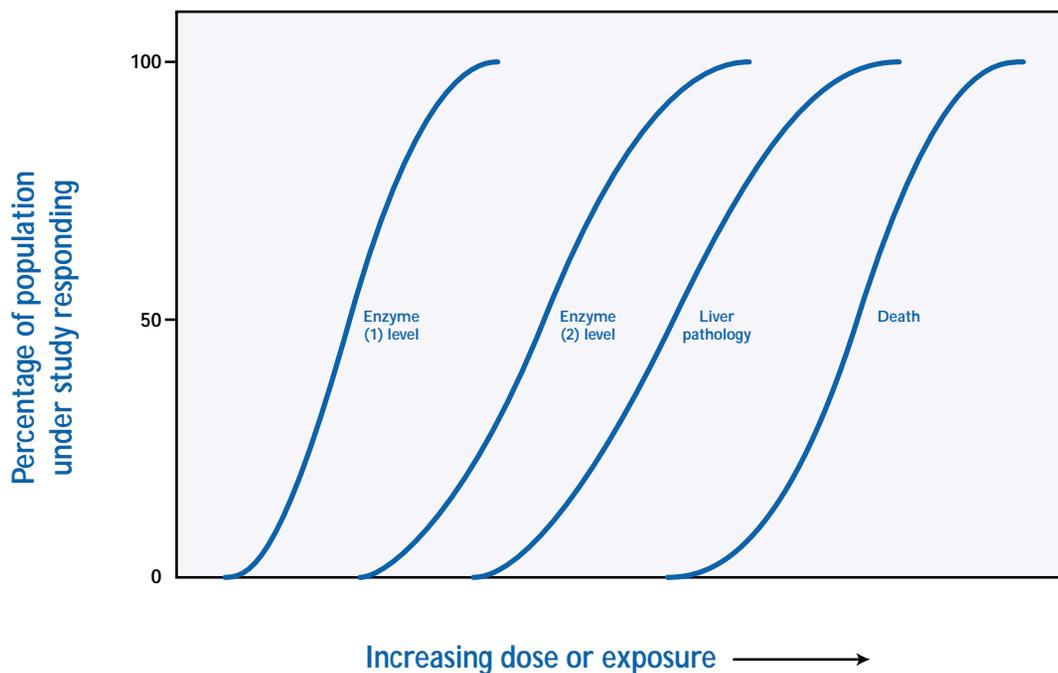
The shape of the dose response curve below the experimental range can have multiple shapes depending on the model used (Figure 4). The choice of the model should, where possible, be based on mechanistic information.

Figure 4: Hypothetical curve for an animal carcinogenicity study



(adapted from Levy and Wegman, 1988)

Figure 5: Different dose–response curves for different effects from a hypothetical substance



The dose response curves for different effects will have different shapes and will occur at different doses (See Figure 5). The shape of the dose response curve will be different again when dealing with, for example, an essential trace element such as copper where there will be at low doses a dose response curve for the effects of deficiency and at higher doses another dose response curve describing the effects of excess.

6.2 Methodologies

All methodologies make the distinction between neoplastic and non-neoplastic end-points in risk assessment. The impetus for this distinction was the concept of a lack of threshold in the dose–response for carcinogens based on the initial premise that all carcinogens are mutagens (Ames *et al.*, 1973). One mutation or one DNA damage event was considered sufficient to initiate the process that leads to the development of cancer.

In contrast, the dose–response was assumed to have a threshold for non-cancer effects, the assumption being that, for non-cancer effects, there is a dose below which the risk of adverse effects will be nil; in effect, that there is a ‘safe’ dose.

In recent times, as it has become evident that not all carcinogens have genotoxicity as their prime mode of action (Ashby and Tennant, 1991), the dose–response curve has been assumed to be non-threshold for genotoxic carcinogens and threshold for non-genotoxic carcinogens (Vermeire and van der Heijden, 1990; Health Council of The Netherlands, 1994; Moolenaar, 1994a). Accordingly, non-threshold and threshold models have been applied to genotoxic and non-genotoxic carcinogens, respectively, in some countries such as Canada and some European countries (Whysner and Williams, 1992; Health Council of The Netherlands, 1994; Moolenaar, 1994a, 1994b,

New Zealand Ministry of Health, 1995) and in the WHO Drinking Water Guidelines (WHO, 1993). More recently, however, the WHO considered that these approaches are not suitable to the development of generic guidance values in Environmental Health Criteria documents because they ‘...require socio-political judgements of acceptable health risks.’ (WHO, 1994).

In these examples, the distinction between a genotoxic carcinogen and a non-genotoxic carcinogen is a science policy decision for regulatory purposes and does not necessarily reflect the mechanism of carcinogenesis. It does not mean that a non-genotoxic carcinogen does not affect the genetic material of the cell under some circumstances, nor that a genotoxic effect is the only event required for the development of cancer by a genotoxic carcinogen.

With advances in biological knowledge, mechanistic data, pharmacokinetic data and other relevant data are increasingly being taken into account in classifying and assessing the risks of carcinogens. The US EPA (1996) is in the process of revising its guidelines for cancer risk assessment and, whilst relying almost exclusively on the non-threshold, low dose extrapolation for cancer risk assessment as in the past, also seems to be accepting an approach which considers mode of action and multiple dose–response relationships.

6.3 Threshold Approaches

A threshold is considered to occur because of biological mechanisms such as the ability to metabolise or excrete a toxin or to repair damage up to a certain dose.

The approach with these models is to derive exposure limits such as an ADI, a Provisional Tolerable Weekly Intake (PTWI), Tolerable Daily Intake (TDI) or R_fD (Barnes and Dourson, 1988; WHO, 1993; WHO, 1994; Dourson *et al*, 1996). This approach makes no attempt to calculate a level of risk at low exposures. Rather, it derives a dose which is apparently without effect in a human population or suitable animal model, and then applies a factor to derive an exposure which

has a high likelihood that no effect will occur in the general human population.

These exposure limits are derived by first determining the No Observed Adverse Effect Level (NOAEL) or, if the NOAEL cannot be determined, the Lowest Observed Adverse Effect Level (LOAEL) and dividing the value by factors to account for:

- interspecies differences (extrapolating from animals to humans);
- intraspecies differences (differing sensitivities between individuals);
- the severity of the adverse effect; and
- the quantity and quality of the scientific data.

Traditionally, safety factors for intraspecies and interspecies differences have each been assigned values of ten, and the other two have been assigned values between 1 and 10. An additional factor of ten is sometimes used if the NOAEL was not established in the study. The individual factors are then multiplied to determine an overall safety factor by which the NOAEL is divided to give the ADI, PTWI, TDI or R_fD.

Historically, the most common overall factor used by a number of regulatory bodies is 100, if a large toxicological database has been assessed, although the overall factor can range from 10 to 10 000. From the data available on humans and experimental animals, it appears that interspecies and intraspecies differences are in general less than 10, hence the often-used overall safety factor of 100 for these two factors is conservative and adequately protective of public health (Johannsen, 1990; Renwick and Walker, 1993).

The decision on the magnitude of factors to use is predominantly based on expert or informed judgement. Whilst this approach to selecting the number and magnitude of the safety factors appears to be arbitrary, current knowledge of the biological processes which cause inter- and intraspecies variation (e.g. metabolic and other pharmacokinetic rate differences) support the choice of safety factors.

6.4 Non-Threshold Approaches

These approaches do not recognise the possibility of a threshold effect and are appropriate for radiation and for some genotoxic carcinogens. It is, as a science policy decision, applied to all carcinogens by the US EPA.

Non-threshold models assume linearity between the lowest experimentally derived dose and the zero dose (the origin). This implies that there is a calculable probability of an adverse effect (risk) no matter how small the dose. This does not mean that there is no dose that could be considered safe unless safety must be equated with zero risk (Hrudey and Krewski, 1995).

Numerical estimates of risk probabilities are generated by fitting one or more mathematical models to the data in the experimental dose range and extrapolating to the low environmental exposure doses. For example, low-dose extrapolation using a linear model is a default approach for cancer risk assessment in the USA (US EPA, 1986; 1996) and is one approach which has been used by the WHO for genotoxic carcinogens in deriving drinking water guidelines (WHO, 1993).

The outcomes are estimates of either:

- i) the dose at a predetermined acceptable risk level (note that this requires some judgement on what constitutes an acceptable level of risk); or
- ii) the estimated risk level at any particular dose.

6.5 Threshold vs Non-Threshold Approaches

This area of scientific debate largely centres on the management of carcinogens.

The important conceptual distinction between non-threshold methods and those which derive an acceptable exposure from the NOAEL using a safety factor is that the safety factor approach makes no attempt to determine a finite level of risk at low exposures whereas the linear methods make an estimate of the risk at low exposures.

The NOAEL is assumed to be the threshold dose for the effect. Both approaches have advantages and disadvantages.

The advantages of the threshold approach are that the NOAEL is relatively easy to determine, and the process is simple to use, easy to understand and allows the use of expert judgement. In the few cases where epidemiological data have become available, the ADIs derived by this method have been validated (Lu and Sielken Jr, 1991). Additionally, the approach has been applied seemingly in a consistent fashion by the WHO in the last three decades in deriving ADIs for pesticides (Lu, 1995). The safety factor approach remained essentially unchanged until 1994 (WHO, 1994), although a number of articles were published suggesting modifications or improvements (e.g. Zbinden, 1979; Crump, 1984; Johannsen, 1990; Lewis *et al*, 1990; Lu and Sielken Jr, 1991; Calabrese and Gilbert, 1993; Calabrese and Baldwin, 1994).

Because it provides numerical estimates of risk at all doses, the non-threshold approach, in principle, has the potential advantages (if the estimates are correct) of allowing: computation of comparative risks in the sub-experimental range, which may be a useful tool in risk management and communication; potency comparisons between chemical agents at a particular risk level; and estimates of the increased risks if a particular dose is exceeded. It has been argued (McMichael, 1991) that risk estimates by this approach approximate those seen in humans in some cases and where there are disparities they are overestimates of the risks.

Both the threshold and non-threshold methods, however, are likely to be unduly influenced by the selection of doses. The choice of the NOAEL is limited to one of the doses included in the experimental design. The biological no effect dose may occur at this dose or at a dose not included in the study. The closeness with which the selected NOAEL truly reflects the actual no effect dose has an obvious impact on the degree of protectiveness in the derived ADI, PTWI or R_y/D. Furthermore, the NOAEL is influenced by the biological effects monitored, the number of

animals in the test groups, the spontaneous incidence of the adverse effect, and the criteria used to determine when the incidence in a test group exceeds that in the controls (Renwick and Walker, 1993).

Additional limitations of the threshold approach include: the NOAEL is often perceived as a biological threshold, whereas it is a threshold limited by the experimental protocol; risk is expressed as a fraction of the guidance dose (e.g. ADI); it makes limited use of the dose–response slope; the choice of safety factors has been arbitrary to some extent and the process does not generate a range of estimates of risk, but rather a single estimate of a dose below which no adverse effects are likely to be produced.

Dose selection in non-threshold models has been discussed by Lovell and Thomas (1996) who suggest that the estimate of q_1^* (the 95 per cent upper confidence limit of the slope estimate used for the linear multi-stage model) is so dependent on the doses selected that it is almost independent of, or at least insensitive to, the actual tumour incidences in the dose groups. Specifically, the highest dose in an animal bioassay has overwhelming influence on the estimate of q_1^* , thus leading to the overestimation of risk at very low doses, with the extent of overestimation increasing as the environmental exposure becomes lower. Typically, the highest dose in a carcinogenicity bioassay is the maximum tolerated dose (MTD), a dose that causes no more than a ten percent decrease in body weight and no other overt toxicity. The MTD is very much greater than doses expected from non-occupational environmental exposures. Therefore, the dose which is the least relevant to environmental risk assessment has the greatest influence on low dose risk estimates.

Non-threshold models currently in use are inflexible and generally do not take account of the complexities of the events between exposure to an agent and the induction of a neoplasm. Risks estimated at doses below the range of experimental data can vary considerably depending on the model used, even though the various mathematical models used generally fit

the experimental data equally well (Crump, 1985; Paustenbach, 1995). The numerical expression of the estimated level of risk falsely gives the impression that it represents an exact measure of actual risk. This numerical expression provides little or no information on the uncertainties related to the estimated level of risk, nor does it allow comparison with values for non-cancer health effects.

Low-dose linearity assumes a positive slope of the dose–response curve at zero dose and implies that a single, irreversible genetic event at the initiation stage of carcinogenesis leading to transformation of a cell, is sufficient by itself to lead to the development of cancer. The major difficulty in this debate is the impossibility of testing experimentally the shape of the dose–response curve at extremely low doses (Purchase and Auton, 1995).

A transformed cell which has acquired the potential to develop into a tumour, will probably realise that potential only rarely (US EPA, 1996), most likely because of the natural large scale repair of DNA damage and other defence mechanisms of the body (DOH, 1991; Abelson, 1994). Furthermore, whilst it is generally accepted that mutagens and mutations play a role in the development of cancer, carcinogenesis is more than mutagenesis, with a number of non-mutagenic as well as mutagenic events taking place during the process (Bishop, 1991). The shape of the dose–response curve at any one of these steps, not just the mutagenic events, can influence the shape of the dose–response curve for the carcinogenic response. Factors, such as genetic make-up, lifestyle and other environmental factors, may also have a modifying influence on the processes of carcinogenesis.

6.6 Mechanistically Derived Models

These use models, which describe biological mechanisms by mathematical equations. They assume that the toxic effect results from the random occurrence of one or more biological events. These are known as stochastic events (Klaassen, 1996).

Mechanistically-derived models have been particularly used for cancer modelling and especially based on radiation exposures. The simplest form is a ‘one hit’ linear model in which only one ‘hit’ or critical cellular interaction results in the alteration of a cell. This model would propose that a single molecule of a genotoxic carcinogen would have a ‘minute but finite chance of causing a mutational event’ (Klaassen, 1996). From these models more complex models based on multihits or multistage events have been derived. Although conceptually based on biological mechanisms, most of these models do not rely on independently validated parameters describing the mechanisms but rely on fitting curves to empirically observed data.

More recently these models have been adapted to take into account information based on knowledge of the relevant physiology and toxicokinetics (Physiologically-based toxicokinetics (or pharmacokinetics) modelling—PBTK). These models take into account the

effective dose at the target organ. A further development has been to make generalised mechanistic models take into account specific biological processes. An example of these biologically based dose response models is the Moolgavkar-Venson-Knudson model that uses a two-stage model for carcinogenesis (Klaassen, 1996).

6.7 Benchmark Dose Approach

The benchmark dose (BMD) approach has been used in dealing with both cancer and non-cancer end points. It is described in EHC170 and a modified version for use with carcinogenic soil contaminants is described in NHMRC (1999). The benchmark dose corresponds to a predetermined increase (usually 5 per cent) of a defined effect in a test population. Mathematically it is the statistical lower confidence limit on the dose that corresponds to that predetermined increase although some agencies are using a best estimate rather than a lower confidence limit (IEH, 1999b).

Table 11: Models used in risk extrapolation

Statistical or distribution models

- Log-probit
- Logit
- Weibull

Mechanistic models

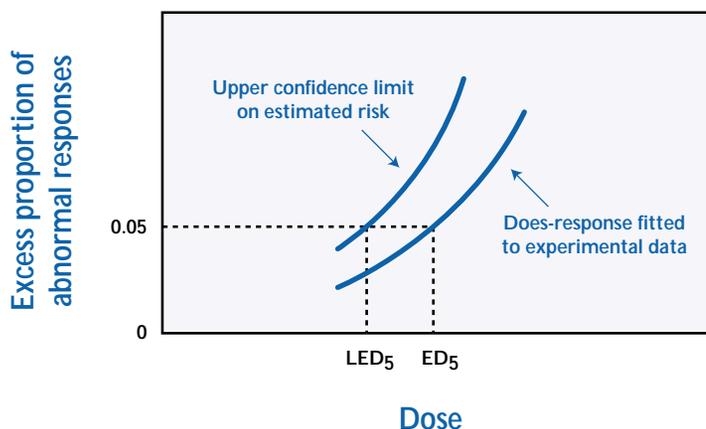
- One-hit
- Multihit
- Multistage
- Linearised multistage
- Stochastic two-stage model (Moolgavkar-Venson-Knudson)

Model enhancement

- Time to tumour response
- Physiologically based toxicokinetic models
- Biologically based dose–response models

(from Klaassen, 1996, p. 82)

Figure 6: Graphical illustration of the benchmark dose



(adapted from WHO, 1994)

In this example, $LED_5 = BD$, and LED_5 is lower confidence limit of the effective dose causing a 5 per cent increase in a defined effect.

For developmental toxicity the BMD_5 values have been similar to statistically-derived NOAELs for a wide variety of developmental toxicity endpoints (Klaassen, 1996). BMD approaches are also being developed and tested in regard to acute inhalation toxicity (Fowle *et al*, 1999), to the relationship between the BMD and the MTD (Gaylor and Gold, 1998), and to addressing statistical procedures available for calculating BMDs and their confidence limits for non-cancer endpoints (Gaylor *et al*, 1998).

Particular advantages of the BMD approach include:

- taking into account information from the entire dose response curve rather than focussing on a single test dose such as is done with the NOAEL approach;
- the use of responses within or near the experimental range versus relying on extrapolations to doses considerably below the experimental range;

- the use of a consistent benchmark response level that cross a range of studies and endpoints;
- it is less influenced than NOAEL approaches by the arbitrary selection of doses (Crump, 1984);
- it is able to be rigorously described; and
- it uses all available relevant information.

Its disadvantages are that it may not be possible to define the shape of the dose response curve because of limited dose groups or the number of animals per group and it also requires greater statistical expertise than the NOAEL type approach (IEH, 1999b)

Use of a benchmark dose with 5 per cent extra risk provides a more data sensitive and less model sensitive endpoint than using 1 per cent extra risk. (Klaassen, 1996; NHMRC, 1999)

When the benchmark response is within or near the experimental range of data the corresponding values of the benchmark doses are not greatly sensitive to the choice of the model used but the best scientific choice of a model would be a biologically based mechanistic model.

6.8 Inter- and Intra-Species Considerations

The following material is from WHO (1999b, p. 20) with slight adaptation.

The strains and species of laboratory animals exposed in toxicity studies have been selected to show minimum inter-individual variability. In contrast to laboratory animals, humans represent a very heterogeneous population with both genetic and acquired diversity.

Therefore, two principal areas are considered when interpreting dose–response data acquired in animal species in relation to human risk:

- a) Inter-species consideration: comparison of the data for animals with a representative healthy human. Species differences result from metabolic, functional and structural variations; and
- b) Intra-species or inter individual consideration: comparison of the representative healthy human with the range of variability present within the human population in relation to the relevant parameter(s).

For each of these areas, there are two aspects to be considered in assessing risk, i.e. toxicokinetics (the delivery of the compound to the site of action) and toxicodynamics (the inherent sensitivity of the site of action to the chemical). Any approach that allows for the incorporation of adequate data on toxicokinetic or toxicodynamic differences between test animal and humans, or between different humans, will increase the scientific validity of risk assessment.

Sources of inter-species and inter-individual variations in toxicokinetics include: differences in anatomy (e.g. gastrointestinal structure and function); physiological function (e.g. cardiac output, renal and hepatic blood, glomerular filtration rate and gastric pH); and biochemical differences in, for example, enzymes involved in xenobiotic metabolism. Sources of inter-species and inter-individual differences in toxicodynamics (or inherent sensitivity) also include anatomical considerations. For example, the effect may occur

in an organ of questionable relevance to humans, such as the rodent forestomach. Physiological differences, such as the hormonal control of the target organ, and biochemical differences, e.g. species differences in key biochemical components such as $\alpha_2\mu$ -microglobulin and its role in rat kidney cancer, may also be relevant (Flamm and Lehman McKeeman, 1991).

In some cases, it may be possible to conclude that effects detected in animals are unlikely to be relevant to humans. In other cases, there may be data to indicate that humans are likely to be more or less sensitive than animal species; this information is important for consideration in the selection of critical effects.

If compound-specific toxicokinetic data are introduced into risk assessment, then it is essential that these are related to the species, protocol and active chemical entity (e.g. parent compound or metabolite) involved in the toxicity that is the basis for the hazard identification (Monro, 1990, 1993; Renwick, 1993).

6.8.1 Species differences

Metabolism and structural/functional variations are both important determinants of species differences. Common areas of metabolic variation between species are digestive tract enzymes, levels of circulating enzymes, liver enzymes and detoxification processes.

In extrapolating between species, three aspects need to be considered:

1. differences in body size, which requires dose normalisation or scaling (often done by expressing the dose per kg body weight);
2. differences in toxicokinetics, particularly bioactivation and/or detoxification processes; and
3. the nature and severity of the target for toxicity.

Inter-species normalisation (or scaling) is generally based on physical characteristics (e.g. body weight, body surface area), although occasionally it is based on caloric demand or, where there are data in four species, multiple species regression.

When clearance of the parent substance is limited by enzyme activity rather than blood flow or when metabolites are the toxic agents, more sophisticated physiologically-based pharmacokinetic models are more appropriate, provided that adequate data are available. Currently, such data are available for only a small number of substances.

6.8.2 Human variability

Although data from animal studies using fairly homogeneous populations may provide limited information on inter-individual variability within the test species, the greater potential variability in heterogeneous human populations must be addressed in risk assessment. Sources of inter-individual variability in human populations include, for example, variations in genetic composition, nutrition, disease state and lifestyle.

6.9 Mixtures

Currently there is no agreed Australian approach to assessing mixtures of agents. Where data (including mechanistic data) are available on the interaction of agents this should be taken into account in the risk assessment.

Environmental exposures can involve more than one type of agent and may require a different mode of assessment than for single agent exposures (See Section 3.5). For such complex exposure scenarios, risk assessment considerations are most advanced for chemical mixtures.

Humans continue to be consistently exposed to a complex, ever-changing mixture of environmental chemicals in the air they breathe, the water they drink, the foods and beverages they consume, the surfaces they touch and the products they use (Sexton *et al*, 1995). Moreover, most current established exposure standards are for single compounds only (Lang, 1995). An increased understanding of chemical mixtures is important especially as exposure from multiple sources increases.

The Agency of Toxic Substances and Disease Registry (ATSDR) in the US uses one approach that includes performing a critical synthesis of relevant data and then identifying generalisable

rules that can be used in site-specific assessments of health risk following exposure to mixtures. This approach allows research to: identify what chemical mixtures may affect public health; evaluate the potential for exposure of human populations to chemical mixtures; study the pharmacokinetic behaviour of chemical mixtures; identify various end points that would be effected; study the mechanism of action, progression and repair; and identify (both generic and specific) that would allow the determination of the health of the organism and develop qualitative and quantitative health assessment methods so as to assess multiple health effects (Hansen *et al*, 1998).

Where chemicals share structural similarities such as Dioxins, PCBs and Polycyclic Aromatic Hydrocarbons the use of Toxic Equivalency Factors has been proposed. Different substances are given toxicity 'scores' that are fractions of the toxicity of another in the chemical group for which there is adequate toxicity data. Given a mixture of the substances, a cumulative toxicity score can be determined. The IPCS has published TEFs for several dioxins and these are shown in Table 12.

Table 12: Toxic equivalency factors (TEFs) for human and mammalian risk assessment

Congener (Dioxins)	WHO TEF
2,3,7,8 – TetraCDD	1
1,2,3,7,8 – PentaCDD	1
1,2,3,4,7,8 – HexaCDD	0.1
1,2,3,6,7,8 – HexaCDD	0.1
1,2,3,7,8,9 – HexaCDD	0.1
1,2,3,4,6,7,8 HeptaCDD	0.01
OctaCDD	0.0001

CDD: Chlorinated dibenzodioxin

World Health Organization TEFs derived from expert meeting held in Stockholm on 15–18 June 1997. Cited in Van den Berg, *et al* (1998).

Biological methods such as bioassays are being appraised for their application to the assessment of the toxicity of mixtures. Rodents or other mammals may be administered extracts as toxicity values such as LD₅₀s can be determined. These methods are expensive and time consuming which usually precludes their use in risk assessment. Similar techniques using aquatic species such as *Daphnia* are less expensive and time consuming but are disadvantaged by the greater toxicokinetic and toxicodynamic differences between the species used and humans (Pollak, 1996). There are *in vitro* tests such as the Microtox test and the Submitochondrial Particle Test but these require validation for use in risk assessment.

Useful information for exposures to mixtures of hazards may be available from epidemiological studies of closely similar mixtures.

Sexton and colleagues (1995) propose nine 'needs' crucial to mixture-related research and which are summarised as follows:

1. A need for a balanced research approach between whole mixture analysis ('top-down' approach) in which research begins with the entire mixture and attempts to characterise the mixture's toxicity by studying it in fractions according to toxicity or by its entirety and component analysis or ('bottom-up' approach) in which research begins with individual components and attempts to predict the toxicity of the whole mixture by developing an understanding of the interactions among the individual components;
2. A need for mechanistically- and physiologically-based predictive models to improve the ability to extrapolate realistically (e.g. from animals to humans) and ensure that studies simulate actual conditions;
3. A need for well-designed toxicological studies that help to explain, for example, how often chemical interactions are dependent on exposure conditions;
4. A need to determine boundaries for mixture-related outcomes such as quantifying the results of mixture-related research to determine when, why and how often mixtures deviate from additivity;
5. A need to identify and focus on high priority mixtures so as to protect public health through criteria such as expected exposure conditions, the number and types of people likely to be affected or seriousness of health outcomes;
6. A need to develop better understanding of exposure-related variables (e.g. routes, duration, frequency). The more closely toxicological studies mimic real-life, the more relevant the results would be for screening, protecting and predicting due to the complicated nature of human exposures;
7. A need for new and better methods that take advantage of advances in information technology to ensure greater precision and certainty;
8. A need to identify, quantify and express uncertainty in mixture-related risk assessment so as to develop approaches and methods that will allow for quantitative estimation of scientific uncertainty associated with scientific policy decisions related to specific mixtures; and
9. A need for collective and comprehensive research strategies by researchers and regulators.

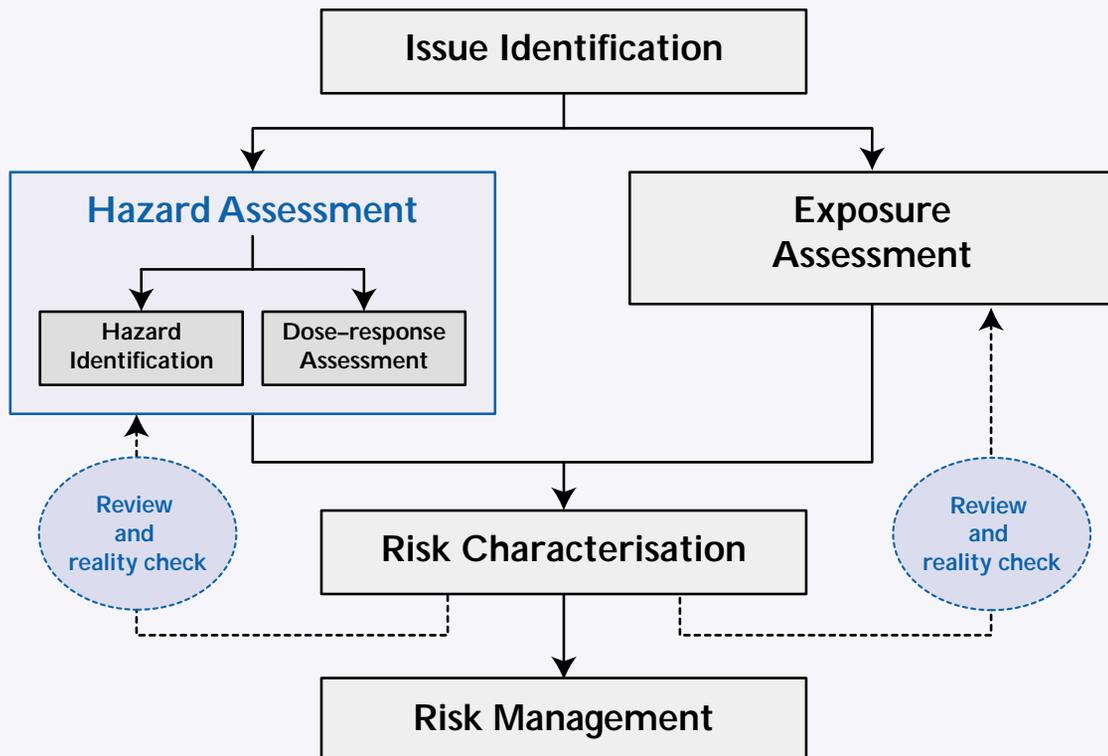
Potential health effects caused by concurrent exposures to multiple chemicals require consideration in a risk assessment. However this process is not straightforward and further work is being conducted to address the issues involved.

6.10 Hormesis

It is important to be mindful of the phenomenon of hormesis, i.e. demonstrated beneficial effects of an agent at low (but not homeopathic) doses but with toxicity occurring at higher doses. Hormesis

is known for several chemicals and generally requires very detailed dose–response characterisation for its detection. Presently there is no clear guidance on how to incorporate such information into health risk assessment, but dealing with exposures to an agent eliciting possible health benefits and health risks will require especial cooperation between risk managers and assessors (see Calabrese, 1996; Calabrese and Baldwin, 1998; Belle, 1998).

A separate but related issue is the concept of the Acceptable Ranges of Oral Intakes for Essential Trace Elements where there is a need to ensure that TIs do not fall below the minimum requirements. (WHO (1996) regards iron, zinc, copper, chromium, iodine, cobalt, manganese, molybdenum and selenium as unequivocally essential for human health.)



Hazard Assessment—Part 4:

Hazard Assessment Reports

7.1 Introduction

The overall toxicity assessment report should consider:

- the nature of adverse effects related to the exposure;
- the dose–response relationship for various effects;
- the weight of evidence for effects such as carcinogenicity.

This Section covers:

- A checklist for the hazard assessment report (Section 7.1)
- Sources of toxicological data and their likely acceptability ranking (Section 7.2)

7.1.1 Checklist for toxicological appraisals

The following checklist is adapted with slight modification from US EPA (1995) and should be the basis of toxicological appraisals. A summarised version can be used if Tolerable Intake data from WHO or NHMRC are used.

7.1.2 Hazard identification

1. What is the key toxicological study (or studies) that provides the basis for health concerns?
 - How good is the key study?
 - Are the data from laboratory or field studies? Are the data for single species or multiple species?
 - If the hazard is carcinogenic, comment on issues such as: observation of single or multiple tumour sites; occurrence of benign or malignant tumours; certain tumour types not linked to carcinogenicity; use of the maximum tolerated dose.
 - If the hazard is other than carcinogenic, what endpoints were observed, and what is the basis for the critical effect?

- Describe other studies that support this finding.
 - Discuss any valid studies which conflict with this finding. See also Section 4.4 for further information on assessing data.
 - As many relevant studies as possible should be collated and rigorously assessed as to their strengths and weaknesses to determine the key studies. This is particularly important where quantitative risk estimates will be undertaken or where there are apparently contradictory studies; in the latter case, the studies that are considered to be adequate in their design and interpretation will need to be appraised to determine the overall weight-of-evidence. See Section 4.7 for further information on weight of evidence.
2. Besides the health effect observed in the key study, are there other health endpoints of concern?
 - What are the significant data gaps?
 3. Discuss available epidemiological or clinical data. For epidemiological studies:
 - What types of studies were used, i.e. ecologic, case-control, cohort?
 - Describe the degree to which exposures were adequately described.
 - Describe the degree to which confounding factors were adequately accounted for.
 - Describe the degree to which other causal factors were excluded.

For further information refer to Section 5.4 ‘Assessing the relationship between a possible cause and an outcome’.
 4. How much is known about the biological mechanism by which the agent produces adverse effects?
 - Discuss relevant studies on mechanisms of action which may include metabolism studies.

- Does this information aid in the interpretation of the toxicity data?
 - What are the implications for potential health effects?
5. Comment on any negative or equivocal findings in animals or humans, and whether these data were considered in the hazard identification.
 6. Summarise the hazard identification and discuss the significance of each of the following.
 - confidence in conclusions;
 - alternative conclusions that are also supported by the data;
 - significant data gaps; and
 - major assumptions.

7.1.3 Characterisation of dose–response

1. What data were used to develop the dose–response curve? Would the result have been significantly different if based on a different data set?

If animal data were used:

- What species were used? The most sensitive, average of all species, or other?
- Were any studies excluded? Why?

If epidemiological data were used:

- Which studies were used? Only positive studies, all–studies, or some other combination?
- Were any studies excluded? Why?
- Was a meta-analysis performed to combine the epidemiological studies? What approach was used? Were studies excluded? Why?

2. What model was used to develop the dose–response curve? What rationale supports this choice? Is chemical-specific information available to support this approach?

For non-carcinogenic hazards:

- How was the Tolerable Intake (or the acceptable range) estimated?
- What assumptions or uncertainty factors were used?
- What is the confidence in the estimates?

For carcinogenic hazards:

- What dose–response model was used? What is the basis for the selection of the particular dose–response model used? Are there other models that could have been used with equal plausibility and scientific validity?
- What is the basis for selection of the model used in this instance?

3. Discuss the route and level of exposure observed in the toxicology or epidemiology studies, as compared to the expected human exposures in the situation under appraisal.

- Are the available data from the same route of exposure as the expected human exposures? If not, are pharmacokinetic data available to extrapolate across route of exposure?
- What is the degree of extrapolation from the observed data in the toxicological or epidemiological studies to the expected human exposures in the situation under appraisal. (one to two orders of magnitude? multiple orders of magnitude)? What is the impact of such an extrapolation?

7.2 Sources of Toxicological and Tolerable Intake Data

The following sources are grouped into ‘levels’ which are given in order of preference. In general, published Australian ADIs should be used but other data may be used with appropriate justification. Different agencies are likely to have used differing risk assessment and standards-setting methodologies and these differences should be appraised by the risk assessor. All documents, particularly those in the second and third categories require rigorous appraisal for relevance, validity and accuracy.

7.2.1 Level 1 sources

1. National Health and Medical Research Council documents and documents from other joint Commonwealth, State and Territory health organisations. These may be a source of Australian guidance values.
2. ADI List from the Therapeutic Goods Administration (regularly updated at www.health.gov.au/tga/docs/html/adi.htm).
3. World Health Organization (WHO) documents. Australia is a party to the WHO process and has incorporated their material in a variety of environmental health criteria. A range of documents include those from the WHO/ILO/UNEP International Programme on Chemical Safety (IPCS) which produces Environmental Health Criteria monographs, and Concise International Chemical Assessment documents (CICADs). Documents detailing international Acceptable Daily Intakes (ADIs), Tolerable Daily Intakes (TDI) or Tolerable Weekly Intakes (TWI) may be found in evaluations by the WHO/FAO Joint Meeting on Pesticide Residues (JMPR) and by the Joint FAO/WHO Expert Committee on Food Additives (JECFA).
4. enHealth Council documents.
5. National Environmental Health Forum documents distributed by the Commonwealth Department of Health and Ageing.
6. International Agency for Research on Cancer (IARC) monographs.
7. WHO/FAO Joint Meeting on Pesticide Residues (JMPR) Monographs.
8. NICNAS Priority Existing Chemical (PEC) reports.
9. US Agency for Toxic Substances and Disease Registry (ATSDR) documents for general toxicological reviews and Reference Doses.
10. National Toxicology Program (NTP) carcinogenicity appraisals which report in detail the results of carcinogenicity tests on a wide range of chemicals.

11. OECD Standard Information Data Sets (SIDS) and SIDS Initial Assessment Reports (SIAR).

12. EPA Reference Doses.

7.2.2 Level 2 sources

Peer-reviewed journals

These may provide opinions that do not meet general scientific agreement. With justification, and acceptance by the local jurisdiction, they may be suitable for use if no Guidance Values are available.

Industry publications

With justification, and acceptance by the local jurisdiction, they may be suitable for use:

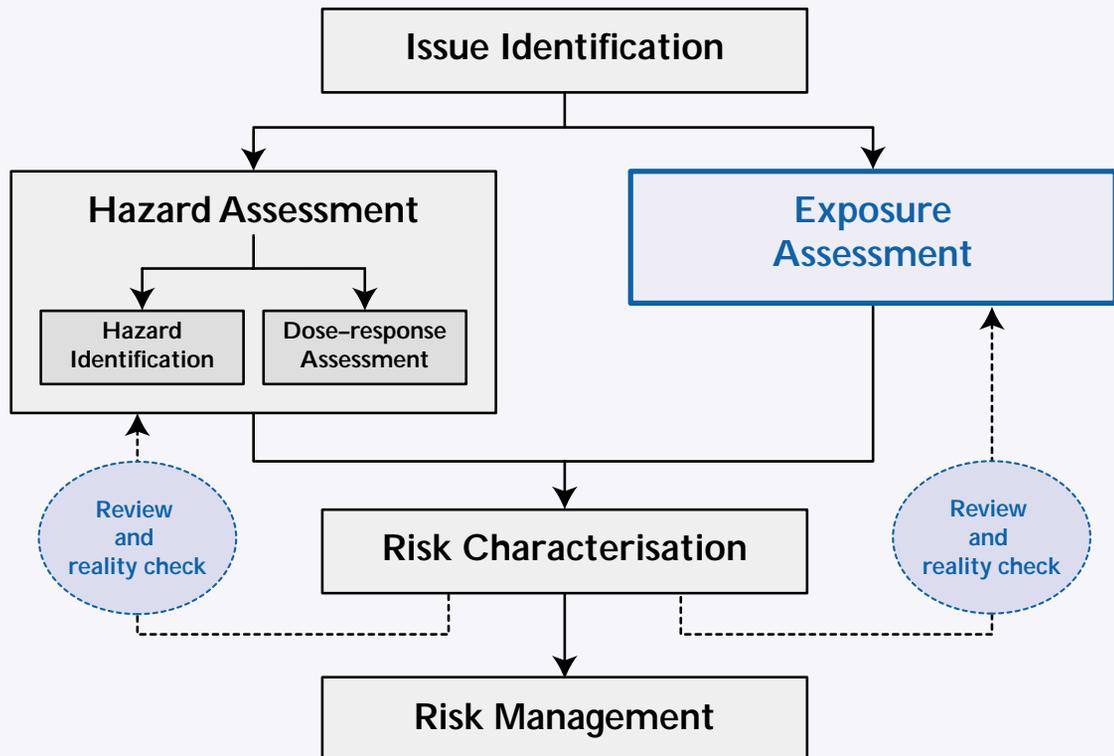
1. European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC): Monographs, JACC Reports and Technical Reports
2. Chemical Industry Institute of Toxicology (CIIT) reports
3. Unpublished industry reports submitted for regulatory purposes. These may have restricted availability but information may be available in evaluation reports from regulatory agencies that have reviewed individual reports.

Occupational health and safety sources

These may be a useful source for toxicological data and reviews but occupational exposure criteria must not be used in a general public health context without appropriate adjustment for the different durations of exposure, the inclusion of susceptible sub-population in the general community (e.g. children) and the methodological differences in the setting of criteria.

7.2.3 Level 3 sources

These are sources not covered in Levels 1 and 2. The use of this information requires justification that no other sources are available and an appraisal of the methodology detailing the level of conservatism and range of uncertainties inherent in the approach. With justification, and acceptance by the local jurisdiction, they may be suitable for use if no Guidance Values are available.



Exposure Assessment

8.1 Introduction

Exposure assessment involves the determination of the magnitude, frequency, extent, character and duration of exposures in the past, currently, and in the future. There is also the identification of exposed populations and potential exposure pathways. Environmental monitoring and predictive models can be used to determine the levels of exposure at particular points on the exposure pathways. The contaminant intakes from the various pathways under a range of scenarios, including worst case situations, can then be estimated (US EPA, 1989).

An initial requirement for exposure assessment is an understanding of the presence (or absence) of an agent and its concentrations and distribution.

Accurate and useful exposure assessment requires a detailed understanding both of the strengths and weaknesses of the exposure assessment techniques, and the specific exposure factors used in the assessment. Considerable effort needs to be made to accurately characterise the population to which the exposure assessment is relevant.

'Direct measurement of the exposures of the (potentially) affected population provides the best exposure data but this is not always available or practicable and default exposure factor data are often required.' (Langley, 1993, p. 90)

An understanding of transport and fate models for the agent is also important. Transport and fate will be affected by:

- environmental medium (e.g. air, surface, water, soil, ground water or biota);
- geographic scale (e.g. global, national, regional or local);
- pollutant source characteristics (e.g. continuous or instantaneous releases from industrial, residential and commercial point or area sources);
- the nature of the risk agent (e.g. whether it is a specific agent or group of agents);
- the receptor population (e.g. humans, animals, plants, microorganisms, and habitats, as well as specific sub-populations exposed to

high levels of the agent or who are particularly sensitive to exposure);

- exposure routes (e.g. ingestion, dermal contact or inhalation);
- environmental conditions (e.g. pH, presence of organic matter, clay content, temperature); and
- the timeframe (e.g. retrospective, current or prospective).

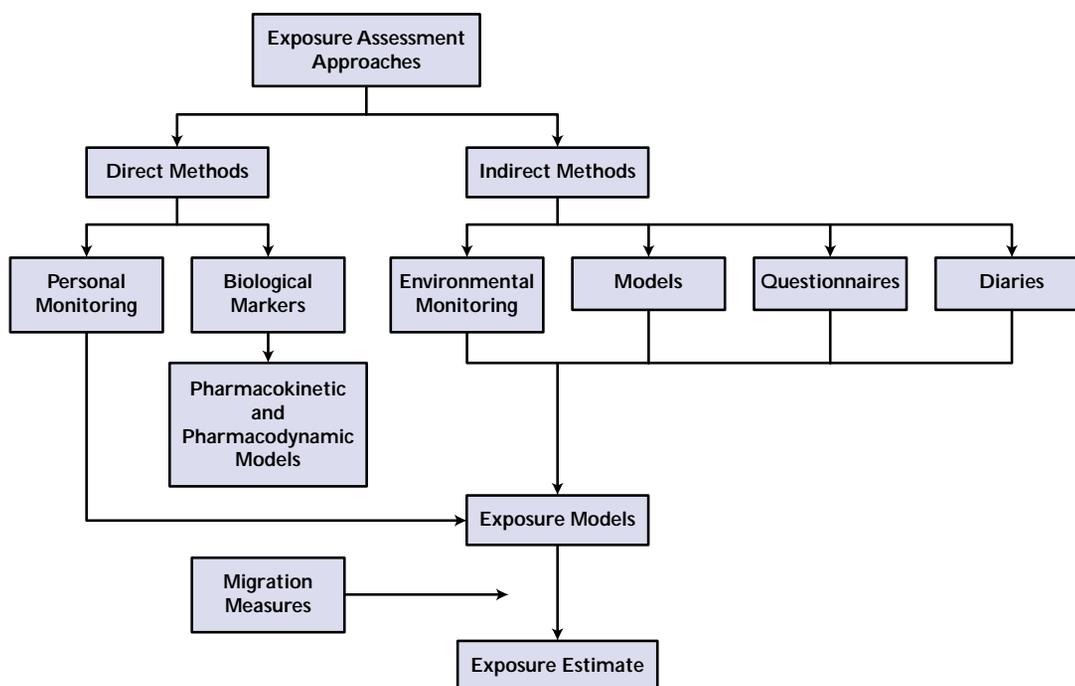
(Fiksel and Scow, 1983, cited in Covello and Merkhofer, 1993)

There are various components to estimating exposure and these are shown in Figure 7.

8.2 Issues in Exposure Assessments

1. Children usually receive a higher exposure to environmental agents per unit body weight than adults because of behavioural and physiological factors (e.g. hand-to-mouth activities for soils, higher respiration rates per unit body weight, increased gastrointestinal absorption of some substances).
2. For soil, ingestion is usually by far the most important exposure route for small children (*ibid*).
3. One exposure route will normally predominate (*ibid*).
4. In large-scale contamination (i.e. regional) more exposure pathways will be involved than in small-scale (very localised) contamination.
5. All exposure pathways must be considered for health risk assessment. As the total amount of a chemical absorbed by a persons body influences the risk to health exposure assessment must take into account all sources of exposure irrespective of whether these are from food, water, the work place, outdoor air or a combination of these and other sources (Langley, 1991; IEH, 1999a).
6. Bioaccumulation may be a significant concern for some substances with long biological half-lives e.g. cadmium, organochlorine pesticides and this factor should be considered.

Figure 7: Components of exposure assessment



(adapted from National Academy of Sciences (NAS), 1991)

8.3 Environmental Distribution

For the development of sampling plans for chemical agents and the process of exposure assessment an understanding and the movement of chemical agents between environmental compartments and the effects of environmental partitioning will be necessary.

Partitioning will reflect the fact that substances will move to the environmental compartment for which they have the most affinity (Calamari, 1993; Calamari, 1999). Transformation may occur in any environmental compartment.

Fugacity modelling (Mackay, 1991) enables an estimation of which compartment will contain most of the agent and where the highest concentrations in the 'unit of world' are. Mackay's

'unit of world' is a box 1km square and 6km deep that includes air, terrestrial and aquatic biomass, soil, water and sediment.

Especially where monitoring data are inadequate, fate models are useful for estimating chemical concentrations. These models can span a wide range of complexity in terms of spatial dimensions and temporal assumptions (i.e. steady-state versus non-steady-state). Types of fate models include:

- simple dilution models where a measured concentration in an effluent is divided by a dilution factor or the chemical release rate is divided by a dilution factor or the chemical release rate is divided by the bulk flow rate of the medium;

- equilibrium models which predict the distribution of a chemical in the environment based on partitioning ratios or fugacity (the escaping tendency of a chemical from one environmental phase to another);
- dispersion models which predict reductions in concentrations from point sources based on assumed mathematical functions or dispersion properties of the chemical; and
- transport models which predict concentration changes over distance and can represent dispersion, biochemical degradation and absorption (from WHO, 1999b, p. 42).

8.4 Environmental Persistence

The terrestrial, aquatic and atmospheric fate of agents needs to part of the exposure assessment. The agents may be relatively inert (e.g. asbestos) or subject to biodegradation and abiotic degradation. Persistent substances, or those with long half-lives in the environment or biota, will increase the opportunities for exposure over time.

The source of the data and the relevant environmental comparisons with Australian conditions needs to be taken into account. For example, Australian soils and climatic factors may result in different environmental persistence for some pesticides in Australia compared to North American or Northern European conditions.

8.5 Environmental Sampling and Analysis

Data collection entails the acquisition and analysis of information about hazards on a site that may affect human health and which will be the focus for the particular risk assessment (US EPA, 1989).

Adequate data collection is the foundation to an acceptable health risk assessment.

Sampling is often carried out to more clearly define detected or suspected contamination and, if remediation occurs, to verify that contaminated material has been removed and that any contamination remaining does not constitute a health or environmental risk.

The greatest concern, in collecting samples, is to ensure that the samples taken adequately represent potential exposures for the situation. Consequently it is essential to be fully apprised of the context of the risk assessment, the objectives of the task, the environmental conditions at the site locations and what analytes will be tested in each sample, before sampling commences (Lock, 1996).

Inappropriate sample collection procedures 'yield samples that are not representative of the population of interest; are of little use; seriously compromise the purpose of sampling; and contribute to the uncertainty of the analytical results' (Keith, 1990, p. 610).

Laboratory errors can occur and if an aberrant or an unexpected result is provided the potential for laboratory error should always be considered.

An important aspect of Environmental Sampling and Analysis is that the environment is not static and sampling results can vary over time. The interpretation of Environmental Sampling data should take this into account.

8.5.1 Data quality objectives

Data quality objectives 'provide critical definitions of the confidence that must be inherent in the conclusions drawn from the data produced by the whole project' and determine the degree of uncertainty or error that can be tolerated in the data (Keith, 1990, p. 611).

Data Quality Objectives which clearly specify the amount, nature and quality of the data to be collected should be detailed. Data Quality Objectives will be situation-specific. More detail is given in EPA QA/G 4 Guidance for the data quality objectives process. Washington: US Environment Protection Agency. EPA 600R96055.

The criteria for both accepting and rejecting data should be rigorous.

Consideration will need to be made as to whether routinely collected historical data will be as appropriate to use as data collected *de novo* for the risk assessment.

8.5.2 Sampling strategies

In sampling, the statistical considerations need to be matched to expertise in situation assessment and a knowledge of the particular situation (Lord, 1987). The sampling plan and decisions regarding the number, type and location of samples need to be developed with an understanding of the potential exposure pathways and routes (US EPA, 1989).

Sampling will be influenced by, and will influence, possible risk management decisions (Heyworth, 1991). The proposed human activities for the particular setting will critically affect the nature of the sampling program.

The reasons for sampling include (Heyworth, 1991):

1. determining the nature of contamination;
2. determining the concentration and distribution of the agent;
3. monitoring site conditions to determine if remedial actions are required;
4. designing and implementing remedial actions; and
5. determining if remedial actions have been effective.

There are often three phases of sampling:

- an initial assessment to determine if detailed investigation is necessary;
- a detailed sampling and analysis plan; and
- post-remedial validation.

For any of these phases, a sampling program with multiple stages may be required, especially for large and complex situations.

8.5.3 Sampling methodologies

Numerous techniques are available for environmental sampling.

General references are:

- Keith LH (1990). Environmental sampling: a summary. *Environmental Science and Technology*. **24**(5), 610-617;

- Keith LH (ed) (1988). *Principles of Environmental Sampling*. Washington: American Chemical Society; and
- Perkins JL (1997). Modern Industrial Hygiene. Volume 1. *Recognition and Evaluation of Chemical Agents*. New York: Van Nostran Reinhold.

Sampling is often most effectively done as a staged and iterative procedure where earlier results can focus later sampling stages.

Fugacity modelling (Section 8.3) may provide assistance in determining where elevated concentrations of an agent are likely to be found.

Some key issues are (Keith, 1990):

- When sampling water, allowance should be made for the fact that stratification can occur in bodies of water particularly in lakes deeper than 5 metres, deep rivers, and in situations where two streams merge, such as where an effluent enters a river;
- Groundwater contamination is affected by 'depth to water, recharge rate, soil composition, topography (slope), as well as other parameters such as the volatility and persistence' of the substance (Keith, 1990, p. 614). There is always a significant risk of cross contamination of aquifers when sinking bores and special precautions should be made to protect against this;
- The contamination of water samples is always a problem and this is most pronounced when very low concentrations are being sought; and
- Considerable variation in an environmental medium over time may occur and environmental sampling may need to be spread over a period of time to give an accurate representation of potential human exposures.

8.5.4 Sampling patterns

Sampling plans will depend on the medium being sampled. If there is sufficient information about a situation, random sampling may be inappropriate or inefficient and judgemental sampling may be more appropriate. Air and water over a small area are likely to be more homogeneous than soil.

Further general information on sampling plans is available from:

- Gilbert RO (1987) *Statistical Methods for Environmental Pollution Monitoring*. New York: Van Nostrand Reinhold;
- Heyworth J (1991) Sampling and Statistical Analysis for Assessing Contaminated Sites. In: El Saadi O, Langley AJ. *The Health Risk Assessment and Management of Contaminated Sites*. Adelaide South Australian Health Commission. p. 15–30;
- Keith L.H (1990). Environmental sampling: a summary. *Environmental Science and Technology*. **24**(5), 610–617; and
- Keith LH (ed) (1988) *Principles of Environmental Sampling*. Washington: American Chemical Society.

8.5.5 Sampling density

‘Statistical equations are tools to be used as aids to common sense and not as a substitute for it’ (Keith, 1990, p. 612). Statistical formulae for determining sampling density are usually based on the requirements that the results will be normally distributed (i.e. in a bell-shaped curve) and that a particular concentration is equally likely to occur at any point. Some analytical techniques require an estimate of the mean of the results and the standard deviation of the results before sampling density can be calculated. These requirements can rarely be met during the stages of initial and detailed investigations as sites are often heterogeneous with a highly skewed distribution of results.

Sampling is a screening process and false positive and false negative results will occur. From a health perspective the aims of sampling are to reduce the likelihood of a false negative that could result ultimately in significant adverse health effects, and to enable the identification and adequate remediation of contaminated sites sufficient to protect human health.

A considerable amount of expert judgement is required to determine the amount of sampling. The final amount will depend on an integrated appraisal of factors including:

1. proposed or current human activities;
2. the number of stages of sampling considered feasible;
3. the scale and distribution of potential human exposures; and
4. potential remediation and management strategies.

The sampling density requirements will vary from medium to medium.

8.5.6 Sample handling, storage and transport

Sample handling and transport should be done according to relevant regulatory documents or Australian Standards.

Some key issues are (Keith, 1990):

- contamination may arise from substances in the sampling devices and storage containers. PVC and plastics other than teflon tend to sorb organics and leach plasticisers and other chemicals used in their manufacture. Some pesticides and halogenated compounds strongly adsorb to glass (Keith, 1990);
- the loss of volatile analytes or reduced concentrations from irreversible absorption on the walls of sampling containers can be a significant problem; and
- sample preservation can be of considerable importance. If incorrectly stored, materials can have accelerated breakdown, chemicals may be lost by volatilisation, and proliferation or diminution of microbiological organisms can occur. The nature of the storage container, its seal, and the degree of refrigeration needed should always be considered and addressed.

Specific references for air, food, water, and soil are detailed in Appendices 1–4.

8.5.7 Chain of custody

The consultant’s report must provide the following chain of custody information (EPA NSW, 1997, p. 12):

1. the sampler;
2. nature of the sample;
3. collection date;
4. analyses to be performed;
5. sample preservation method;
6. departure time from site; and
7. dispatch courier(s).

AS 4482.1-1997 Appendix H provides a Chain of Custody form.

8.5.8 Analytical methodologies

Good (1993) considers an appropriate test method must be (p. 45):

- ‘accurate: it must be shown to give results which differ little from the concentration we would accept as the ‘true’ value. This is generally demonstrated by comparison with other, well respected techniques;
- precise: it gives results which show acceptably small variation from batch to batch and analyst to analyst when applied as prescribed; and
- robust: results are not unduly affected by minor variations in test conditions.’

If these three criteria have been measured, the method can be relied upon to provide an answer within a predictably narrow range around the accepted ‘true’ value for a given sample. For a method to be widely useful however, it must also be (*ibid*, p. 45):

- ‘not too complex: A procedure so complex as to be only useable by a few highly trained persons will probably be of limited practical value;
- not expensive: The costs of site assessments are already high;
- reasonably comprehensive: Methods should determine a reasonably wide range of compounds potentially present; and

- available: Even the best method is of little use if its use is restricted by copyright or other instrument, or it resides in an obscure journal unknown to potential users.’

The original analytical records (e.g. traces, chromatographs) should be retained and should be reviewed when the data are about to drive a significant action.

General reference

- Manahan SE (1993). *Fundamental of Environmental Chemistry*. Boca Raton: Lewis Publishers.
- Perkins JL (1997). Modern Industrial Hygiene. Volume 1. *Recognition and Evaluation of Chemical Agents*. New York: Van Nostran Reinhold.

Specific references

Specific references for air, food, water, and soil are detailed in Appendices 1–4.

8.5.9 Choice of analytes

The choice of analyte will be principally governed by the ‘Issues Identification’ stage for the particular situation.

8.5.10 Field instruments

Field instruments should be regarded only as a screening tool and their results require laboratory validation.

Field instruments require regular maintenance and calibration, and skilled and diligent use.

The accurate use of such instruments relies on factors including:

- the method of sampling;
- the nature of the contaminant;
- the presence of interfering gases or vapours resulting in overestimates or underestimates of environmental concentrations;
- the type and make of the instrument;

- the type of calibrant used;
- the length of time since the last calibration;
- the cleanliness of the instrument; and
- the skill and knowledge of the operator.

They may be useful for assisting in the identification of areas where sampling should be concentrated. They do not replace analysis in a laboratory.

Examples of field instruments are Photo Ionisation Detectors (PIDs) and X-ray Fluorescence (XRF). Information on time, date and method of calibration should be provided with reports.

8.5.11 Quality assurance of data used in site-specific health risk assessment

The following information is adapted from Good (1993, p. 44).

- **Quality assurance (QA)**
All of the actions, procedures, checks and decisions undertaken to ensure the representativeness and integrity of samples and accuracy and reliability of analysis results.

In the field this includes selection of appropriate sampling methods, documentation and sample storage, cleaning of tools before sampling and between samples, cleaning of containers, and maintenance of sample environment to minimise sample contamination and analyte losses.

In the laboratory, QA involves proper sample control, data transfer, instrument calibration, selection of properly trained staff and suitable equipment, reagents and analytical methods.
- **Quality control (QC)**
Those parts of QA which serve to monitor and measure the effectiveness of other QA procedures by comparison with previously decided objectives. In the field, this may include checking of sampling equipment cleanliness by keeping rinses for analysis, cross-checking of sample identities, duplicate sampling of sites and performance of 'field

blanks' and 'field spikes'. In the laboratory, QC procedures involve measurement of the quality of reagents, cleanliness of apparatus, accuracy and precision of methods and instrumentation by regular analysis of 'blanks', sample replicates, 'spiked recoveries' and standard reference materials (SRMs), with proper recording of results for these checks and immediate investigation of observed problems.

According to these definitions, 'adequate QA is achieved when the results of QC demonstrate that agreed objectives such as freedom from contamination, method accuracy and precision can be reliably achieved. An important decision then is the correct level of QC' (*ibid*, p. 47).

'As a general rule, the level of required QC is that which adequately measures the effects of all possible influences upon sample integrity, accuracy and precision, and is capable of predicting their variation with a high degree of confidence. QC is more often performed inadequately than very well' (*ibid*, p. 47).

- **Blanks**
A reagent blank (or preferably two for very low level analysis), prepared by processing reagents only in exactly the manner used for each sample. The aim of the blank determination is to establish the magnitude of that component of the analytical signal which can be ascribed to contributions from reagents, glassware, etc. The contribution established should be subtracted from the gross analytical signal for each analysis before calculation of sample analyte concentration.
- **Replicate analysis (matrix duplicate)**
Repeat analysis of at least one sample. The variation between replicate analyses should be recorded for each batch to provide an estimate of the precision of the method.
- **Recovery check or reference material analysis recovery check (matrix spike)**
Analysis of one or more replicate portions of samples from the batch, after fortifying the additional portion(s) with known quantities of

the analyte(s) of interest. Recovery check portions should be fortified at concentrations which are easily quantified but within the range of concentrations expected for real samples.

- **Reference material analysis**

Analysis of a sample similar in matrix type to the samples, with accurately known concentration of the analyte(s) of interest. Results of recovery checks and reference material analyses for each batch should be recorded so that the bias of a method may be estimated, and day-to-day method efficiency may be monitored.

- **Surrogate spikes and internal standards**

Wherever appropriate, especially for chromatographic analysis of organics, the use of surrogate spikes and internal standards is highly recommended. Inclusion into methods requires little additional effort and greatly enhances confidence in qualitative and quantitative results obtained.

- **Surrogate spikes**

Surrogate spikes are known additions, to each sample, blank and recovery/reference sample analysis, of known amounts of compounds which are similar to the analytes of interest in terms of:

- extractability;
- recovery through clean-up procedures; and
- response to chromatographic or other measurement.

but which:

- are not expected to be found in real samples;
- will not interfere with quantification of any analyte of interest; and
- may be separately and independently quantified by virtue of (e.g.) chromatographic separation or production of different mass ions in a GC/MS system.

Surrogate compounds may be alkylated or halogenated analogues or structural isomers of analytes of interest.

The purpose of surrogate spikes, which are added immediately before the sample extraction step, is to provide a check for every analysis that no gross processing errors have occurred which could have led to significant analyte losses or faulty calculation.

- **Internal standards**

Immediately prior to instrumental analysis, each sample, blank and recovery or reference material extract is fortified with a set amount of one or more compounds which:

- are not found in real samples;
- will not interfere with quantification of analytes of interest; and
- may be separately and independently quantified.

The purpose of internal standards in chromatograms is to provide extra peaks which serve to check the consistency of the analytical step (e.g. injection volumes, instrument sensitivity and retention times for chromatographic systems). Analyte concentrations may be determined by measuring the RATIO of the analyte response to that of an internal standard, with marked improvements in quantitative precision.

- **Control charts**

Nadkarni (1991) claims that the heart of a QA/QC program is a control chart. 'This is a numerical picture (a plot) of the variation of measured QC parameter (e.g. blank and recovery values). Data are plotted in the sequence in which they were obtained, and reviewed frequently in order to detect any problem with minimal delay. The use of these charts is highly recommended.'

(Good, 1993, p. 47)

8.5.12 Safety plans

The safety of people assessing a situation and nearby residents must always be considered in environmental sampling. Site safety plans should be developed where there may be risks.

A general reference, framed around contaminated sites but applicable to a wider range of situations is:

- National Environment Protection Council (1999). National Environment Protection Measure for the Assessment of Site Contamination. Guideline 9. Protection of Health and the Environment during the Assessment of Site Contamination. Adelaide: National Environment Protection Council. This is accessible at www.nepc.gov.au.

8.5.13 Assessment of summary statistic data and presentation of data

(adapted from Langley, 1993a, p. 23–28)

Vast amounts of data can be generated about a single environmental health investigation. To enable an efficient and accurate appraisal of a situation requires that the data be collated in a form that allows an understanding of the location, extent, trends, and likely ‘behaviour’ of any environmental hazards. Mapping of data is essential.

An adequate understanding of what is (and will be) occurring is almost impossible to achieve from pages of raw data especially where there are abnormal results or more than a handful of results. At its worst sample identification numbers, sampling points, technical logs, and results for each analyte will be on separate pages.

There is a constant tension between consultants who wish to maintain individuality to their reports and government agencies which seek uniform reports. A uniform approach to the location and presentation of data makes for more rapid and accurate assessments of reports.

The major problems that can occur with data sets and assessments are:

- a failure to collate data and to condense into comprehensible tables;
- providing cluttered data sets, tables and graphs;
- treating the sum of the data as somewhat greater than the sum of its parts. This is exemplified by elaborate contour maps based on a very limited number of data points;

- providing fairly definitive conclusions insufficiently underpinned by supporting data;
- considering the numbers in isolation from other data important to interpretation e.g. situation history and characteristics of the sampled medium; and
- inappropriate ‘compositing’ of data.

Summary statistics

No single summary statistic (e.g. an arithmetic mean or the median) fully characterises a situation. Instead a range of summary statistics is needed to build up a picture of potential agents and exposures.

Each summary statistic will have a contribution, but will also have certain limitations. For example, the mean is affected by each individual score and is particularly sensitive to extreme scores. However it is less sensitive to sampling variation than the median or mode i.e. it is less affected by repeated series of random samples from the one population. The median is less sensitive than the mean to extreme scores and usually more sensitive to sampling variation (but less so than the mode) (Pagano, 1986).

Given the complex nature of most data sets, a range of summary statistics needs to be presented as the mix of summary statistics will be more useful than a single summary statistic. Examples of ways of presenting summary statistics, particularly where there are multiple agents are shown in the Summary Statistics section for Contaminated Sites (Appendix 1).

As much of our sampling is judgemental rather than random, caution needs to be taken with the use of conventional statistical methods which usually assume the random collection of data and the use of normally distributed data. Much risk assessment data is log normally distributed or has skewed distributions and this will require different statistical methods for analysis.

Outlying data should be appropriately considered and not neglected.

Contouring

While graphical representations of contours can provide useful information about situations such as the distribution and 'trends' of environmental hazards, contouring often is based on extreme extrapolations from inadequate amounts of data. If the distribution of the environmental hazard is heterogeneous it is unlikely that there will be sufficient data points or sufficient associations between adjoining points for contouring to be used with any confidence in its meaning (e.g. most contaminated sites are likely to have a heterogeneous distribution of contamination). Where there is widespread or relatively homogeneous distribution of an environmental hazard contours may provide fairly useful information on a macro scale. Examples are plumes of regional contamination such as around a lead smelter or sewer outfall.

When contouring is used, there is a need to demonstrate that the model used for contouring is valid.

Mapping of data

Mapping the results is essential but poor design can cause clutter that obscures important data.

If there is 'too much' data available, this may be addressed by putting only significant results onto the map. However, this should be done cautiously as 'censoring' some of the data can obscure trends. 'Normal' results are important if elevated results were anticipated and may need to be included to provide a useful comparison to the abnormal results. Other superficially unimportant data can provide surrogate information about the environmental hazards.

A series of transparent overlays, each with a different data, can be very useful to reduce cluttering.

Geographic information systems

Geographic information systems (GIS) allow spatial relationships between populations and hazards to be examined and it can be useful for the Hazard Identification and Exposure

Assessment phases of risk assessment. Modern GIS tools allow visualisation of relationships between data in two or three dimensions, for instance, it can allow visualisation of certain symptoms or diseases in regard to their geographic location. The relationships may be between health, environment and socio-economic data at many geographic scales, starting with the individual person e.g. a person's place of residence or work. Data can be aggregated for a geographical area and patterns between geographical areas visualised.

GIS may also allow certain complex analyses to be done such as shortest path or best path analysis. Path analysis allows predictions of population behaviour in relation to geographical variations. Path analysis will allow traffic flow patterns and densities to be predicted to assess the variations in exposures to benzene across a city.

In the case of a specific hazard, path analysis may allow the estimation of exposure to given pollutants, allowing opportunities for strategic public health interventions to be undertaken. For example, estimating shopping location patterns to identify the populations most likely to have been exposed to a Legionella-contaminated cooling tower or enabling preliminary rankings of risk for a number of towers when a case of Legionella is reported. The Agency for Toxic Substances and Disease Registry (ATSDR) in the USA has used GIS to identify populations residing near hazardous waste sites.

3D representations of data

Data presented as 3D illustrations can be particularly useful in uncluttering information and providing a 'picture' of what is occurring. In contrast 3D graphs of data are often misleading compared to 2D graphs.

Some principles of graphical representation

Tufte (1983) points out that 'graphical excellence is that which gives to the viewer the greatest number of ideas in the shortest time with the least ink in the smallest space' (p. 51). He goes on to say that 'graphical excellence is the well-designed presentation of interesting

data—a matter of substance, of statistics, and of design...and consists of complex ideas communicated with clarity, precision, and efficiency’.

Tufte (1983) censures cluttered tables and other failings of graphic design such as:

- excessive zeal in the use of computer software graphics packages so that bold cross-hatching and the use of wavy lines lead to ‘optical art’ effects; and
- overdoing the use of horizontal and vertical lines in tables. Tufte quotes Tschichold (1935), ‘tables should not be set to look like nets with every number enclosed’.

Some basic principles of graphic representation are given in Table 13.

For effective graphic presentation, Cleveland (1994) recommends:

- avoid excessively complicated graphs;
- avoid pie charts, perspective charts (3D bar and pie charts, ribbon charts), pseudo-perspective charts (2D bar or line charts);
- use colour and shading only when necessary and then, only very carefully;
- when possible, accompany graphs with tables of data;
- if probability density or cumulative probability plots are presented, present them with identical horizontal scales (preferably on the same page), with the mean clearly indicated on the curves; and
- do not depend on the audience to correctly interpret any visual display of data: provide a narrative in the report interpreting the important aspects of the graph. (US EPA, 1997)

Table 13: Useful vs not useful graphics

Useful	Not useful
No cryptic abbreviations	Numerous abbreviations requiring searching the text for explanation
No elaborate encoding	
Words run in natural left to right direction	Words run vertically or in several directions. Letters running vertically may be even worse
No elaborate shadings, cross hatchings and overpowering colouring.	
Simple labelling or graphic means no legend or key is required	Elaborate or obscurely coded patterns requiring continual return to legend or key.
Simple, upper and lower case font with serifs, modestly and consistently used.	Multiple overbearing fonts, in upper case sans serif
Clearly printed	Murky and clotted printing
Enlightens and arouses curiosity	Graphic repels interest and obscures meaning.

(Langley, 1993a; adapted from Tufte, 1983)

It needs to be absolutely clear when log rather than logarithmic scales are being used on the axes of graphs.

Besides the work by Tufte (1983, 1990), other useful general references are:

- Kosslyn SM (1994). *Elements of graph design*. New York: WH Freeman and Co.
- Cleveland WS (1994). *The elements of graphing data*. Summit, New Jersey: Hobart Press.

Cost of graphics

Graphic work is usually time-consuming and the cost of this may be significant. However, particularly for large and complex situations, some form of graphic representation is imperative for the assessor and other stakeholders to visualise accurately a model of what is occurring on a site. Without such representations inaccurate (and probably costly) decisions will be made and risk communication and community consultation will be much more difficult.

Photography

A photographic record that is well-labelled for date, location and orientation is a valuable reference during the inspection (e.g. topography, soil staining, stack emissions, algal blooms, industrial processes, plant toxicity, proximity of housing), and assessment (e.g. the soil strata demonstrated in test pits and soil cores). Good photography will provide considerable assistance for those unable to undertake an inspection of the situation.

Supplying data on disc

Consultants, assessors and government agencies should have access to data on disc or other electronic formats as it:

- avoids a further source of transcription error; and
- facilitates the further analysis of data using other software packages.

8.5.14 Censored data

Censored data are those which are below the level of detection. Summary statistics can be biased according to the values substituted into mathematical formulae to allow calculations of, for example, means. Often the value of the level of detection is substituted, upwardly biasing the sample statistics. The approach to censored data must be clearly stated.

Levels of reporting

The first step in dealing with censored data is to ensure that the levels of detection or levels of reporting are appropriate. The levels of reporting must be less than the relevant criteria against which the results will be assessed. A level of reporting of no more than 10 per cent of the relevant criterion should be adopted. Where this may entail substantial costs, a higher level may be tolerable.

Diminishing levels of reporting

Improved analytical techniques have led to levels of reporting decreasing enormously. For example, the detectability of benzene in water has increased by over 10 000 fold since the 1960s (Hrudey, 1998). For some substances picogram concentrations (10–12g) can be detected in commercial laboratories and femtogram (10–15g) in research institutions.

Dealing with censored data

Heyworth (1991, p. 24) summarises Helsel (1990) and provides a summary of the three essential methods for dealing with censored data:

1. Simple substitution methods

Simple substitution methods refer to those methods which substitute a single value, such as one-half the detection limit for each censored value. While these methods are commonly used they have no theoretical basis. The choice of the substitution value is essentially arbitrary and the estimates of summary statistics will be biased by these fabricated results.

2. Distribution methods

The distribution method uses the characteristics of the assumed distribution of the data. For environmental monitoring the log normal distribution is usually assumed and values of data above and below the reporting limit are assumed to follow this distribution.

Estimates of the mean and standard deviation are computed using the best match from the observed data and percentage that fall below the limit. Estimation methods include maximum likelihood estimation and probability plotting procedures. These methods will produce unbiased estimates only when the observed data fits the distribution exactly and the sample size is large. This, of course, is a rare case. However, they provide better estimates than those obtained by simple substitution.

3. Robust methods

The robust method combines the observed data above the detection limit with extrapolated below-limit values to compute summary statistics. In contrast to the distribution methods the actual data above the reporting limit are used to fit a distribution rather than assuming a distribution.

This method has the advantage that estimates of extrapolated values can be directly retransformed and summary statistics computed in the original units, thereby avoiding transformation bias. Also this method is not as sensitive to the fit of the distribution for the largest observations because actual observed data are used to fit the distribution.

The probability plotting method used to fit the distribution in robust methods can be computed quite readily by most commercially available statistical packages.

Helsel (1990) recommends the use of robust methods, particularly when the data cannot be assumed to follow a defined distribution. He concludes that the use of these methods, rather than simple substitution methods for

environmental data, should reduce estimation errors for summary statistics substantially.

'Simple substitution is an inappropriate method of dealing with less than detectable values as it has no theoretical basis' (Heyworth, 1991, p. 25). Simple substitution methods of dealing with censored data may result in significant over-estimates of risk if the level of reporting is used as a value for censored data and the concentration of the agent does not approach the level of reporting, or is not present at all. Under-estimates of risk can occur if, for example, a value of half the level of reporting is used but actual concentrations of the agent are actually greater than this.

The use of either the distributional or robust methods is recommended, but the latter is preferred. Commonly available statistical packages readily enable the use of robust methods for dealing with censored data.

The values for the median and interquartile range generally are not affected by censored data (*ibid*).

8.6 Meteorological Data

Meteorological data will be particularly important in the evaluation of both point source and generalised air pollution and potential exposures of populations. When environmental monitoring is being undertaken, there is a need to have concurrent meteorological data.

8.7 Content of Environmental Sampling and Analysis Reports

8.7.1 Integration of reports

Where there is a series of reports, each succeeding report should summarise the important and relevant points from the preceding reports. This will assist in the rapid comprehension of new material by all parties involved.

Non-integrated reports result in far less efficient appraisals of data.

8.7.2 Sampling issues

The basis of the sampling program should be clearly justified.

8.7.3 Analytical issues

Chain of custody

An uninterrupted chain of custody should be present to ensure the quality of the results.

Accreditation of laboratories

Laboratories should be accredited by an appropriate body for the particular analyses being undertaken. A broad form of accreditation may not be applicable for the particular test.

Liaison with laboratories

There should be one person responsible to coordinate samplers, risk assessors and laboratories to ensure that appropriate data ensues. This person should be identified in the report. This coordination should also ensure that analytical methods and sampling protocols deliver data useful to the risk assessment and that the communication occurring between the various parties is meaningful and extends beyond the transfer of samples and data.

Choice of analytes

The analytes chosen must be applicable to the risk assessment, either directly (e.g. lead near a lead smelter) or as surrogate measures of an environmental hazard (e.g. turbidity as a measure of water quality, coliforms as a measure of food safety).

Analytical techniques

The analytical techniques should comply with techniques described in relevant protocols.

8.7.4 Situation descriptions

A situation description should, where relevant, contain the following (adapted from Edwards *et al.*, 1994, p. 5; EPA NSW, 1997, p. 8):

- **Situation definition and description.** Where this applies to specific geographical areas, the boundaries of these should be clearly and accurately identified with respect to roads, adjacent properties and geographical features.

A current plan of the site, with scale bar, indicating the site orientation (including north) and general contours of the property, local water drainage and other environmentally significant features is essential as well as a locality map. If historical factors are relevant to the site are important, a series of aerial photographs with dates may be warranted;

- **Zoning.** This will include previous present and proposed zoning and relevant development and building approvals records;
- **Present and past industrial and non-industrial activities/uses** with as much precision as possible. For industrial activities this may require details of: raw materials; products; intermediate products and byproducts; and wastes;
- **Present (and previous) buildings and structures** where relevant;
- **Waste Disposal Practices and Locations.** Locations of solid waste disposal areas and liquid waste lagoons, settling tanks and sumps should be identified in the maps and figures;
- **Discharges** to land, air and water;
- **Product Spills, Losses, Incidents and Accidents (including fire).** These should be listed chronologically together with an indication of the material spilled, estimates of quantity, extent of fire damage, and communities and structures affected;
- **Sewer and underground service plans;**
- **Chemical storage and transfer areas;**
- **Adjacent Land Uses.** The emissions and contaminant plumes from adjacent land uses should be considered;
- **Relevant history of complaints;**
- **Local knowledge of residents and staff;**
- **Details of building and related permits, licences, approvals and trade waste agreements; and**
- **Validity and integrity assessment** of the above information.

8.7.5 Site inspections

The remaining sections are adapted from EPA NSW (1997)

Where relevant a site inspection performed as part of a risk assessment should contain the following:

- topography;
- conditions at the site boundary;
- visible signs of environmental hazards e.g. discolouration and staining of soil, plant and animal toxicity;
- presence of waste materials;
- odours;
- condition of structures e.g. presence of abnormal deterioration, moulds and fungi, adequacy of ventilation;
- quality of surface waters;
- flood potential; and
- details of relevant local sensitive environments e.g. rivers, lakes, creeks, wetland, local habitat areas, endangered flora and fauna.

8.7.6 Sampling and analysis plan and sampling methodology

Where relevant, a risk assessment report should contain the following:

- Sampling, analysis and data quality objectives (DQOs);
- Rationale for the selection of:
 - sampling pattern;
 - sampling density including an estimated size of the residual contamination;
 - spots that may remain undetected;
 - sampling locations including locations shown on a site map;
 - sampling depths for soil and water, height for air;

- samples for analysis and samples not analysed;
- analytical methods; and
- analytes for samples.
- Detailed description of the sampling methods including:
 - sample containers and type of seal used;
 - container pretreatment;
 - sampling devices and equipment e.g. auger type;
 - equipment decontamination procedures;
 - sample handling procedures;
 - sample preservation methods and reference to recognised protocols, e.g. APHA (1992) or US EPA SW 846;
 - sample pretreatment; and
 - detailed description of field screening protocols.

8.7.7 Field quality assurance and quality control (QA/QC)

Where relevant a risk assessment should contain the following:

- details of sampling team;
- decontamination procedures carried out between sampling events;
- logs for each sample collected—including time, location, initials of sampler, duplicate locations, duplicate type, chemical analyses to be performed, site observations and weather conditions;
- chain of custody fully identifying—for each sample—the sampler, nature of the sample, collection date, analyses to be performed, sample preservation method, departure time from the site and dispatch courier(s);
- sample splitting techniques;
- statement of duplicate frequency;

- field blank results;
- background sample results;
- rinsate sample results;
- laboratory- prepared trip spike results for volatile analytes;
- trip blank results; and
- field instrument calibrations (when used).

8.7.8 Laboratory QA/QC

Where relevant a risk assessment should contain the following:

- a copy of signed chain-of-custody forms acknowledging receipt date and time, and identity of samples included in shipments;
- record of holding times and a comparison with method specifications;
- analytical methods used;
- laboratory accreditation for analytical methods used;
- laboratory performance in inter-laboratory trials for the analytical methods used, where available;
- description of surrogates and spikes used;
- per cent recoveries of spikes and surrogates;
- instrument detection limit;
- matrix or practical quantification limits;
- standard solution results;
- reference sample results;
- reference check sample results;
- daily check sample results;
- laboratory duplicate results;
- laboratory blank results; and
- laboratory standard charts.

8.7.9 QA/QC data evaluation

Where relevant a risk assessment should contain the following:

- Evaluation of all QA/QC information listed above against the stated Data Quality Objectives, including a discussion of:
 - documentation completeness;
 - data completeness;
 - data comparability (see next point);
 - data representativeness; and
 - precision and accuracy for both sampling and analysis for each analyte in each environmental matrix informing data users of the reliability, unreliability, or qualitative value of the data.
- Data comparability checks, which should include bias assessment—which may arise from various sources, including:
 - collection and analysis of samples by different personnel;
 - use of different methodologies;
 - collection and analysis by the same personnel using the same methods but at different times;
 - spatial and temporal changes (because of the environmental dynamics); and
 - relative per cent differences for intra- and inter-laboratory duplicates.

8.7.10 Basis for assessment criteria

Where relevant a risk assessment should contain the following:

- table listing all selected assessment criteria and references;
- rationale for and appropriateness of the selection of criteria; and
- assumptions and limitations of criteria.

8.7.11 Results

Where relevant, a risk assessment should contain the following:

- summary of previous results, if appropriate;
- summary of all results, in a table that:
 - shows all essential details such as sample numbers and sampling depth;
 - shows assessment criteria; and
 - highlight all results exceeding the assessment criteria;
- site plan showing all sample locations, sample identification numbers and sampling depths; and
- site plan showing the extent of soil, air and water contamination exceeding selected assessment criteria for each sampling depth.

8.8 Modelling Exposures

Modelling is used in exposure assessment ‘as a means of forecasting human or other exposures in the absences of complete monitoring or other data’ (WHO, 1999). Modelling provides ‘a mathematical expression representing a simplification of the essential elements of exposure processes’ (*ibid*). Point estimates and probability distributions are used in exposure modelling.

8.9 Use of Point Estimates and Probability Distributions

8.9.1 Introduction

Point estimates are most commonly used in Australia for exposure assessments. A point estimate is a single value chosen to represent a population e.g. 70kg as the weight of an adult. Point estimates are usually typical values for a population or an estimate of an upper end of the population’s value e.g. 70 years as the duration of residence on a property. An upper end value may be chosen for reasons of conservatism and/or to provide a ‘worse case’ scenario.

Where a risk assessment uses a series of upper end estimates, the result can be a worse than ‘worse case’ scenario due to the compounding

effects of the estimates e.g. the person with the upper end value for weight is unlikely to also have: the upper end value for water consumption; the upper end value for contamination; the upper end value for duration of residence; the upper end value for soil ingestion, etc.

The estimate of the point estimate of a mean is usually more certain than a point estimate of the level intended to represent the 95th or 99th percentile. This will present problems if there are limited data for the use of point estimates if the point estimate is intended to be, for example, the 95th percentile. For the same reason, similar problems will arise if the tails of a probability distribution are to be estimated.

Increasing attention has been paid to the use of Monte Carlo-type exposure assessments and such methods have been acknowledged by the US EPA and the UK Department of the Environment (US EPA, 1992a; Ferguson, 1994).

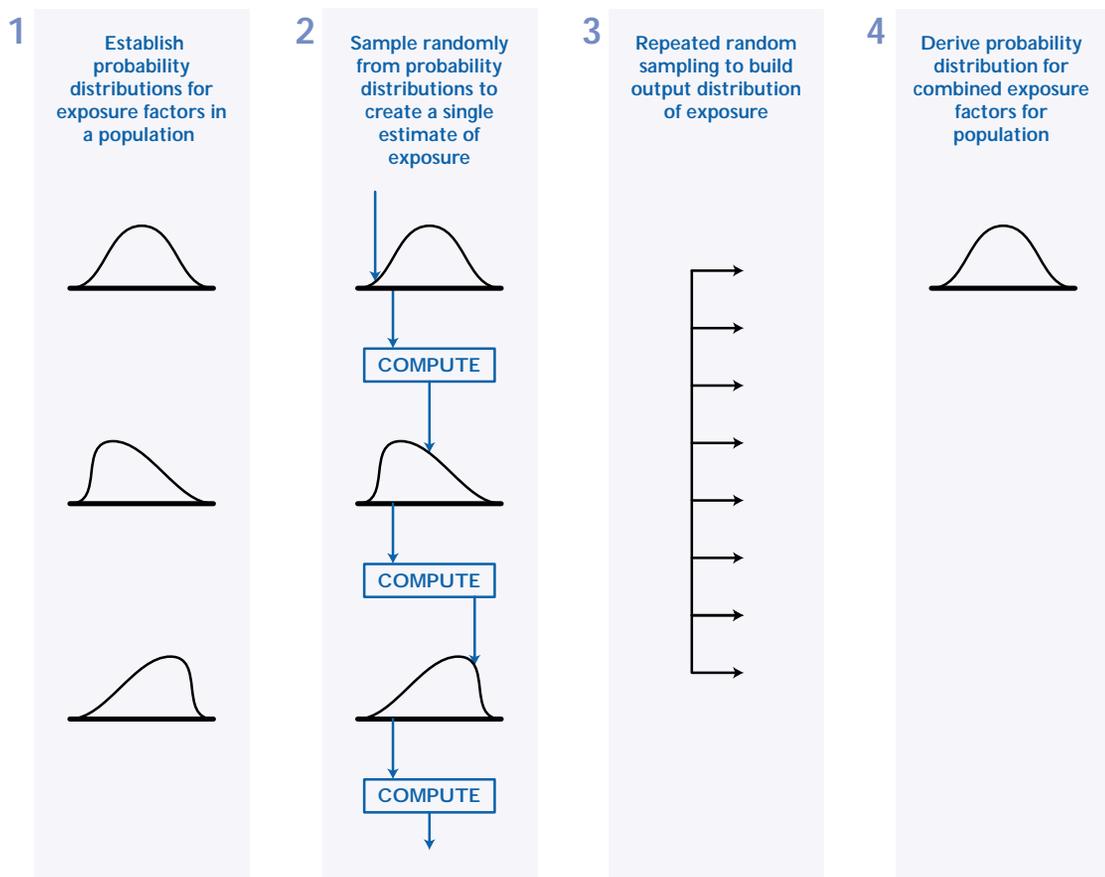
‘While methods using probability distributions are ‘more informative and inherently more representative’ (Ruffle *et al*, 1994, p. 403) than point estimates, if applied appropriately point estimates still have a major role in exposure assessment as they are readily understood and applied, and may incorporate safety factors that could be lost with Monte Carlo-type exposure assessments.’ (Langley and Sabordo, 1996)

The Monte Carlo-type exposure assessments rely on the use of probability distribution functions. A ‘distribution of possible values for each of the parameters (is) described along with the probability of occurrence of each value’ (Alsop *et al*, 1993, p. 407). Using standard mathematical formulae several thousand iterations of a mock mathematical model are performed.

For each iteration, values for each parameter are selected randomly from each distribution based upon the probability of occurrence. The estimated risk values are combined to provide a frequency distribution of possible risk (*ibid*). (from Langley *et al*, 1998).

Figure 8 demonstrates the process of using the Monte Carlo method to estimate the probability distribution of exposures in a population.

Figure 8: Principles of the Monte Carlo method



(adapted from Ferguson, 1994)

Monte Carlo analysis may add value to a risk assessment (US EPA, 1997, p. 5) when:

- exposures and risks are likely to approach or be above levels of concern;
- screening assessments using conservative point estimates fall above levels of concern;
- it is necessary to disclose the degree of bias associated with point estimates of exposure;
- when exposures and exposure pathways need to be ranked;
- where there is a need to appraise the relative values of collecting different types of further information (Cullen and Frey, 1999);
- when the costs of action are likely to be high and the gains are likely to be marginal;
- where the outcomes of action affect different exposure pathways and the benefits need to be ranked (Cullen and Frey 1999);
- sensitivity analysis is needed to appraise the impact of default values and key pathways; and

- when the consequences of simplistic exposure assessments are likely to be unacceptable.

Monte Carlo analysis may not add value to a risk assessment (Cullen and Frey, 1999, p. 8) when:

- exposures and risks are likely to be negligible;
- when the costs of reducing the exposure and risk are smaller than the cost of probabilistic analysis;
- when safety is an urgent concern and action must be taken rapidly;
- when probability distributions are so uncertain and/or incomplete that detailed probabilistic judgements are unreasonable; and
- when there is little variability or uncertainty in the data.

If a Monte Carlo assessment is performed the methodology must be 'transparent' or problems will arise in community consultation. As with any form of risk assessment, the basic principles of the method must be able to be understood by the affected community.

For small scale situations, the use of Monte Carlo methods is likely to be too complex and/or costly and it may be more appropriate to do direct measurements of exposure. The exposures of high end exposure 'outliers' must always be acknowledged in risk assessments and ways of identifying and accommodating them must be considered. This is particularly important in the assessment of an existing situation (e.g. a contaminated site where housing has already been developed), rather than a forecast exposure scenario, where the presence of an 'outlier' will severely test the credibility of a risk assessment that does not accommodate a range of exposure scenarios. (Langley and Sabordo, 1996)

8.9.2 Monte Carlo vs Latin Hypercube

Monte Carlo-type methods use 'random (or pseudo-random) numbers to sample from the input distribution ... [so that] ... samples are

more likely to be drawn from values that have higher probabilities (e.g. near the mode)' (AIHC, 1994, p. 3.3). This could be important if there is concern about exposures represented by the tails of the distributions (e.g. 99 percentile exposures). Large numbers of iterations are required in an attempt to overcome this. Even so, Monte Carlo-type methods are more likely to result in unduly frequent combinations of modal exposure scenarios (*ibid*).

Latin Hypercube techniques use random sampling within equiprobable intervals of the distribution so that there will not be clustered sampling near the mode. It also 'maintains complete independence of the variables' but this also means if correlations are intended between variables appropriate mathematical actions must be taken (*ibid*).

8.9.3 Use of Monte Carlo type techniques in Australia

To date there has been very limited use of Monte Carlo techniques in Australia for Environmental Health Risk Assessment.

8.9.4 Weaknesses with the Monte Carlo technique

Some of the key limitations of the Monte Carlo technique are:

1. **Complexity**
While the Monte Carlo method has a very general applicability, changing one variable may mean large amounts of recalculation because of the extent of the iterative process when using this model. The complexity reduces the 'transparency' of the method. This may create difficulties in community consultation and risk communication; it obscures errors, and creates difficulties for checking by both the modellers and administering authorities.
2. **Loss of factor distinctions**
The method does not indicate 'which variables are the most important contributors to output uncertainty' (US EPA, 1992, p. 22928).

3. Unrealistic probability assessments

US EPA (1992) notes that simulations such as that found with the Monte Carlo model often 'include low probability estimates at the upper end that are higher than those actually experienced in a given population, due to improbability of finding these exposures or doses in a specific population of limited size, or due to non-obvious correlations among parameters at the high ends of their ranges'. This results in overestimation of exposure dose or risk. The Science Advisory Board of the US EPA has noted that 'for large populations, simulated exposures, doses and risks above the 99.9 percentile may not be meaningful when unbounded log normal distributions are used as a default' (*ibid*, p. 22922).

4. Assessment endpoints

With Monte Carlo-type assessments there is still a need to determine what is an acceptable level of exposure. Smith (1994) considers that 'the level of exposure exceeded by 1 in 20 exposed persons would seem to be an appropriate reasonable maximum' (p. 438). This would allow 5 per cent of the population not to be included in the exposure assessment.

5. Variability-uncertainty confusion

Smith (1994) highlights the need to distinguish between 'variability' (measurable factors that differ across populations such as height) and 'uncertainty' (unknown, difficult to measure factors such as frequency of trespassing on a site). Currently available software packages do not distinguish between variability and uncertainty. An administrator reviewing a Monte Carlo risk assessment will, however, need to appreciate the differences between variability and uncertainty and the nature and extent of both (*ibid*).

6. Limited exposure data

Limited information is available about many variables for the exposure assessments. As a consequence of this, many input variables are described as triangular distributions. Smith (1994) stresses the need to collect and verify distributions from many currently undescribed

input assumptions (p. 438) to improve accuracy. The use of Monte Carlo methods may be inappropriate where the predictions of exposure are so dominated by uncertainties. McKone (1994) gives the example of benzo(a)pyrene, where information on benzo(a)pyrene exposure is 'not readily available' (p. 461) so that the use of Monte Carlo methods to assess variability in population exposures is somewhat redundant.

7. Simplification of complex situations

Exposure assessments are comprised of combinations of modelling, sampling, and modelling/sampling combinations (McKone, 1994). Even the use of complex models still provides a static picture of a dynamic world albeit a more elaborate representation of reality (McKone, 1994) and such a picture must be placed within a sound theoretical framework.

8. Misleading precision

The use of more complex models does not necessarily increase precision (McKone, 1994, p 461). The costs of collecting and analysing data, and constructing new models must be balanced by the value of the information obtained (*ibid*, p. 461). There is a need to appraise the value of information along with its uncertainties in defining the capabilities and limits of exposure models (p. 461). (Langley and Sabordo, 1996, p. 141).

9. Characterisation of extreme values

The 50th percentile can always be estimated with less uncertainty than the 99th percentile (Finley *et al*, 1994). Problems in estimating the extreme percentiles can come from limitations in the measurement techniques (e.g. incorrect and implausible estimates of dietary consumption may be accepted into the survey); the duration over which exposure data was collected (see short term and long term variation, below); and whether there are sub-populations who may have unusual exposures (e.g. vegetarians, subsistence fishermen) (Finley *et al*, 1994). Estimating extreme percentiles can be a very time-consuming process.

8.9.5 Estimating distributions for exposure factors

Several factors affect the choice of distributions (Finley *et al*, 1994):

- **Variability and uncertainty**

Variability, as an inherent characteristic of a population, will not be reduced with additional data but will be more accurately characterised. Uncertainty however, will be reduced with additional data.

Uncertainty may arise from factors intrinsic to the available data (e.g. limitations of study design and analytical techniques) or from the application of data to non-sampled populations (e.g. extrapolating Scandinavian data to an Australian population) (Finley *et al*, 1994).

The characterisation of uncertainty related to exposure factors has been developed further than two other areas of uncertainty that may in fact be more significant: the relationship between the absorbed dose and the ultimate delivered dose to a target organ; and the uncertainty about the response to the dose (Finley *et al*, 1994).

- **Factor inter-dependence**

Some factors such as body weight and skin surface area are interdependent and this needs to be considered. Age specific data should be used as the factor may be strongly related to age (e.g. inhalation rates).

- **Short-term and long-term variation**

Interpersonal variability will be decreased if the length of time over which a factor is measured is increased. Short term data tend to overestimate inter-individual variation (*ibid*). For example, the 95th percentile of dietary intakes from studies taken over one to three day periods will be significantly higher than for studies taken over longer periods such as one month to one year. This has been seen in the studies of tap water consumption and fish consumption (Finley *et al*, 1994). It can be particularly marked for rare exposures (e.g. rarely eaten food such as shellfish).

Studies of shellfish consumption taken over short periods of time may suggest only a very small proportion of the population consumes the foodstuff and, if the common practice of excluding all non consumers is undertaken, there will be a poor characterisation of the variability in the general population (Finley *et al*, 1994).

- **Parametric versus non-parametric distribution characterisation**

For data to meet parametric distributions (e.g. normal or log normal), appropriate statistical tests must be met. Theoretically normal or log normal density distributions do not have an upperbound limit yet for many factors (e.g. height, weight, fluid consumption) there are obviously physiological limitations to the factors. Some of the currently available software enables such factors to be set within the model.

- **Shapes of distributions**

Triangular shape distributions are often used in Monte Carlo-type assessments but may be viewed as conservative characterisations of truncated normal or log normal distributions (Finley *et al*, 1994, p. 535).

When establishing probability distributions, the distributions should be determined, where possible, from relevant data sets. If there is a need to estimate a probability distribution, it should be appreciated that that many environmental health factors are likely to be lognormally distributed rather than symmetrically distributed. Examples of risk variables that have been characterised by lognormal distributions are (Murphy, 1998):

- Body weight (each sex)
- Bioaccumulation
- Breathing rate
- Cancer potency factors
- Concentrations in
 - Air
 - Soil
 - Tissue

- Water
- Drinking water rate
- Exposed skin
- Fish consumption
- Lifetime
- Residence time
- Shower duration
- Shower water use
- Soil ingestion rate
- Surface area/ body weight
- Total water use
- Toxic susceptibility

Much environmental data is lognormally rather than normally distributed. Table 14 gives some examples of output variables that can be represented by probability distributions.

8.9.6 Selecting appropriate data sets

For describing a probability distribution, the relevant studies and the quality of the data produced may vary considerably. Unless data sets are rigorously scrutinised the resulting uncertainty in the range of risk estimates could be greater than obtained using point estimates (Finley *et al*, 1994, p. 536).

Finley *et al* (1994) recommend the following criteria for assessing data:

- consistency with other studies;
- relevance of the survey population to the general population or the population being appraised as part of a risk assessment;
- minimisation of confounding variables; and
- whether there are sufficient data to adequately characterise variability and the extremes of the distribution.

Haines *et al* (1994) propose several approaches to the development of distributions when objective data is missing or scarce or not quite relevant:

- when data are sparse but relevant expert judgement can be used to propose percentiles using available data as ‘collaborators’ of the expert judgement;
- where data are not quite relevant to propose a distribution for a parameter, expert judgement again can be used collaborating the judgement with analogous data; and
- where there is an absence of data the formal elicitation of expert judgement to construct a distribution (p. 693) can be used.

If there are a variety of studies then the purposes, designs and methodologies that are similar may be able to be combined (Finley *et al*, 1994).

Haines *et al* (1994) highlight the need to examine the tails of probability distribution functions and submit them to a ‘reality check’ and examine the combination of factors that resulted in the extreme values. They highlight the extreme sensitivity of these tail values to assumptions and reinforce the need to assess the sensitivity of the tails to the assumptions. The assumptions need to be examined as to whether they are mutually consistent (*ibid*).

8.9.7 Principles for the use of Monte Carlo-type techniques

The purpose and scope of the risk assessment should be clearly articulated in the Issues Identification section. Burmaster and Anderson (1994) stress that any method of exposure assessment must have a clearly defined assessment end point and provide all relevant information so that the assessment can be reproduced and evaluated (p. 477). Burmaster and Anderson (1994) detail fourteen principles for good practice in Monte Carlo assessments.

These are:

1. Detail all formulae.
2. Detail point estimates of exposure where these are demanded by regulatory agencies.
3. Detail sensitivity analyses to enable the identification of relevant and important input variables. Those variables which will drive the

Table 14: Some key variables for which probability distributions might be needed

Model component	Output variable	Independent parameter variable	
Transport	Air concentration	Chemical emission rate Stack exit temperature Stack exit velocity Mixing heights	
	Meteorological factors	Wind speed Wind direction	
Deposition	Deposition rate	Dry-deposition velocity Wet-deposition velocity Fraction of time with rain	
Overland	Surface-water load	Fraction of chemical in overland runoff	
Water	Surface-water concentration	River discharge Chemical decay coefficient in river Mixing depth	
Groundwater	Groundwater concentration	Predictions of plumes	
Soil	Surface-soil concentration	Surface-soil depth Exposure duration Exposure period Cation-exchange capacity Decay coefficient in soil	
Food chain	Concentration in animal products	Soil ingestion rates Plant to animal bioconcentration factors	
	Plant concentration	Plant interception fraction Weathering elimination rate Crop density Soil-to-plant bioconcentration factor	
	Fish concentration	Water-to-fish bioconcentration factor	
Dose	Inhalation dose	Inhalation rate Body weight	
	Ingestion dose	Plant ingestion rate Soil ingestion rate Body weight	
	Dermal-absorption dose		Exposed skin surface area Soil absorption factor Exposure frequency Body weight

(adapted from NRC, 1994, p. 169; adapted from Seigneur *et al*, 1992.)

risk assessment must obviously be included in the Monte Carlo analysis but reasons for excluding insignificant variables must also be detailed.

4. Use probabilistic techniques (which may be demanding in terms of time, money and other resources) only where exposure pathways are likely to be significant.
5. Provide detailed information about input distributions. The minimum stated by Burmaster and Anderson is:
 - a graph showing the full distribution and the location of the point value used in the [point estimate] risk assessment; and
 - a table showing the mean, standard deviation, the minimum (if one exists), the 5th percentile, the median, the 95th percentile, and the maximum (if one exists) (p. 478). There needs to be a sufficient justification of the selected distribution which should be based on adequately referenced sources and the statistical, physical, chemical, and biological mechanisms relevant to the distribution.
6. Detail how the input distributions capture and represent both the variability and the uncertainty in the input variables (p. 478) so as to enable both variability and uncertainty to be described and analysed separately.
7. Use measured data to test the relevance of the input distribution to the population, place and time of the exposure assessment. Further data may need to be gathered to supply missing information or supplement incomplete information.
8. Describe the methods by which measured data were used to derive a probability distribution.
9. Detail any correlations between data where there are relatively high correlations. Sensitivity analysis may be necessary to determine the effects of correlations between variables on the exposure analysis.
10. Provide detailed information and graphs for each output distribution. Burmaster and Anderson suggest the following as a minimum:
 - a graph of the variable with administratively set allowable risk criteria as annotations and point estimates of risk using the administratively set point estimates of exposure; and
 - A table of the mean, the standard deviation, the minimum (if one exists), the 5th percentile, the median, the 95th percentile, and the maximum (if one exists) (p. 479).
11. Provide records of sensitivity analyses and their impact that will enable the determination of the most important input variables (or groups of variables).
12. Assess the numerical stability of the central moments (mean, standard deviation, skewness, and kurtosis) and the tails of the output distributions. The latter are particularly sensitive to the nature of the tails of the input distributions and, as they stabilise very slowly, sufficient iterations are required to demonstrate the numerical stability. Burmaster and Anderson suggest that commonly more than 10 000 iterations are required. Software that enables Latin hypercube sampling results in more rapid stability of these output tails. Burmaster and Anderson state that the changes in the tails of only a few input distributions contribute strongly to changes in the upper tail of the output distribution (p. 480).
13. Detail the name and statistical quality of the random number generator used. Some generators are inadequate because of short recurrence periods.
14. Interpret the results and detail the limitations of the methodology such as the effects of biases not elsewhere interpreted.

Burmaster and Anderson state that the principles are not mutually exclusive nor collectively exhaustive (Langley and Sabordo ,1996, p. 140–1).

8.9.8 Administrative requirements for the use of Monte Carlo methods

Regulatory authorities in Australia will require assessments using Monte Carlo methods to meet the following criteria:

1. Meeting the 14 principles of good practice detailed above.
2. The provision of adequate information to the authority to enable review of the assessment. This may require the provision of the software (and underlying formulae) and data.
3. A demonstration of the relevance of the exposure data to the site: data from other countries or cultural backgrounds may not be relevant.
4. An explanation of the data and method which will be able to be understood by the relevant community.
5. The use of 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 (Langley and Sabordo, 1996, p. 141).

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.

8.10 Environmental Monitoring

8.10.1 Personal monitoring

Where practicable, personal monitoring may play a central role in the exposure assessment component in the risk assessment process.

Monitoring methods used in exposure assessment can be categorised into direct and indirect approaches. In the indirect approach to exposure monitoring, factors that affect exposure are measured rather than exposure itself. Fixed-site monitors are used to measure pollutants in media, especially air and water (Covello and Merkhofer, 1993).

Personal monitoring is a direct approach whereby individual human exposures at the point of contact are measured directly by instruments (personal exposure monitors or PEMs) that accompany the individual (Wallace and Ott, 1982). PEMs are designed to measure the concentrations of agents in the air, water, or in food. In the case of food and water, individuals actively test the water or food before they consume it. PEMs are available for a limited range of agents.

Personal monitoring has been commonly used to measure exposures to carbon monoxide, volatile organic compounds, to electromagnetic fields, and by radiation workers, who routinely carry dosimeters or film badges that measure exposures to radiation.

Personal monitoring can be used to address some of the problems of exposure monitoring. It may be able to collect data that integrates the great diversity of exposure pathways. Similarly it can take into account the natural variability of the environment over time and space that makes it difficult to translate measurements obtained from fixed monitoring stations into actual exposures experienced by people that move from place to place.

If enough subjects are selected for monitoring, a population exposure can be constructed. Because of time and cost constraints of portable sampling devices, such techniques are not often used for assessing exposures in the general environment. They are used more frequently in the occupational setting.

Passive and active personal samplers are available. Passive monitors capture the ambient air sample without mechanical assistance. Active samplers

direct the sample to the monitor via a pump that is calibrated to pump air at a certain rate. Active samplers provide more information than passive samplers, because pollutant concentrations or the dose can be estimated more directly using active sampling. Passive samplers do provide time-weighted average concentrations rather than specific concentrations, but they are less costly and bulky than active samplers and they are useful in screening to determine if exposure has occurred (NRC, 1994).

When personal monitoring has been used in a risk assessment the following factors should be considered:

- the duration and frequency of monitoring (transient periods of high exposure may not be detected if monitoring is not conducted at the relevant times);
- environmental changes that may have affected the monitoring such as wind shifts;
- the accuracy and timing of calibration of equipment;
- the accuracy and sensitivity of the monitoring technique (many techniques are designed for the occupational setting and may be insufficiently sensitive for assessing general environment exposures where criteria are usually much lower);
- confounders e.g. a formaldehyde PEM may respond to a range of aldehydes (such as acrolein from wood smoke) and will also detect formaldehyde from a range of sources including cigarette smoke. This lack of source-specificity may present a limitation when particular sources need to be addressed by risk assessment;
- the relationship between short-term sampling and long-term exposures;
- bulky equipment may affect behaviour and hence exposure;
- tampering with equipment;
- time and cost constraints (i.e. it may be time consuming and costly to obtain enough direct

measurements to establish an accurate frequency distribution of exposures within a population);

- bias in sample selection and poor response rates (this can lead to results which cannot be generalised to the relevant population);
- accurate, valid and practical measuring methods must be available (the number of substances which can be reliably measured with personal monitoring is still small); and
- some analyses require specialised laboratories (and there may also be laboratory inaccuracy).

Personal monitoring is usually only feasible where relatively small numbers of people are exposed to a limited range of substances. It is used particularly in the occupational environment. In other situation such as when assessing exposure to air pollutants, environmental monitoring will be the usual method.

8.10.2 Biological monitoring

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. By comparison, 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, 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 1991a). It can be useful in identifying highly exposed individuals or sub-populations.

The biological samples used for monitoring include: blood, urine, fat, breast milk, hair, and expired air.

Biological monitoring should not be commenced before:

1. The objective of the biological monitoring is defined clearly.
2. A reference range of results is established that is applicable for the population under study. 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.
3. 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 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.
4. 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.
5. A process has been established to enable consistent analysis and epidemiological appraisal of results.
6. The ethical and confidentiality aspects of collecting, maintaining and distributing information and results are fully considered.

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

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 which 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; and
- The results may have more value for a group than an individual. (*ibid*)

8.11 Choice of Tissue

8.11.1 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.

8.11.2 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.

- 24 hour sample collections may be more appropriate than spot samples but many people find 24 hour collections are onerous.
- Urine samples require rapid processing and cooling.

8.11.3 Hair and toenails

- Hair and toenails can provide an integrated measure of exposure over a more prolonged period than blood or urine.
- Hair and toenails are only useful for chemicals known to accumulate in those tissues.
- Hair and toenails 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.

8.11.4 Breast milk

- The collection of 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 breast feeding first commenced.

8.11.5 Expired air

- Expired air is used to determine exposures to ethanol and some solvents.

8.12 Choice of a Test

Optimally, a biological monitoring test would give a result which reflected the exposure, the concentration of the substance in the target organ and the risks of adverse effects (Friberg, 1985). Few tests are available which approach this ideal (Langley, 1991a).

Where exposures from the environment are low this creates problems concerning 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:

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

Substances for which biological monitoring of general environmental exposures is practicable are detailed in Table 15.

There is 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), occupational exposures (e.g. benzene, ethylene oxide, styrene oxide, vinyl chloride, aromatic amines, polycyclic aromatic hydrocarbons).

Table 15: Substances likely to be suitable for biological monitoring

Substance	Fluid/ tissue	Comments
Lead	Blood	Urinary lead does not accurately reflect either recent exposures or body 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 occupational groups (WHO, 1986; NHMRC, 1987).
Cadmium	Urine/ 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 µgCd/g Creatinine or µgCd/24hr). 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. World Health Organisation (cited in Mueller <i>et al</i> , 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 before study must be done during exposure (or at most within 1–2 days afterwards). Considerable interference from organic sources of arsenic (e.g. 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, Urine	At equilibrium, the concentration of mercury in the blood reflects daily intake and is probably the single best indicator of exposure. This measure will also include methylmercury from fish and a fractionated analysis of mercury salts and alkylmercuric compounds may be required (Aitio <i>et al</i> , 1988). Methylmercury exposure will not affect urinary mercury levels although urinary levels show significant diurnal variation. Some international comparison data is available (<i>ibid</i>).
Polychlorinated biphenyls (PCBs)	Blood, adipose tissue (fat)	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 available. It is difficult to obtain adipose tissue samples and blood sampling is usually preferred.
Organochlorine pesticides e.g. aldrin, dieldrin, chlordane, heptachlor	Blood, Adipose tissue (fat)	Long biological half-life so that body burden can be assessed. Some comparison data available, especially for blood. It is difficult to obtain adipose tissue samples and blood sampling is usually preferred.
Organophosphorus pesticides e.g. malathion, chlorpyrifos	Blood	Cholinesterase levels will enable physiological response to be monitored. Wide range of normal values require individual baseline values to enable an assessment of 'normality'.

(Langley, 1991a)

Besides the pesticides mentioned in Table 15 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 to 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 NOHSC 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'.

8.13 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, 1993). Three classes of biomarker are identified by WHO (1993, p. 12):

- 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; and
- 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 (ECETOC, 1989; Fowle, 1989; Fowle and Sexton, 1992; NRC, 1992). Sensitive subpopulations can be better pinpointed by biomarkers that measure increased absorption rate or a more severe biological response to a given environmental exposure (Lauwerys, 1984; ECETOC, 1989; Fowle and Sexton, 1992; Hemminki, 1992; NRC, 1992) (from WHO, 1999b, p48).

8.14 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 Section 4.8–4.11.

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, 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 that 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 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);
- Release of findings (which should be at a group rather than individual level for reasons of confidentiality if the results are made public); and
- How the information will be used to address the relevant environmental health issues.

8.15 Exposure Assessment of Volatile Agents

Volatile agents require specialised sampling techniques to ensure that the contaminants are not lost during and after sampling so that analytical results accurately represent the concentrations present. The inhalation route will be more important than for non-volatile contaminants. It is often impractical to undertake environmental (i.e. air) sampling because of the constant variations over time of the concentrations as a result of fluctuation in temperature, wind speed and direction. Other factors that will have a significant effect are: soil disturbance; the physico-chemical properties of the soil and contaminants; and whether there is a renewable source or whether the contamination will dissipate over time. Exposure assessment will often depend on modelling.

Currently, field monitoring data are the most appropriate data to use in assessing exposures to volatile substances. Environmental fate and modelling characteristics present problems for the use of short term field monitoring data. This is particularly marked for the decay of exposures to finite sources of volatile substances.

8.16 Default Values for Exposure Assessments

Defaults used in air, water, and food risk assessments and standard setting are detailed, where available in Appendices 2–4. It is population and site-specific data. Stakeholder consultation may be useful in establishing site-specific data. Defaults may be useful for ‘back of the envelope’ appraisals to establish whether there is a need to move to site-specific appraisals.

The use of a default of 100 per cent bioavailability has to be employed in the absence of data on bioavailability but such defaults may misrepresent the true situation for toxins such as metals. Bioavailability may be significantly different for differing exposure routes (inhalation, ingestion and dermal exposures) and differing exposure circumstances (e.g. ingestion when fasting or with food).

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8.16.1 Body weight, kg

Adult male	= 70
Adult female	= 58
Average	= 64 ³

8.16.2 Daily fluid intake (milk, tap water, other beverages), ml/day

Normal conditions:

Adults	= 1000–2400, representative figure = 1900 ⁴
Adult male	= 1950
Adult female	= 1400
Child (10 years)	= 1400

High average temperature (32°C):

Adults	= 2840–3410
--------	-------------

Moderate activity:

Adults	= 3700
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8.16.3 Respiratory volumes

8-h respiratory volume, litres

Resting:

Adult male	= 3600
Adult female	= 2900
Child (10 years)	= 2300

Light/non-occupational activity:

Adult male	= 9600
Adult female	= 9100
Child (10 years)	= 6240

Daily inhalation volume, m³

(8-h resting, 16-h light/non-occupational activity)

Adult male	= 23
Adult female	= 21
Average Adult	= 22
Child (10 years)	= 15

Proportion of time spent indoors = 20 h/day

8.16.4 Dietary intake

There are six principal sources of dietary intake data for Australia that can be used for exposure assessments:

- National Dietary Survey of Adults: 1983 1. Foods consumed;
- National Dietary Survey of School Children (aged 10–15 years): 1985 1. Foods Consumed;
- Apparent Consumption of Foodstuffs and Nutrients - Australia: 1996–1997;
- Victorian Dietary Survey 1985
- CSIRO State Nutrition Surveys; and
- National Nutrition Survey—Australia 1995.

³ WHO uses 60kg for calculation of acceptable daily intakes and water quality guidelines (WHO, 1987, 1993)

⁴ WHO and NHMRC use a daily per capita drinking-water consumption of 2 litres in calculating water quality guidelines (WHO, 1993; NHMRC/ARMCANZ, 1996)

8.16.5 Soil exposures

The following default values have been used in exposure models since 1991 to derive Health-based Soil Investigation Levels. They are adapted from Langley and Sabordo (1996, p184). These values should be used unless values more pertinent to the relevant population can be provided and justified. Factors should be relevant to the population about whom the exposure assessment is being done.

1. Dermal absorption factors

- Where available, substance specific data for bioavailability and dermal adherence should be used.
- A child's soil contact area will be equivalent to the area of both hands, both legs and both feet (Hawley, 1985). This area of skin will be taken as 0.21m² (*ibid*).
- The child will wash once each day.
- The soil adherence factor will be 11 mg per 21.5cm² (*ibid*) i.e. a total of 1 074 milligrams of soil on the exposed skin.
- Australian washing/bathing values are to be used where available (See Langley *et al*, 1998).

2. Inhalation factors

- Inspirable soil particulates inside a house will be 75 per cent of the level of inspirable particulates outdoors (Hawley, 1985). US EPA (1989) found indoor airborne lead levels were 0.3 to 0.8 outdoor levels for houses without air-conditioning.
- 75 per cent of the inhaled dust will be retained in the respiratory tract and 25 per cent will be exhaled (Hawley, 1985).
- Half the inspirable dust will be sufficiently small to reach the pulmonary alveoli. This will be the respirable dust fraction and will be considered to have a diameter of less than 10 microns).
- Australian dust values are to be used where available. The data could be used for any

State but local data should be available for each capital city. It is proposed that a reasonable point estimate to use, based on this data, is 50 micrograms per m³ for respirable dust. This is conservative but plausible as it is the highest range for which data were recorded for the urban area and the second highest range for the suburban area in Adelaide. (Langley and Sabordo, 1996).

3. Ingestion factors

- Where bioavailability data for ingested soil contaminants is unknown, the value of 100 per cent absorption will be used. If bioavailability data are available it can be used providing the values are able to be justified.
- Soil ingestion rates are taken to be:

Age (years)	Soil intake (mg/day)
0-1	Negligible
1-5	100*
5-15	50*
Adult	25*

*conservative estimates.
(ANZECC/NHMRC, 1992)

- Consistent soil eating behaviour (geophagia) is considered rare although intermittent eating of unusual substances (pica) including soil is more common. There should be an awareness of these behaviours and specific behavioural and environmental management measures may be indicated to reduce the exposures if a particular individual is identified with these behaviours (Imray and Langley, 1999).

4. Duration of residency

- While the median duration of occupancy may be around 10 years in Australia, a period of 70 years should be used for duration of residency to reflect that a significant number of people will spend prolonged periods in a residence.

5. Duration in a workplace

- While the median duration in a workplace is decreasing in Australia, a period of 30 years should be used for duration in a workplace to reflect that a significant number of people will spend prolonged periods in a workplace. National Occupational Exposure Standards have been developed with an undefined career duration.

8.17 Sources of Exposure Assessment Data

Data must be pertinent to the relevant population. Where available, data from Australian populations are preferred.

Sources of information and data include:

- Taylor R and Langley A (1998). *Exposure Scenarios and Exposure Setting*.
- Langley AJ and Sabordo L (1996). *Exposure Factors in Risk Assessment*.
- Langley AJ, Taylor A and Dal Grande E (1998). *1996 Australian Exposure Factors*.
- enHealth (in press) *The Australian Exposure Assessment Handbook*
- The Australian Bureau of Statistics can provide a range of Australian data.

The American Industrial Health Council's 'Exposure Factors Sourcebook' (1994) provides examples of probability distributions for a range of exposure factors. These largely relate to the US population. These, and similar US-based data, should only be used if they can be demonstrated to be relevant to the Australian population.

8.18 Appraising Exposure Assessments

These are modified from US EPA (1992).

Factors that tend to result in underestimates of exposure:

- Overlooking a significant pathway;
- Failure to evaluate all contaminants of concern in the mixture;

- Comparison of exposure-related data against contaminated media or exposed populations rather than against appropriate background levels;
- Using insufficiently sensitive detection limits so that meaningful values are reported as not detected;
- Composite sampling;
- Failure to consider the additive effects of multiple pathways;
- Relevant individual pathways within the same exposure route may not have been summed; and
- Use of multiple lower range point estimates.

Factors which can cause overestimates of exposure include:

- The use of unrealistically conservative exposure parameters;
- Portraying hypothetical potential exposures as existing exposures;
- Failure to consider route specific bioavailability;
- The use of 100 per cent default bioavailability values;
- The cumulative effect of using multiple upper range point estimates (e.g. at the 90 per cent or 95 per cent level); and
- Attributing a significant value to results that fall below an appropriate detection limit. Substituting such values may create the impression of values where none exist.

Factors that may cause underestimates or overestimates include:

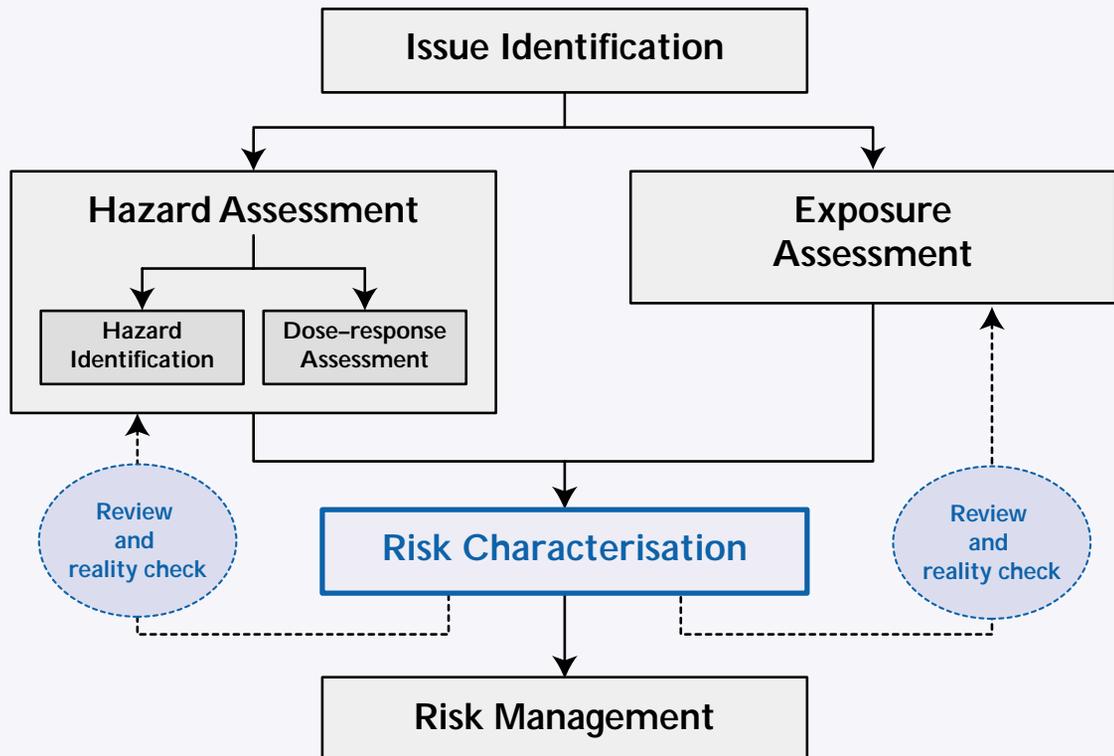
- Computational errors;
- Inaccurate analytical data;
- Use of inappropriate factors e.g. for intake routes;
- Insufficient uncertainty assessment to put the exposure assessment in perspective;

- Use of an inappropriate number of significant figures for the numeric estimates in a situation where using more than one significant figure may imply more confidence in the results than is warranted;
 - The unthinking and uncritical use of models. While the concept of ‘garbage in, garbage out’ is well accepted, some risk assessment models result in ‘quality in, garbage out’ (see Calabrese and Kostecki, 1992);
 - The failure to take into account correlations among input distributions when using simulations such as Monte Carlo. It will be unnecessary to use Monte Carlo simulation if the relationship between variables is known; and
 - Inappropriate monitoring or sampling (e.g. grab sampling vs static or period sampling).
4. What are the key descriptors of exposure?
 - Describe the range of exposures to groups such as: ‘average’ individuals, ‘high end’ individuals, general population, high exposure group(s), children, susceptible populations.
 - How was the central tendency estimate developed? What factors and/or methods were used in developing this estimate?
 - How was the high-end estimate developed?
 - Is there information on highly-exposed sub-groups? Who are they? What are their levels of exposure? How are they accounted for in the assessment?
 5. Is there reason to be concerned about cumulative or multiple exposures because of ethnic, racial, or socioeconomic reasons?
 6. Summarise exposure conclusions and discuss the following:
 - results of different approaches, i.e. modelling, monitoring, probability distributions;
 - limitations of each, and the range-of most reasonable values; and
 - confidence in the results obtained, and the limitations to the results.

8.19 Exposure Assessment Reports

The following checklist details matters that should be appropriately addressed in an exposure assessment. With justification, particular material may be omitted. It is adapted from US EPA (1995):

1. What are the most significant sources of environmental exposure?
 - Are there data on sources of exposure from different media? What is the relative contribution of different sources of exposure?
 - What are the most-significant environmental pathways for exposure?
2. Describe the populations that were assessed, including the general population, highly exposed groups, and highly susceptible groups.
3. Describe the basis for the exposure assessment, including any monitoring, modelling, or other analyses of exposure distributions such as Monte-Carlo or krieging.



Risk Characterisation

9.1 Introduction

Risk characterisation is the final step in the risk assessment process that:

- integrates the information from hazard assessment and exposure assessment;
- provides an evaluation of the overall quality of the assessment and the degree of confidence the risk assessors have in the estimates of risk and conclusions drawn;
- describes the risks to individuals and populations in terms of nature, extent and severity of potential adverse health effects;
- communicates results of the risk assessment to the risk manager (US EPA, 1995, p. 4); and
- provides key information for risk communication.

The final risk characterisation is rarely accurately quantitative because of the limitations of the data and this will be reflected in the uncertainty assessment. The process requires considerable expertise. If data are collected and analysed according to the principles and guidelines in this document the process will become more transparent and consistent. Some parts of the risk assessment process such as 'data collection' and 'exposure assessment' will be, at least in part, quantitative. These guidelines are intended to assist the qualitative process of determining whether environmental health intervention is required or not required. Due to the complexities of the matter, the risk characterisation process cannot be reduced to a 'cookbook'.

Risk characterisation may involve comparing environmental data, exposure data, intakes, and biological monitoring results with established criteria.

9.2 Key Principles in Environmental Health Risk Characterisation

There are a number of key principles for health risk characterisation (adapted from EPA NSW, 1998; US EPA, 1995):

1. Actions should always adequately protect public health and the environment, putting these responsibilities before all other considerations.
2. Risk assessments should be transparent. The nature and use of default values and methods, assumptions and policy judgements in the risk assessment should be clearly identified. Conclusions drawn from the evidence should be separated from policy judgements.
3. Risk characterisations should include a summary of the key issues and conclusions of each of the other components of the risk assessment, as well as describing the nature and likelihood of adverse health effects. The summary should include a description of the overall strengths and limitations (including uncertainties) of the assessment and conclusions.
4. Risk characterisations (and risk assessments) should be consistent in general format, but recognise the unique characteristics of each specific situation.
5. Health risk assessment must be undertaken with an appreciation that the health risk assessment is part of a larger assessment that encompasses ecological risk assessment.
6. To protect public health and the environment an appropriate degree of conservatism must be adopted to guard against uncertainties.
7. Ensure that comparisons have been made against environmental health criteria that have been endorsed by the relevant Commonwealth, State or Territory environmental health agencies.
8. Where there are no Environmental Health Criteria for a particular agent refer to the administrative authority at the relevant Commonwealth, State or Territory level.
9. Ensure that human health risk assessments are undertaken, where necessary, according to methods in this document, or its revisions as published from time to time.

10. When deriving environmental health criteria use toxicological data or exposure criteria from agencies or organisations relevant to the State or Territory (e.g. local or Commonwealth health agencies such as NHMRC, or the enHealth Council) or to which Australia is party (e.g. World Health Organization). (See Section 4 Hazard Assessment—Hazard Identification—Toxicology).
11. Ensure that human health risk assessments are undertaken using national toxicological assessments (e.g. NHMRC) or WHO assessments or, where neither has been made, methods agreed to by the administrative authority for contaminated sites at the relevant Commonwealth, State or Territory level.
12. The risk assessor's knowledge of the peer-reviewed scientific literature relevant to risk assessment should be up-to-date.
13. Variations in risk assessments as a result of particular statutory requirements, resource limitations, and other specific factors should be explained as part of the risk characterisation. For example, a reason will be required to explain why certain elements are incomplete.

9.3 Quantitative and Qualitative Risk Characterisation

The level of risk can be described either qualitatively (i.e. by putting risks into categories such as 'high', 'medium' or 'low') or quantitatively (with a numerical estimate). Current risk assessment methods do not enable accurate quantitative estimates of risk for low levels of exposure to environmental hazards. Numerical estimates of risk will rarely be feasible because of variability in the agent and population and limitations in toxicological and exposure data which will be reflected in the uncertainty assessment, but a degree of quantification may be possible for some components such as data collection and exposure assessment.

Estimates do not have to depend on the use of numbers to be useful; ordinary language may be used to indicate the level of risk. A finely divided ranking system can give a relatively accurate indication of quantity without using numbers (ACDP, 1996). Clearly defined qualitative categories can enable reliable and effective risk management decisions.

Tolerable Intakes are a form of quantitative risk characterisation as they are an estimate of the intake of a substance that over a lifetime is without appreciable health risk. (WHO, 1994).

Numbers may give a misleading implication of accuracy, especially when based on poor or uncertain information. The generation of a precise value in QRA should not be mistaken for accuracy (IEH, 1999b). The problems are compounded where results are interpolated over several orders of magnitude and where information on the mechanisms of tumour induction is limited.

The most conservative mathematical models used in QRA are virtually insensitive to the actual experimental data and should be viewed only as a risk management solution, not a risk assessment technique (IEH, 1999b, p. 34).

A detailed critique of quantitative cancer risk assessment is provided in Hrudey (1998).

While qualitative risk conclusions can avoid the false sense that the extent of the risk is known precisely, the use of terms such as 'high', 'medium' or 'low' may have different interpretations to different groups and they should be clearly defined. This is often best achieved by being put in context or compared to other risks relevant to the community. If comparisons do not directly relate to alternative options, they should be used cautiously, especially if like is not compared to like or if comparisons are being used to imply acceptability. Flippant comparisons are counterproductive (DOH, 1998). Many risk comparisons are inappropriate because of a weak evidentiary base supporting the estimate or because they are perceived by the community as irrelevant (e.g. a recent risk assessment used a comparison with 'death in the Balkan War').

Comparisons should be used only where the evidentiary base and the method for risk estimation are similar and where the uncertainties in all the comparative estimates are shown (Thomas and Hrudey, 1997, p. 218–219).

It is important to consider contingent risks. This requires not looking at risks in isolation so that, for example, the risks of immunisation (or chlorination) are considered in the context of the risks of not having immunisation (or chlorination).

9.4 Risk Conclusions

The following is adapted from US EPA 1995.

Risk conclusions

What is the overall picture of risk, based on data collection, exposure assessment, toxicity assessment and risk characterisation?

What are the major conclusions and strengths of the assessment in each of the three main areas (i.e. hazard identification, dose–response, and exposure assessment)?

What are the major limitations and uncertainties in the three main areas?

What are the science policy issues in each of the three major areas?

What alternative risk assessment approaches were evaluated?

What is the basis for the selection of options?

Risk context

What are the qualitative characteristics of the hazard (e.g. voluntary vs. involuntary, technological vs. natural, etc.)? Comment on the findings, if any, from studies of risk perception that relate to this hazard or similar hazards.

What are the alternatives to this hazard (e.g. are there other water treatment processes or food additives available)? How do the risks compare?

How does this risk compare to other risks?

How does this risk compare to other similar risks that the regulatory agency has made decisions about?

Where appropriate, can this risk be compared with past regulatory agency decisions or common risks with which people may be familiar?

Describe the limitations of making these comparisons.

Comment on significant relevant community concerns that will influence public perception of risk for the hazards addressed in the risk assessment.

Existing risk assessments

Comment on other risk assessments that have been done on this agent by Commonwealth, State or Territory agencies, or other organisations. Are there significantly different conclusions that merit discussion?

Other risk assessments

Comment on risk estimates generated by different stakeholders (P/CCRARM, 1997).

Other information

Is there other information that would be useful to the risk manager, or the public in this situation that has not been described above?

9.5 Uncertainty

Uncertainty is always present and this reinforces the need for a systematic and rigorous approach that most accurately portrays the level of actual risk. Uncertainty is a key reason why risk assessment is being performed. Uncertainty analysis must be addressed for each step of the risk assessment and for its cumulative effect from all of the steps.

The assessment of uncertainty is a critical part of the risk assessment process. Uncertainty characterisation is an essentially qualitative process relating to the selection and rejection of specific data, estimates, scenarios, etc (US EPA, 1992). Uncertainty assessment can be more quantitative and it may be represented by more simple measures such as ranges, simple analytical

methods such as sensitivity analysis and may progress to complex measures and techniques (Langley, 1993).

Uncertainty (i.e. the lack of knowledge about the correct value, for example a specific exposure measure or estimate) must be distinguished from variability (i.e. different levels of exposure experienced by different individuals).

There are three broad types of uncertainty when estimating risks (US EPA, 1992):

1. Uncertainty arising from missing or incomplete information (*scenario uncertainty*) e.g. descriptive errors, aggregation errors, errors in professional judgement, and incomplete analysis.

2. Uncertainty affecting a particular parameter (*parameter uncertainty*) e.g. measurement errors, sampling errors, variability, and use of generic or surrogate data. If expert judgements are used they should be incorporated in a 'consistent, well documented manner'.

3. Uncertainties in the scientific theory affecting the ability of a model to make predictions (*model uncertainty*).

Uncertainty may need to be addressed by the collection of further data and uncertainty analysis can be particularly useful for identifying research that will be of value.

Table 16: Example of an uncertainty table for exposure assessment

Assumption	Effect on exposure ^a		
	Potential magnitude for over-estimation of exposure	Potential magnitude for under-estimation of exposure	Potential magnitude for over- or under-estimation of exposure
Environmental sampling and analysis			
Sufficient samples may not have been taken to characterise the media being evaluated, especially with respect to currently available soil data.			Moderate
Systematic or random errors in the chemical analyses may yield erroneous data.			Low-High
Exposure parameter estimation			
The standard assumptions regarding body weight, period exposed, life expectancy, population characteristics, and lifestyle may not be representative of any actual exposure situation.			Moderate
The amount of media intake is assumed to be constant and representative of the exposed population.	Moderate		
Assumption of daily lifetime exposure for residents.	Moderate to high		

^a As a general guideline, assumptions marked as 'low', may affect estimates of exposure by less than one order of magnitude; assumptions marked 'moderate' may affect estimates of exposure by between one and two orders of magnitude; and assumptions marked 'high' may affect estimates of exposure by more than two orders of magnitude.

(adapted from US EPA, 1989a, p. 6-51)

Reasons for addressing uncertainties in assessments include:

- the combination of uncertain information from various sources;
- Having to make decisions about whether further resources should be used on seeking further information and data to reduce uncertainty;
- as a means of highlighting biases that may have crept into the process;
- as assessment is an iterative process, uncertainty analysis may enhance the outcome of the process by highlighting areas warranting further work or consideration;
- risk assessment may be one of several processes involved in a particular situation. Being able to characterise the uncertainty will assist the decision-makers and ultimately improve the decision making (amended from US EPA, 1992); and
- uncertainty assessment assists risk assessors to meet their responsibility to present not just numbers but also a clear and explicit explanation of the implications and limitations of their analyses.

In summarising the output from the uncertainty assessment, the important implications for risk management need to be highlighted. The risk assessor and the risk manager need to work together (or, at least, understand each other's needs and limitations). The risk assessor should emphasise the following aspects of the uncertainty assessment results:

- the implications for relying on any point estimate that might have been produced without consideration of uncertainty;
- the shape and breadth of the uncertainty distribution which will provide information about how prudent various risk estimates might be;
- their insights regarding the balance between the health costs of overestimating and underestimating risk;

- the sensitivity of the uncertainty estimates to fundamentally unresolved scientific controversies; and
- the implications for research and further data gathering, identifying which uncertainties are most important; which uncertainties are amenable to reduction by directed research efforts; and an estimate of the effort that would be required to significantly reduce uncertainty.

(adapted from NRC, 1994, p. 168; Finkel, 1990.)

Uncertainty issues to be addressed in each risk assessment step

1. **Hazard identification:** What are the uncertainties about the capacity of the environmental agent(s) for causing adverse effects in laboratory animals and in humans concerning:
 - the nature, reliability, and consistency of the particular studies in humans and in laboratory animals;
 - the available information on the mechanistic basis for activity; and
 - experimental animal responses and their relevance to human outcomes.
2. **Dose-response assessment:** What are the uncertainties about the biological mechanisms and dose-response relationships underlying any effects observed in the laboratory or epidemiology studies providing data from the assessment relating to:
 - the relationship between extrapolation models selected and available information on biological mechanisms;
 - how appropriate data sets were selected from those that show the range of possible potencies both in laboratory animals and humans;
 - the basis for selecting interspecies dose scaling factors to account for scaling dose from experimental animals and humans; and

- the correspondence between the expected route(s) of exposure and the exposure route(s) utilised in the hazard studies, as well as the interrelationships of potential effects from different exposure routes.
3. **Exposure assessment:** What are the uncertainties related to the paths, patterns, and magnitudes of human exposure and number of persons likely to be exposed?
- The basis for the values and input parameters used in each exposure scenario. If based on data, information on the quality, purpose, and representativeness of the database is needed. If based on assumptions, the source and general logic used to develop the assumption (e.g. monitoring, modelling, analogy, professional judgement) should be described.
 - The major factor or factors (e.g. concentration, body uptake, duration/frequency of exposure) thought to account for the greatest uncertainty in the exposure estimate, due either to sensitivity or lack of data.
 - The link of the exposure information to the at-risk population including important subgroups of the population such as highly exposed or highly susceptible groups or individuals (and the reasons they are highly exposed or highly susceptible, if known). This component includes the conservatism or non-conservatism of the exposure scenarios. In addition, information that addresses the impact of possible low probability by possibly high consequence events may need to be addressed.
4. **Risk characterisation:** Detail what other assessors, decision-makers, and the public need to know about the primary conclusions and assumptions, and about the balance between confidence and uncertainty in the assessment? What are the strengths and limitations of the assessment?
- Numerical estimates, where practicable, should be included with the descriptive information that is integral to the risk assessment. For decision-makers, a complete characterisation (key descriptive elements along with numerical estimates) should be retained in all material relating to an assessment used in decision-making. Differences in assumptions and uncertainties, coupled with non-scientific considerations called for in various environmental statutes, can clearly lead to different risk management decisions in cases with ostensibly similar risks, i.e. the level of risk alone does not determined the decisions.
 - Consideration of alternative approaches involves examining selected plausible options for addressing a given uncertainty. The description of the option chosen should include the rationale for the choice, the effect of option selected on the assessment, a comparison with other plausible options, and the potential impacts of new research.(adapted from US EPA, 1992a)

9.6 Exposure Durations and Exceedances of Acceptable Daily Intakes (ADIs)

Appropriate durations of exposure need to be assessed so that transient (short term) and important exposures are not obscured by the use, for example, of average lifetime exposures. This is important in the Australian context where Acceptable Daily Intake values from WHO are often used. The duration and magnitude of exceedances of the ADIs must be obvious in exposure assessments.

WHO publications provide comment on exceedances of ADIs:

‘Because in most cases, data are extrapolated from life-time animal studies, the ADI relates to life-time use and provides a margin of safety large enough for toxicologists not to be particularly concerned about short-term use at exposure levels exceeding the ADI,

providing the average intake over longer periods does not exceed it' (WHO, 1987).

and:

'It is impossible to make generalisations concerning the length of time during which intakes in excess of the PTWI (provisional tolerable weekly intake) would be toxicologically detrimental.

Any detrimental effect would depend upon the nature of the toxicity and the biological half-life of the chemical concerned' (WHO, 1989).

The following discussion on the significance of exceeding the ADI applies equally to other recommended limits of intake or exposure, such as TDI or PTWI.

Three questions should be considered if there are potential exceedances of the ADI:

- What proportion of the population should be allowed to exceed the ADI?
- To what extent can the ADI be exceeded without any real concern?
- How long does the person need to exceed the ADI before there is a cause for real concern?

The significance of any minor excursions of intake above the ADI can only be put into context by reference back to the animal data and to the NOEL which gave rise to the ADI (Renwick and Walker, 1993, p. 464).

Renwick and Walker describe three parameters governing the precision of the NOEL:

- the sensitivity of the toxicological end point which depends on the incidence of the lesion in control animals and/or its inter-animal variability;
- the group size studied which tends to be less important than;
- the increment between doses. There may be considerable increments between doses and this can result in a NOAL that can be significantly lower than the actual or absolute NOEL.

Commonly, a NOEL will be chosen from a dataset which contains a number of repeat-dose toxicity studies, and this is likely to increase the precision of the NOEL. For a discussion on issues in the selection of the most appropriate overall NOEL/NOAL see Section 11.2.

Renwick and Walker (1993) conclude that the significance of the exceedance must be assessed on a substance-specific basis and by reference to the toxicological (and especially the NOEL) data.

9.6.1 Appraisal of short term exposures

Consideration will need to be given as to whether excursions above the Tolerable Intake provide an acute risk.

Tolerable intakes refer to long-term, usually lifetime, exposures. There may be a need to assess risks from short-term exposures. To assist in such appraisals, acute Reference Doses are being developed (WHO, 1997). These are an estimate of the amount of a substance in food or drinking water, expressed on a body-weight basis, that can be ingested over a short period of time, usually during one meal or one day, without appreciable health risks to the consumer on the basis of all known facts at the time of the evaluation (WHO, 1997). In the first instance acute Reference Doses are being set for pesticides.

The most relevant endpoint to establish an acute reference dose depends on identifying the best relevant study on a case-by-case basis.

The following types of studies will need to be assessed when establishing an acute reference dose:

- acute oral toxicity (LD₅₀) studies;
- short term studies of toxicity;
- developmental toxicity studies;
- reproductive toxicity studies;
- human data; and
- mechanistic studies (WHO, 1997).

Appraisal of Assessments

10.1 Introduction

Accurate and timely site-specific health risk assessments depend upon coherent and logically developed reports. The Commonwealth, States and Territories and Local Government should require standardised formats modelled on material in Section 8.5 - 'Environmental Sampling and Analysis' part of this document. Section 8.7 can be used as a checklist to be completed by the health risk assessor.

Reports should be:

- timely;
- comprehensive in their appraisal of all relevant data; and
- clear in their content and conclusions.

Reports do not create confidence in their content and are likely to experience rejection or delays in appraisal by regulators if they:

- obfuscate;
- do not meet appropriate levels of coherence or logic; or
- do not meet the requirements of the standardised formats or the checklist of health risk assessment contents.

The general attributes of a good report are:

- the scope and objectives of the report are explicitly stated;
- the report's content is laid out impartially, with a balanced treatment of the evidence bearing on the conclusions;
- the risk assessment presentation includes a description of any review process that was employed, acknowledging specific review commentary;
- the key findings of the report are highlighted in a concise executive summary;
- the report explains clearly how and why its findings differ from other risk assessment reports on the same topic; and

- the report explicitly and fairly conveys scientific uncertainty, including a discussion of research that might clarify the degree of uncertainty.

As the risk assessment process is intended to assist risk managers in decision-making, a key test will be whether the risk assessment report achieves that aim.

(AIHC, 1989)

10.2 General Appraisal

A person reviewing or authoring an assessment will consider questions such as:

10.2.1 Key aspects

Have the objectives of the report been defined clearly?

- Is there a clear understanding of the relevant current or future human activities and whether any constraints (e.g. encumbrances, exclusions) will be acceptable?
- Was the environmental sampling reasonably sufficient to identify, to locate, to demarcate and to characterise any potential hazardous agents?
- Is it clear how results of any environmental sampling plan were analysed and interpreted?
- Have data been analysed *en masse* or for the appropriate environmental strata?
- Were environmental fate and transport mechanisms understood?
- Have the data been 'modelled' to demonstrate a three-dimensional understanding of what is occurring?
- How were abnormal results or findings managed?
- Were the uncertainties of the assessment identified and understood?

(adapted from Langley, 1993a, p. 28)

10.2.2 Interpretation of sampling data

An appraisal of data must show an understanding of:

- the context of the risk assessment;
- the topography of the situation;
- the demography of the population;
- environmental factors such as stratification of water bodies, movement of plumes in air or groundwater, soil structure (e.g. presence of clay or fill, and the depths of individual strata), meteorological factors, groundwater flows; and
- the relevant current or future human activities.

Too often numerical data are considered in isolation from other key parameters such as:

- the levels of detection (and reporting);
- quality assurance for the data;
- the uncertainty about the data;
- the geographical relationship of one sample to another; and
- the current or potential human activities.

Other key failings in the analysis of numerical data include:

- Ignoring negative or unexceptional results by focussing on unusual or elevated results: the data set needs to be considered in its entirety;
- Inadequately managing censored data e.g. by assigning a zero value to results below the level of detection or reporting; and
- Accepting relatively high levels of detection or reporting so that the value of much data is obscured. This may have the consequence of failing to reveal gradients that will help to highlight the presence and location of environmental 'hot spots'. Examples have been seen where environmental health criteria levels have been treated as the level of reporting. The very existence of levels of detection and reporting results in the censoring of data.

Censoring of data can be particularly important when the maximum permitted criterion is close to the level of detection (e.g. with potable drinking water standards). The censoring of data must be addressed in an appropriate way (See Section 8.5.14).

Given two similar results, the result that can be explained (e.g. by history, or similarities with results from similar strata) will tend to be of less concern than the result that cannot be explained (Langley, 1993a).

10.2.3 Use of subjective terms

The use of subjective terms in reports (e.g. 'heavy/medium/light contamination') or terms that are used in common parlance but may have legalistic definitions (e.g. 'contamination') are confusing and should be avoided in reports. The use of the term 'hot spot' can result in misleading perceptions of concentrations and the term should be used prudently.

10.3 Specific Appraisal

The following is a checklist adapted from EPA NSW (1998) and Vic EPA (1997a) and should be addressed in human health risk assessments.

10.3.1 Data collection

- Have the objectives of the risk assessment been stated?
- Has the background to the events leading to the risk assessment been provided?
- Have all agent of potential concern been identified and appraised?
- Have all appropriate sources of information regarding chemicals of potential concern been identified and appraised?
- Has justification been given for the selection of the agents of potential concern? Has justification been given for the omission of agents from the analysis?
- Have the sources of the agents been identified?
- Have the environmental fate and transport of the agents been identified?

10.3.2 Hazard identification and dose–response relationship

The general components in an acceptable risk assessment are:

Hazard identification

- All relevant information is presented and reviewed.
- The report highlights critical aspects of data quality.
- A weight-of-the-evidence approach is presented for judgement as to the likelihood of human carcinogenic hazard and includes a clear articulation of the rationale for the position taken.
- The report identifies research that would permit a more confident statement about human hazard.

Dose–response relationship

- Valid data sets and plausible models for high-to-low dose and interspecies extrapolation are presented in dose–response modelling.
- The report offers an explicit rationale for any preferred data set(s) and model(s) used in dose–response evaluation; strengths and weaknesses of the preferred data sets are discussed, and scientific consensus or lack thereof is indicated for critical issues or assumptions.
- The report reveals how dose–response relationships change with alternate data sets, assumptions, and models.

(AIHC, 1989)

Specific considerations are:

- Have all relevant toxicological facts been checked for accuracy and currency?
- Has the adequacy of the available toxicological database been appraised?
- Have the effects on each significant body system (for example, renal, hepatic, cardiovascular,) and the types of effects

(for example, allergy, genotoxicity and carcinogenicity, reproductive and developmental) been appraised and summarised for the relevant exposure routes?

- Has the critical toxic effect(s) and organ/body system been identified?
- Have known toxicity modifying factors (such as synergistic and antagonistic effects resulting from exposure to multiple contaminants) been considered?
- Have toxicologically sensitive sub-populations been identified?
- Has the toxicological basis of the guidance value or potency factor, where applicable, been discussed and the uncertainties noted?
- Have NHMRC (where applicable) or WHO toxicological assessments been considered as the primary toxicological resource?
- Where relevant, have differences between, for example, WHO and US EPA toxicological assessments been appraised and discussed?
- Has the dose–response relationship for agents of potential concern been appraised and discussed?
- Have the data been presented in a form amenable to efficient interpretation and review?

10.3.3 Exposure assessment

The general components in an acceptable risk assessment are:

- the purpose and scope of the exposure assessment and the underlying methodologies are clearly described;
- the specific populations and sub-populations that are the subjects of the assessment are clearly identified, and the reasons for their selections and any exclusions are given;
- available data are considered and critically evaluated, and the degree of confidence in the data expressed. (Reasons for any data exclusion are presented.);

- if models are used, their bases are described, along with their validation status;
- potential sources, pathways, and routes of human exposure are identified and quantified; the reasons why any are not included in the assessment are presented;
- central estimates and, if possible, upper and lower bounds on exposures for the full population, and the distribution of exposures are described; any preferred estimates are noted, together with supporting documentation;
- uncertainties in the estimates are described, and the relative importance of key assumptions and data is highlighted;
- research or data necessary to improve the exposure assessment are described;
- the purpose and scope of the exposure assessment and the underlying methodologies are clearly described;
- the specific populations and sub-populations that are the subjects of the assessment are clearly identified, and the reasons for their selections and any exclusions are given;
- available data are considered and critically evaluated, and the degree of confidence in the data expressed. (Reasons for any data exclusion are presented.);
- if models are used, their bases are described, along with their validation status;
- potential sources, pathways, and routes of human exposure are identified and quantified; the reasons why any are not included in the assessment are presented;
- central estimates and upper and lower bounds on exposures or, if possible, the full population, distribution of exposures are described; any preferred estimates are noted, together with supporting documentation;
- uncertainties in the estimates are described, and the relative importance of key assumptions and data is highlighted; and

- research or data necessary to improve the exposure assessment are described. (AIHC, 1989)

Specific considerations are:

- Has the potentially exposed population been identified?
- Have potentially exposed, unusually susceptible sub-populations been identified?
- Have the estimates of chemical exposure for each significant exposure route and for each chemical of potential concern been adequately quantified and tabulated?
- In cases of presumed insignificant exposure, has the exposure been demonstrated to be small?
- Has the relative significance of each exposure pathway, based on the risk analysis, been discussed?

10.3.4 Risk characterisation

The general components in an acceptable risk assessment are:

- the major components of risk (hazard identification, dose–response, and exposure assessment) are presented in summary statements, along with quantitative estimates of risk, to give a combined and integrated view of the evidence;
- the report clearly identifies key assumptions, their rationale, and the extent of scientific consensus; the uncertainties thus accepted; and the effect of reasonable alternative assumptions on conclusions and estimates;
- the report outlines specific ongoing or potential research projects that would probably clarify significantly the extent of uncertainty in the risk of estimation;
- the report provides a sense of perspective about the risk through the use of appropriate analogy;
- the major components of risk (hazard identification, dose–response, and exposure assessment) are presented in summary statements, along with quantitative estimates

of risk, to give a combined and integrated view of the evidence;

- the report clearly identifies key assumptions, their rationale, and the extent of scientific consensus; the uncertainties thus accepted; and the effect of reasonable alternative assumptions on conclusions and estimates;
- the report outlines specific ongoing or potential research projects that would probably clarify significantly the extent of uncertainty in the risk of estimation; and
- the report provides a sense of perspective about the risk through the use of appropriate analogy. (AIHC, 1989)

10.3.5 Equations

- Have all equations used in the risk assessment been presented in the report?
- Are all equations consistent?
- Have all parameters in each equation been clearly defined?
- Have the correct units been allocated to each parameter?
- Are all equations dimensionally correct?
- Have all unit conversion factors, where applicable, been included in the equations?
- Has all pertinent information been provided to enable calculations to be checked through in a stepwise process?

10.3.6 Data evaluation

- What were the data collection objectives and are they consistent with the requirements of the risk assessment?
- Have the laboratories that did the chemical analyses been noted, and do they have NATA, or equivalent, accreditation to perform the chemical analyses?
- Has laboratory QA/QC been reported and analysed?
- Has field QA/QC been reported and analysed?

- Where appropriate, has the size of a 'hot spot' detectable by the sampling pattern been stated?
- Have statements of the accuracy of the laboratory data for each agent been made?

10.3.7 Assessment and report presentation

- Have all tables and figures been referred to correctly in the text of the report?
- Has information from previous reports on the situation been appropriately selected and incorporated into this report?
- Has irrelevant information from other situations been excluded from the report?
- Have all assumptions and default data been identified and justified?
- Has the analysis been based on an up-to-date literature appraisal?
- Have all conclusions been justified?
- If toxicological data and the exposure scenario lead to the conclusion that a high concentration of agent is permissible, does the result violate ecological, aesthetic, land-use or physical principles?
- Has a risk management decision(s) been made during the course of the risk assessment and, if so, how might it (they) have influenced the calculation of risk?
- Has a detailed uncertainty discussion been included in the report?
- Has information been presented coherently and in an appropriate sequence, to enable efficient appraisal of the report?
- Does the report include or enable ecological risk assessment as required by regulatory authorities?
- What has been the involvement of the public?
- How has information been communicated to the public?
- What processes of community consultation have taken place?

Setting Environmental Health Criteria

11.1 Principles for Setting Criteria

Much of what is talked about in the context of risk assessment, i.e. setting of criteria and ADIs and such, amounts to decision-making which should more accurately be considered risk management if we are to subscribe to our goal of keeping the risk assessors focused on the scientific evidence rather than on making the tough choices inherent in risk management. There is not a risk assessment model that can set environmental health standards; one should only seek to have one that can inform risk management decisions about criteria.

The principles in this chapter detail the processes by which criteria can be established. Generic environmental health criteria developed using this methodology require endorsement by appropriate national health bodies. Situation-specific environmental health criteria developed using this methodology require endorsement by the appropriate health agency before being applied to a particular situation.

Elements of the risk assessment methodology provide a framework for setting risk-based environmental health criteria. A series of risk assessments using a range of assumptions will provide the sensitivity analysis for the criterion-setting process i.e. by varying the assumptions about dose–response and exposure the effects on population risk from different possible criteria can be assessed. ‘Hazard Identification’ establishes the key hazards of concern. ‘Dose–Response’ information (from the scientific literature) and ‘Exposure Assessment’ (using a range of possible values that will reflect the possible values of the criterion) provide the basis for the ‘Risk Characterisation’ which explains the nature and magnitude of the impact from the key hazards of concern at specified exposure levels on the population to whom the criterion will be relevant. ‘Risk Characterisation’ will also detail the uncertainties and assumptions underlying the criterion.

When establishing criteria key issues to be considered are:

- Why is a criterion being proposed?
- Is a criterion necessary? Are there alternative means of achieving the desired outcome? The large improvements achieved by the Clean Air Act (1956) in the UK occurred without any air quality standards;
- How will the criterion be used? Is the criterion to be used as a guideline or a standard? Standards often have greater legal or regulatory standing than guidelines;
- Is the criterion to be generic (applying to many situations) or situation-specific?
- Who will be involved in setting the criterion?
- What population(s) will be affected?
- Are there any sensitive or particularly susceptible sub-populations who are exposed?
- Over what period of time will the population be exposed to the agent for which the criterion is being set?
- What patterns of exposure are likely to occur? Are there likely to be short or long term fluctuations?
- Are background exposures higher than the Tolerable Intake? (Given the size of the safety factors used in the development of Tolerable Intakes, has this had any health consequences for the population? Should actual experience be used in preference to Tolerable Intakes?)
- Are there difficulties in getting relevant and accurate background exposure data?
- How do you deal with Tolerable Intakes so low that they can’t be measured (e.g. for some alkaloids)?
- What are the consequences of setting criteria at the level of detection?
- How can Tolerable Intakes, which are usually based on ingestion, be applied to other exposure routes?
- Has the Tolerable Intake been set using gavage or bolus administrations rather than

administration as part of the diet? Has the substance been administered with an oil carrier or food?

- How is exposure occurring?
- How do you deal with multiple pathways of exposure such as the relatively high exposures in tobacco smoke compared to dietary sources?
- How do you apportion exposures? In Canada, for criteria setting, 20 per cent of total exposures is allowed of each of food, air, water, soil and consumer products;
- Can exposures be altered? How?
- What is the critical health effect? What is its nature, severity and reversibility?
- Are interactions with other agents relevant?
- What are the background levels of exposure to the agent?
- Are there sufficient data to establish a criterion?

A decision tree detailing the use of Health Risk Assessment to develop risk-based environmental health criteria is provided in Figure 9. This model uses a Guidance Value (e.g. ADI) which is apportioned between background exposures and exposures relevant to a particular exposure pathway (e.g. food, water, air or soil). This approach is based on chronic or subacute exposures. It may not be applicable for acute exposures e.g. when dealing with a respiratory irritant.

A slightly different approach will be required where acute exposures may cause the hazard of concern to become manifest. Examples are: setting microbiological standards for water and food where acute exposures precipitate disease; the setting of criteria for sulfur dioxide in air where acute exposures may cause exacerbation of asthma; and, the setting soil values for nickel or chromium (VI) both of which may cause allergic reactions from acute exposures in sensitised

individuals. It is particularly relevant where the susceptible sub-population comprises a significant proportion of the total population; for example, approximately 20 per cent of Australian children have asthma and 10 per cent of women are allergic to nickel. In these situations Guidance Values (which, by definition, are based around long term exposures) will be irrelevant and unsuitable for use. However the remainder of the risk assessment process will still be relevant for establishing criteria.

For most criteria there is a significant margin of safety between the criterion and typical exposures. Safety is enhanced by a further margin of safety arising from the process by which Guidance Values are set. However for some agents, health effects may arise from background exposures (e.g. exacerbation of asthma from urban ozone exposures) and in these instances a risk management decision will need to be taken of the incidence of adverse health effects in the community.

For many agents, there may be several exposure pathways. Copper will be found in water and food (and, of lesser importance, in food and consumer products) so that setting a criterion for copper in another medium (e.g. soil) or a particular foodstuff (e.g. shellfish) will need to take into account the range of other potential exposure pathways. Intakes may need to be apportioned between the different exposure pathways. The apportioning of intakes raises other questions:

- What percentage of the total Tolerable Intake should be used for establishing a set criterion? Inter-agency cooperation will be required to enable appropriate apportionment.
- What is the nature of the background exposures? Are they fixed or changing over time? Are they able to be altered? Are they voluntary (e.g. smoking) or involuntary (e.g. ambient air pollution)? To what degree should voluntary background exposures be taken into account?

11.2 Determination of NO(A)ELs, ADIs (RfD) and TDIs for Humans

The determination of an acceptable daily intake (ADI)⁵ involves the establishment of an overall NOEL/NOAEL for a chemical which is generally the lowest NOEL/NOAEL in the most sensitive species. This approach of using the lowest NOE(A)L is justified unless there is evidence:

1. from pharmacokinetic/metabolic studies that the most sensitive species shows a different toxicokinetic behaviour than humans and is therefore less relevant as a predictor of human toxicity than another toxicity test species; or
2. that the toxic effect which has the lowest NOEL/NOEAL is not relevant for humans; or
3. that the lowest NOEL/NOAEL is derived from an inadequate or invalid study.

Thus it is emphasised that the full database must be used and all relevant findings correlated, when determining the most appropriate health end-point.

It is important to note also that in public or occupational health risk assessments, the establishment of a NOEL/NOAEL is likely to be influenced by a consideration of the relevant route(s) of exposure.

An ADI or TDI is then derived from the NOEL/NOAEL; the qualitative approach taken follows the principles outlined in the IPCS Environmental Health Criteria Monograph No. 104 (WHO, 1990). The uncertainty inherent in extrapolation between and within species has generally been dealt with by the use of safety (uncertainty) factors. These factors generally range from 10 to 2000, depending on the source and quality of data, the biological relevance of the end-point, and the hazard assessment (carried out on a case-by-case basis). Safety factors are not necessarily rigidly applied; the usual safety factor is 100, derived by having a factor of 10 for species

extrapolation and a factor of 10 for individual variation in human populations. In general terms only, a safety factor of 10 would apply when appropriate human data were available and, utilising further safety factor of 10–20, an overall safety factor of 1000–2000 may apply if, for example, the toxicological database is incomplete or the nature of the potential hazards indicate the need for additional caution. The ADI (RfD) is calculated by dividing the NOEL/NOAEL by the safety factor. This approach assumes that exposure at less than the ADI is without appreciable risk but there is no attempt to quantify the level of risk.

For agricultural and veterinary chemicals, once a NOEL/NOAEL has been established and the ADI estimated, a maximum residue level (MRL) for food and, in some cases, water can be established. The MRL is the maximum concentration for a residue resulting from the use of a chemical according to good agricultural practice that is legally permitted or recognised as acceptable in or on a food, agricultural commodity or animal feed; the object of establishing an MRL is to keep human intake to a minimum; thus the MRL for a particular chemical may be set well below the level which would result in intake equivalent to the ADI.

Where data sets allow appropriate analysis, alternative procedures such as the Benchmark Dose or Effective Dose (ED_x) may be used by regulatory agencies in calculating health end-points.

11.3 Determination of Risk-Based Environmental Health Criteria

Risk-based Environmental Health Criteria should be determined taking into account:

1. The bioavailability of a substance. The bioavailability should be assumed to be 100 per cent if specific information is not available;
2. The Provisional Tolerable Weekly Intake (PTWI) or Acceptable Daily Intake (ADI) as determined by the World Health

⁵ US terminology is 'Reference Dose', or RfD.

Organisation/Food and Agriculture Organisation (1987, 1994), or Guideline Dose (GD) for cancer toxic effects as determined by national health advisory bodies; and

3. Other potential sources of the substances that comprise a proportion of the PTWI or ADI, or GD (e.g. background levels of the substance in food, water, air; and the amount of exposure through these routes) (ANZECC/NHMRC, 1992; Imray and Langley, 1998).

The total exposure to a substance 'X' can be represented by the equation:

$$\begin{aligned}
 \text{'Exposure to substance X'} &= \text{BE} \\
 &+ \text{Exposures from contaminated medium by ingestion, inhalation and skin absorption} \\
 &= \text{BE} \\
 &+ \text{amount of substance absorbed from medium.} \\
 &= \text{BE} \\
 &+ (M_{\text{ing}} \times C_{\text{ing}} \times B_{\text{ing}} + M_{\text{inh}} \times C_{\text{inh}} \times B_{\text{inh}} + M_{\text{skin}} \times C_{\text{skin}} \times B_{\text{skin}}) \\
 &= \text{BE} + \text{ME}_{\text{medium}}
 \end{aligned}$$

- BE = Background Exposures (e.g. from food and water).
- M_{ing} = Amount of medium ingested.
- M_{inh} = Amount of medium inhaled and retained.
- M_{skin} = Amount of medium on skin.
- C_{ing} = Concentration of substance in medium ingested.
- C_{inh} = Concentration of substance in medium inhaled and retained.
- C_{skin} = Concentration of substance in medium on skin.
- B_{ing} = Bioavailability, i.e. percentage absorbed, of substance when ingested.

B_{inh} = Bioavailability of substance when inhaled.

B_{skin} = Bioavailability of substance when on skin.

$\text{ME}_{\text{medium}}$ = Substance exposure from medium.'

(ANZECC/NHMRC, 1992, p. 37)

Different levels of bioavailability will occur between the medium ingested, inhaled or in contact with skin.

National environmental health criteria will be set by national health advisory bodies. A variable percentage of the TI will be allowed for exposure to the contaminated medium. This is consistent with the IPCS approach and that used in the four Australian workshops on the health risk assessment and management of contaminated sites.

When the PTWI/ADI is used for establishing investigation levels for individual contaminants, the basis for the PTWI/ADI should be sought from appropriate documents (e.g. WHO, 1987; WHO, 1989). This information should include target organ(s) and effect(s) (e.g. nature, reversibility, and severity, LOAEL for most significant toxic effect); bioavailability; and safety factors accounting for variations in human sensitivity and extrapolations from animal studies.

When a Guideline Dose is derived using the NHMRC 'Toxicity Assessment Guidelines for Carcinogenic Soil Contaminants', the basis for the derivation should be fully documented. Guideline Doses for soil contaminants with cancer effects will be determined by national health advisory bodies or their appointees.

If no PTWI, ADI, or GD is available a specific approach acceptable to the relevant health agencies will need to be determined using WHO (1994) for non-carcinogens, or NHMRC 'Toxicity Assessment Guidelines for Carcinogenic Soil Contaminants' for substances with cancer effects and used for calculations.

It is considered that these methods for determining Risk-based Environmental Health Criteria should protect the entire population with few exceptions. Where a significant proportion of the population demonstrates allergic sensitisation

to a substance (e.g. nickel) this will need to be considered in criteria setting. People who may have unusual sensitivity to agents may need to be considered in a risk assessment (Imray and Langley, 1996).

Similar principles can be used for determining Risk-based Environmental Health Criteria for contaminants with and without cancer toxic effects if a Tolerable Intake is available. The methodology, when applied to soil, was initially endorsed in ANZECC/NHMRC (1992).

Qualifications to setting the Risk-based Environmental Health Criteria are:

- In setting a Risk-based Environmental Health Criteria, total exposure to substance X, (i.e. the sum of the background exposure and the substance exposure from the medium) should not exceed the ADI or PTWI, [or GD] i.e. $BE + ME_{\text{medium}} < ADI$ or $PTWI$, [or GD].;
- The degree to which exposures at a proposed Risk-based Environmental Health Criteria are below the ADI or PTWI, or GD will be set by national health advisory bodies and will depend on factors such as: the nature of the adverse effects, the completeness of toxicological data, exposure variability within a population and the relative sizes of BE and ME_{medium} ; and
- It should be recognised that '...short-term exposure to levels exceeding the PTWI is not a cause for concern provided the individual's intake averaged over longer periods of time does not exceed the level set' (WHO, 1989, p. 9). (adapted from NEPC, 1999)

11.3.1 An Australian model for setting criteria for carcinogens

The following material is drawn, with amendment, from the NHMRC 'Toxicity Assessment Guidelines for Carcinogenic Soil Contaminants' (1999, p. 1–16) which was prepared by a Technical Working Party (TWP).

This approach is consistent with other international risk assessment methodologies. The development and use of an agent-specific Guideline Dose is consistent with current risk assessment practice in Australia as well as with international practice. For example, the Guideline Dose and its use in risk assessment is analogous to the Acceptable Daily Intake (ADI) and the US Reference Dose (RfD). The Benchmark Dose approach is proposed in the Draft Revision to the guidelines for carcinogenic risk assessment (US EPA, 1996).

11.3.2 Background

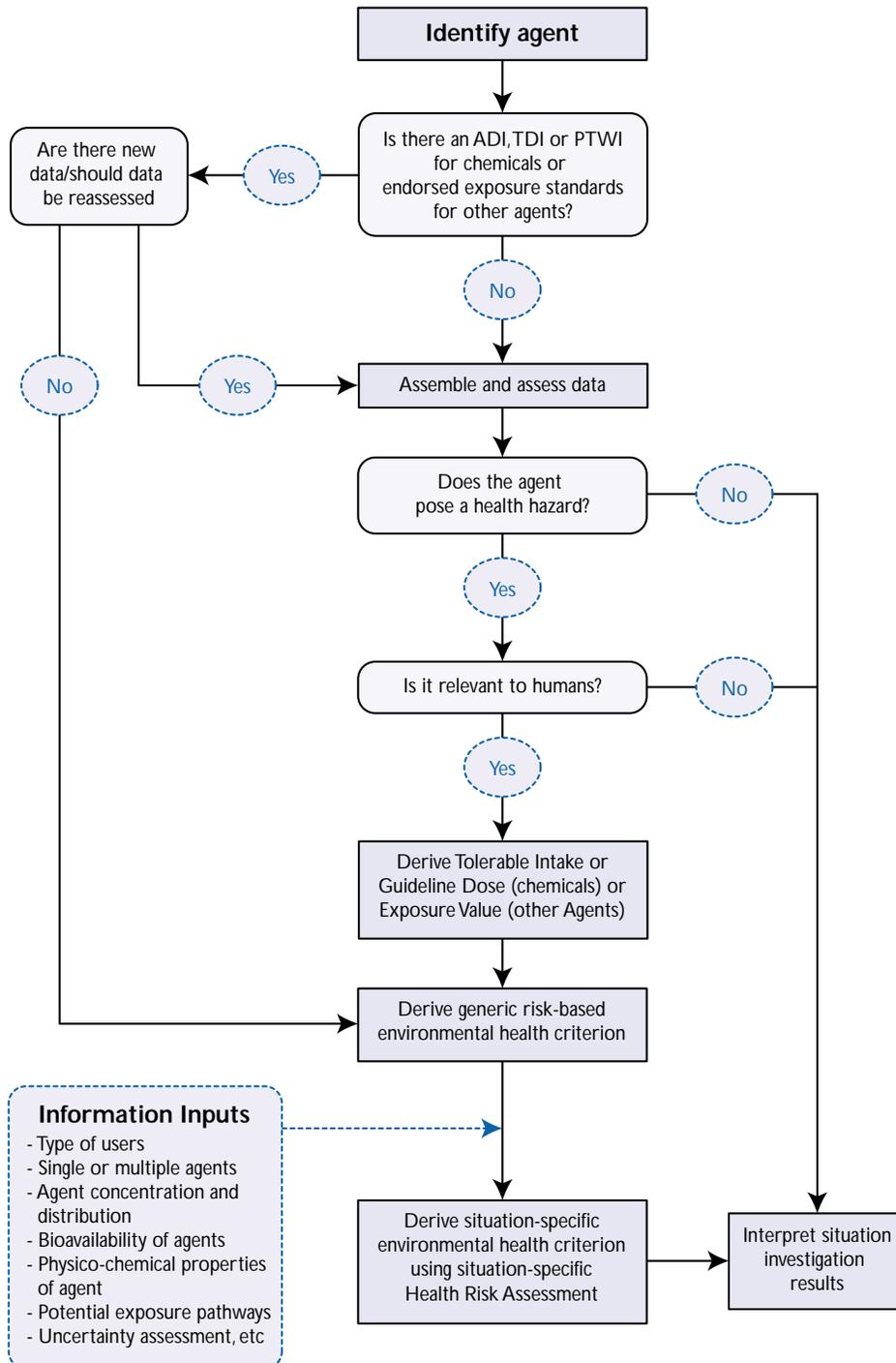
The traditional benchmark dose methodology (traditional BMD) has been developed over the last two decades and is now being given serious consideration as a useful tool in risk assessment (Dourson, 1984; Barnes *et al*, 1995; US EPA, 1995a; 1996). More recently, the approach has also been proposed for cancer risk assessment (e.g. US EPA, 1996)

The methodology for use in Australia avoids some of the limitations inherent in existing cancer risk assessment methods. In particular, the methodology optimises the advantage of using all relevant scientific data in the decision-making process and provides for a clear separation and justification of the major components of the process: public health policy; professional judgement; and scientific principles and data.

The methodology is a two step process. Firstly, the modified-BMD is derived from the experimental data. Secondly, the modified-BMD is divided by cumulative factors to derive a Guideline Dose for human exposure.

The modified-BMD is set using 5 per cent extra risk determined from animal or epidemiological studies. This extra risk is then divided by a series of modifying factors (potentially up to 50,000) after consideration of all the available toxicological data according to a specified decision tree to derive an agent-specific Guideline Dose protective of public health. These factors relate to inter- and intraspecies variation, quality of the database and other factors for the seriousness of

Figure 9: Decision Tree for the development of risk-based environmental health criteria



the carcinogenic response. The factors are derived according to a decision tree which takes into account all of the available data; and uses scientific judgement to address a number of the uncertainties in the risk assessment process and to develop safety factors.

All available, relevant information should be used in the risk assessment process. In cases where there are few or inadequate data, conservatism may be justified and the use of conservative (default) assumptions is supported.

Recommendations on default assumptions are provided for cases where the data are incomplete to bridge data gaps and allow the risk assessment to proceed. All choices, both those based on scientific data and those based on default assumptions, must be supported by reasoned and critical analytical arguments.

The Guideline Dose is established by regulatory authorities and is defined as the daily intake of a chemical agent which, during a lifetime, is unlikely to result in cancer, based on a comprehensive expert assessment of the best information available at the time. It is considered that the Guideline Dose is protective of public health.

The Guideline Dose may be used in the development of health investigation levels, response levels and risk characterisation of human exposures to contaminants in soil.

The Guideline Dose does not attempt to model or predict a response incidence at low environmental exposure. It is an estimate of the dose which is considered protective of public health (the use of compounding factors assures a high level of safety). This places the focus of regulation on the control of exposure to environmental contaminants rather than calculation or discussions of risk. This approach has the added benefit of allowing comparisons with guidance values based on non-cancer health effects for chemical agents.

A numerical value that would constitute an acceptable level of risk for low-level environmental exposure to carcinogens is not recommended. Whilst there has been

considerable debate over the last twenty years about what constitutes an acceptable risk, there is no agreed position internationally on this issue (see Department of the Environment, 1993).

The problems of nominating an acceptable level of risk are compounded by the inability of current methods to accurately quantitate risk at low levels of exposure and hence to provide an accurate value that can be compared to 'an acceptable level of risk'.

Key points about the methodology are:

- Maximum use is made of scientific information, while not requiring the assessor to make a judgement regarding the existence of a biological threshold, nor perform mathematical dose-response modelling well below the range of experimental data because the dose associated with 5 per cent extra risk is set near the lower limit of responses that can be measured experimentally. With the proposed methodology, it is not necessary to resolve the uncertainties, difficulties and controversies associated with mathematical extrapolation to low doses outside the range of experimental data.
- The approach is relatively model-independent when compared with methods which extrapolate to extremely low doses in the sense that the values of the *modified*-BMD which are determined are not greatly influenced by the mathematical model chosen. Therefore, different models can give the data a similar goodness of fit. In contrast, extrapolation well below the experimental range by other quantitative risk assessment methods is very much model dependent and results are highly variable with different models (Maynard *et al*, 1995).
- The *modified*-BMD is standardised to one level of extra risk (i.e. 5 per cent), allowing comparisons of potency between carcinogens in the observed dose range in the animal bioassay or other modelled data. In addition, extra risk in the observed range can be compared between carcinogens for a given dose.

- The *modified*-BMD method is applied to both genotoxic or non-genotoxic carcinogens. In addition, it readily allows for the direct use of mechanistic data when an appropriate mechanistic model relating to dose–response can be developed. The TWP considered that the distinction between genotoxic and non-genotoxic features of carcinogens is relevant to public health protection and should be considered in the cancer risk assessment, but not in determining the shape of the dose–response curve at doses well below the experimental range. The genotoxic properties of an agent are an important part of the assessment and are accounted for in the consideration of the seriousness of the carcinogenic response.
- The *modified*-BMD is a numerical estimate of the dose associated with a particular response and by itself does not reflect the uncertainties inherent in biological data. Due care should be taken to describe the uncertainties (Lu and Sielken Jr, 1991).
- If cancer or genotoxicity was not a consideration in deriving the value and current scientific information does not change the judgement that cancer should not be considered, then use the ADI, PTWI or TDI as described elsewhere for adverse effects other than cancer (ANZECC/NHMRC, 1992):
- If the carcinogenic or genotoxic properties of the chemical agent were assessed and considered in deriving the guidance value, the derivation of the guidance value (and any compelling new scientific evidence) should be reviewed and a decision made whether or not the toxicological properties of the substance should be reassessed. If yes, proceed to step 3. If no, then use the ADI, PTWI or TDI as described elsewhere for adverse effects other than cancer (ANZECC/NHMRC, 1992).

If no ADI, PTWI or TDI is available, proceed as follows:

The methodology can be compared to non-threshold models currently in use which assume low dose linearity (e.g. the US EPA methodology). (See comments on non-threshold model, Section 5.5, page 95).

11.3.3 General principles of the methodology

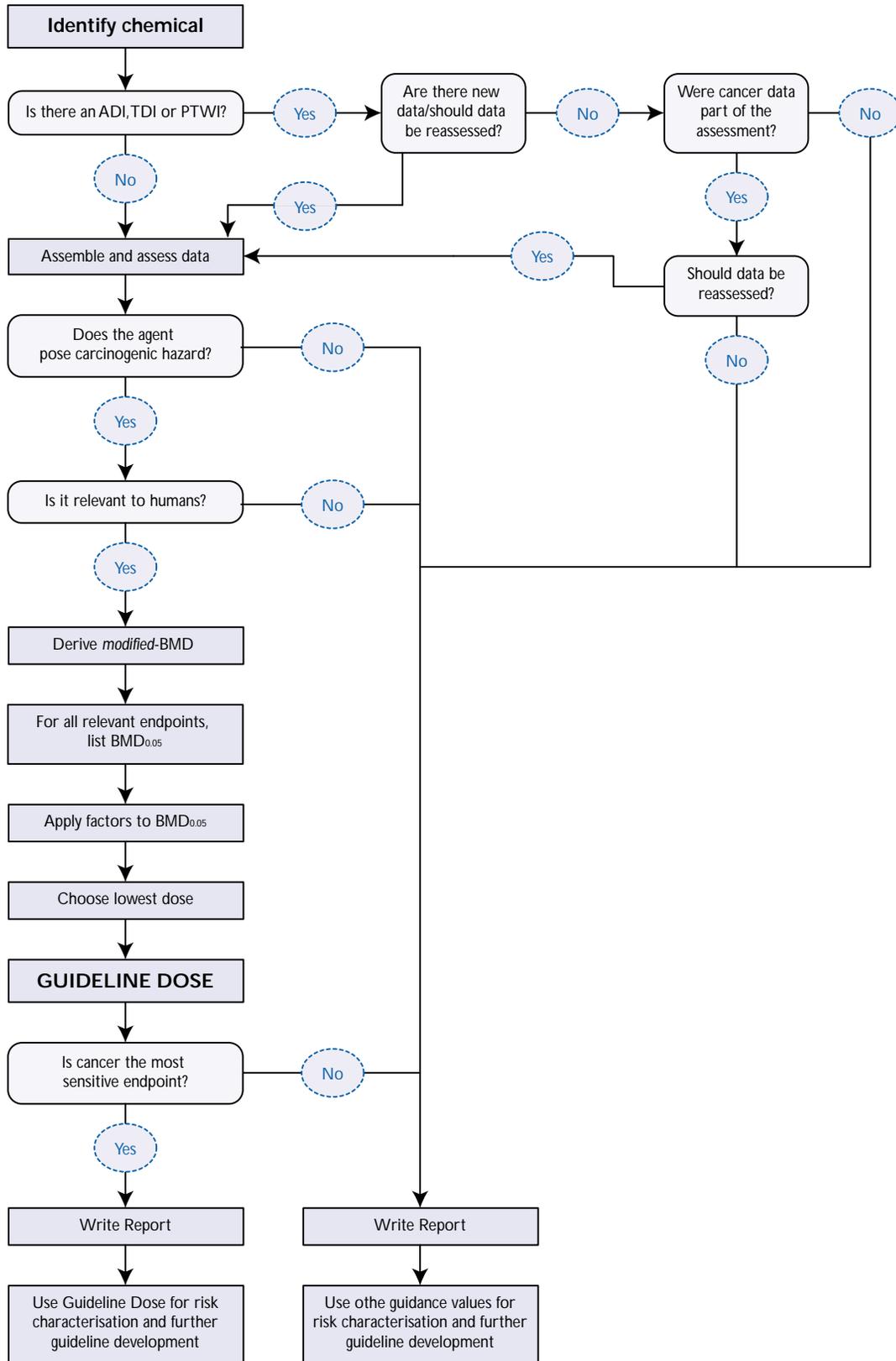
1. Identify the relevant soil contaminants.
2. For each of the contaminants, check whether an ADI, PTWI or TDI has been set by the WHO. In cases where an ADI, PTWI or TDI is available, then:
 - Ascertain whether there are new data which should be assessed or whether the derivation of the tolerable intake should be reviewed. If yes, proceed to step 3.
3. Search the peer-reviewed scientific literature or any other, scientifically sound, available source to find all relevant data. Assess the adequacy of data collected to determine which will be selected for use in undertaking the following steps.
4. Based on studies judged to be adequate, determine whether the contaminant poses a carcinogenic hazard.
5. If the agent does not pose a carcinogenic hazard or if there is insufficient information currently available to make an assessment, no further evaluation of the carcinogenic hazard is needed. Proceed as for adverse effects other than cancer for development of a health-based regulatory value (see Addendum 1). Write findings in the report.

6. If the agent is considered to pose a carcinogenic hazard, determine whether the observed carcinogenic hazards are relevant to humans. If found to be not relevant, no further evaluation of the carcinogenic hazard is needed. Proceed as for adverse effects other than cancer for development of a health-based regulatory value. Write findings in the report.
7. If carcinogenic hazards are considered relevant to humans, apply the *modified*-BMD method and determine a *modified*-BMD for all relevant carcinogenic end-points corresponding to 5 per cent and 1 per cent extra risk.
8. Use route to route extrapolation where appropriate.
9. Derive and apply appropriate factors to calculate Guideline Doses for each *modified*-BMD_{0.05}.
10. Choose the lowest Guideline Dose supported by the highest possible strength and weight of evidence.
11. Compare the Guideline Dose for the cancer end-point with the ADI, PTWI or to determine whether the carcinogenic end-point is the most sensitive one. Use the lowest of these doses for setting health investigation levels or for site specific risk assessment as outlined in the 'Guidelines for Assessment and Management of Contaminated Sites' (ANZECC/NHMRC, 1992).
12. Write the report.

11.3.4 Further actions

Processes are being established to develop and provide Guideline Doses for specific chemicals. As an interim measure, advice on specific chemicals should be sought from the relevant regulatory body. When probabilistic estimates of risk are the only guidance available, there needs to be a full appreciation of the differences between 'real', 'estimated' and 'actual' risk and the limitations of quantitative risk assessment of carcinogens (See Hrudey, 1998).

Figure 10: Decision Tree for cancer risk assessment



Note: appendices refer to NHMRC (1999)
(from NHMRC, 1999)

In the following Appendices, key issues related to the Environmental Health Risk Assessment are detailed.

- Appendix 1—Environmental Health Risk Assessment for Contaminated Sites
- Appendix 2—Environmental Health Risk Assessment for Air Pollutants
- Appendix 3—Environmental Health Risk Assessment for Food
- Appendix 4—Environmental Health Risk Assessment for Water
- Appendix 5—Australian Models of Risk Assessment
- Appendix 6—International Models of Risk Assessment
- Appendix 7—WHO/IPCS Conceptual Framework for Cancer Risk Assessment
- Appendix 8—Microbiological Risk Assessment

Environmental Health Risk Assessment for Contaminated Sites

1.1 Introduction

The risk assessment framework is detailed in Guideline B4 'Health Risk Assessment of Contaminated Sites' in the National Environment Protection Measure for the Assessment of Contaminated Sites (National Environment Protection Council, 1999). Guideline B4 was developed by health agency personnel assisting in the development of the National Environment Protection Measure. Guideline B4 builds on the material in the ANZECC/NHMRC 'Australian and New Zealand Guidelines for the Assessment and Management of Contaminated Sites' (1992).

The framework uses four stages that are compatible with the five stages in this document. The four stages are Data Collection; Toxicological Assessment; Exposure Assessment; and Risk Characterisation. 'Data Collection' is an equivalent component of 'Identifying the Issues' and 'Toxicological Assessment' is equivalent to the combination of 'Hazard identification' and 'Dose-Response Relationship'.

1.2 Identifying the Issues

1.2.1 Data collection

Contaminated sites usually have a heterogeneous distribution of contamination and the sampling methods and the presentation of the data are critical to a good appreciation of the nature and distribution of the contamination.

1.2.2 Sampling

Random sampling

This may lead to large areas of the site being missed for sampling because of a chance distribution of results. It also neglects prior knowledge of the site (Heyworth, 1991).

Stratified random sampling

By dividing the site into areas and randomly sampling within each area, missing large tracts of land can be avoided (*ibid*).

Stratified sampling

The site is divided and different sampling patterns and densities are used in different sub-

areas. It is useful for large and complex sites (Standards Australia, 1997).

Grid (systematic) sampling

This permits the whole of the site to be covered and for sampling points to be more readily identified for further sampling (Heyworth, 1991).

Judgemental sampling

Sampling is localised to areas identified from knowledge of the site. There needs to be a high level of confidence in the reliability of information about the site and that the information reflects the current state of the site (*ibid*).

The statistical advantages of a stratified random grid have been discussed by Heyworth (1991). Against the statistical advantages, are the difficulties in surveying a site (and hence also relocating sampling points if this proves necessary) and the inability to draw vertical cross-sections of the site. Being able to draw cross-sections is useful in predicting the 'dimensions' of the contamination. (van Alphen, 1993). There are some practical difficulties in mapping and conducting the sampling for other than square grids.

Ferguson (1992) critically reviewed a range of sampling designs to determine their performance in detecting a single circular target occupying 5 per cent of the total site area. A herringbone pattern was found more successful than simple random, stratified random, stratified systematic unaligned and regular square grid patterns. Search performance varied with target shape, size and the number of targets. For an elliptical (4:1) target, the performance of a grid pattern was 'greatly degraded when the target lies parallel to the grid directions and, to a much lesser extent, the 45° direction' (p. 36).

Expert judgement will often be the key determinant of the sampling pattern. A random or grid approach should not be used when there is information indicating particular patterns or localisation of an agent. A grid or random sampling will be appropriate when sampling cannot be guided by prior knowledge.

A combination of judgemental sampling and grid sampling may be the most feasible approach for a site. In these instances sampling will be concentrated in areas identified by information with grid sampling providing coverage for the remainder of the setting.

Random or grid sampling will usually be the approach of choice to validate cleanup or intervention although judgemental sampling may be justifiable for assessing particular features in post-intervention sampling.

Information on sampling is also available in: Standards Australia (1997). Australian Standard. Guide to the sampling and investigation of potentially contaminated soil. Part 1: Non-volatile and semi-volatile compounds. AS 4482.1-1997

1.2.3 Sampling density

‘Statistical equations are tools to be used as aids to common sense and not as a substitute for it’ (Keith 1990 page 612). Statistical formulae for determining sampling density are usually based on the requirements that the results will be normally distributed (i.e. in a bell-shaped curve) and that a particular concentration is equally likely to occur at any point. Some analytical techniques require an estimate of the mean of the results and the standard deviation of results before sampling density can be calculated. These requirements can rarely be met during the stages of initial and detailed investigation, as sites are often heterogeneous with a skewed distribution of results.

A considerable amount of expert judgement is required to determine the density of sampling. The final amount will depend on an integrated appraisal of factors including:

- proposed or current activities and users;
- the number of stages of sampling considered feasible;
- the size of the site and final subsites if the site is to be subdivided;
- the distribution of uses on the site and the disposition of structures;

- the site history; and
- potential remediation and management strategies.

If a large site is to be subdivided to smaller residential sites the sampling density on the final sites rather than the initial larger site should also be considered. While sound predictions may be able to be made from the many results available for the larger site which can suggest patterns and trends, more detailed sampling may be needed to address what is occurring on the smaller sites.

1.2.4 Composite sampling

Composite sampling usually interferes with health risk assessment and is generally unsuitable for definitive health risk assessment due to the inherent uncertainties in the resultant data (Lock, 1996).

Localised elevated concentrations can be obscured, the data is harder to interpret without undertaking further single samples, and the compositing process provides an extra opportunity for bias and error. Proposed cost savings can quickly evaporate when further sampling is required to clarify composite results.

Composite sampling should not be used for situation-specific health risk assessments.

Compositing may create a false negative result. For example, if 4 soil samples have individual levels of 5, 5, 5, 165mg/kg, a composite concentration of 45 mg/kg appears to comply with the unadjusted Health-based Investigation Level (HBIL) of 100mg/kg. Comparison with an unadjusted HBIL obscures the presence of a localised elevation and hence the nature of contamination on the site.

Adjusting the soil criterion (e.g. the Health-based Investigation Level) may be done in an attempt to address this problem. If there are 4 constituent samples per composite, the HBIL for arsenic could be divided by 4 so that concentrations are then be compared to $[100/4]$ mg/kg, i.e. 25 mg/kg. However, this may result in false positive exceedances if, for example, natural background levels are elevated but acceptable. If the

background level of arsenic is 35 mg/kg, the concentration determined in an uncontaminated composite manufactured from four samples will exceed the adjusted HBIL of 25 mg/kg. In such a case, the use of composite samples without definitive individual sample analysis may lead to an unnecessary and costly further investigation.

Further information on the problems of, and constraints on, composite sampling is detailed in:

- Lock WH. (1996). *Composite Sampling*. National Environmental Health Forum Monographs Soil Series No. 3. Adelaide: South Australian Health Commission; and
- Standards Australia (1997). *Australian Standard. Guide to the sampling and investigation of potentially contaminated soil. Part 1: Non-volatile and semi-volatile compounds*. AS 4482.1-1997.

1.2.5 Analytical methodologies

General reference

- Manahan SE (1993). *Fundamental of Environmental Chemistry*. Boca Raton: Lewis Publishers
- Perkins JL (1997). *Modern Industrial Hygiene*. Volume 1. Recognition and Evaluation of Chemical Agents. New York: Van Nostran Reinhold.

Specific reference

Analytical methods should be those described in Guideline 3 *Laboratory Analysis of Potentially Contaminated Soils* (NEPC 1999). Guidelines for the laboratory analysis of contaminated sites. Canberra: Australian and New Zealand Environment and Conservation Council. An exception is the method for Total Petroleum Hydrocarbons which will need amending to provide appropriate data for TPH health risk assessment.

1.2.6 Safety plans

The safety of people working on the site and nearby residents must always be considered in environmental sampling. Site safety plans should be developed where there may be risks.

Risks may arise from factors such as:

- dealing with unknown substances;
- deep excavations such as backhoe pits presenting a physical hazard;
- the release of volatile contaminants during excavations or their pooling in excavations;
- generation of dust;
- groundwater surveys can create contamination or cross contamination of aquifers if bores are not appropriately constructed; and
- the presence of underground storage tanks can cause subsidence if corroded or fire and explosion hazards.

The specific reference is:

- National Environment Protection Council (1999). *National Environment Protection Measure for the Assessment of Site Contamination. Guideline 9. Protection of Health and the Environment during the Assessment of Site Contamination*. Adelaide: National Environment Protection Council. This is accessible on www.nepc.gov.au.

1.2.7 Assessment of summary statistic data and presentation of data

Summary statistics

As sites are usually heterogeneous, it is important to have ways of appreciating the nature and distribution of complex patterns of contamination. A combination of summary statistics, graphical display and clear explanatory narrative will be necessary. Table 1 A1 presents several summary statistics for a soil contaminant and highlights the fact that no single summary statistic (e.g. an arithmetic mean or a median) fully characterises a site. Instead a range of summary statistics is needed to build up a picture of a site.

Table 1 A1: Summary statistics for a single analyte and stratum

Stratum: 0–150mm

Chemical name	Pb (Lead) mg/kg	
Number of samples	53	
Range	3 to 5000	
Relevant soil criterion	300	
Median	60	
Arithmetic mean	446	
Arithmetic s.d.	1041	
Geometric mean	85	
Geometric s.d.	6.0	

Frequency distribution^a	n	%
less than soil criterion	37	70
≥1 and <2 times soil criterion	6	11
≥2 and <5 times soil criterion	5	9
≥5 and <10 times soil criterion	1	2
≥10 times soil criterion	4	8

^a An arbitrary method is used to categorise data.

For multiple analytes, an impression of the typical levels, location of contaminants within strata, total 'burden', and statistical distribution of results can be presented as in Table 2 A1.

Censored data

Summary statistics can be biased according to the values substituted into mathematical formulae to allow calculations of, for example, means. Sometimes the value of the level of detection is substituted, upwardly biasing the sample statistics.

Levels of reporting

The first step in dealing with censored data is to ensure that the levels of detection or levels of reporting are appropriate. The levels of reporting must be less than the relevant criteria against

which the results will be assessed. A level of reporting of one tenth of the criterion is preferred but may not be practicable where the criterion is set at a level of detection. They need to be set sufficiently low so as to be able to distinguish trends from background levels. Lower levels of detection may be required for environmentally-based assessments.

The recommended maximum levels of reporting for health risk assessments are detailed in the National Environment Protection Measure for the Assessment of Site Contamination (1999). They are based around the assessment of a 'Standard' Residential Setting but apply to all investigations.

Table 2 A1: Combining sample number, location, depth, multiple analyte results, and extent of variation above the investigation levels in a single table

Locations 7–12: Chemical Screening Results

Depth (mm)	Pb	As	Cd	Cr	Co	Ni	Zn	Cu	Hg	pH
Loc 7										
0–150	200	3	~	100	4	14	210	28	0.25	8.6
150–300	170	3	~	80	6	15	220	100*	0.25	8.7
300–450	10	~	~	60	8	20	34	20	0.05	8.6
Loc 8										
0–150	36	2	~	90	18	75	24	8.0	0.50	8.0
150–300	~	2	~	110	12	28	46	28	0.05	7.6
Loc 9										
0–150	250	3	~	90	4	15	310	50	0.55	8.8
150–300	160	2	~	85	5	13	240	60	0.40	8.4
750–900	4	~	95	11	22	44	26	7.6	-0.05	7.6
Loc 10										
0–150	10	~	~	70	~	8	16	1.0	-0.05	8.3
150–300	24	5	1	85	5	13	34	1.8	0.05	8.1
300–450	12	3	1	90	7	15	30	1.8	-0.05	8.1
750–900	4	~	1	50	6	14	22	1.5	-0.05	8.4
Loc 11										
0–150	290	5	~	80	4	11	540*	24	0.10	8.3
150–300	450*	10	~	85	5	15	760*	1750***	0.70	8.1
300–450	90	5	~	110	9	17	30	1.9	0.05	7.8
	12	2	~	110	9	17	30	19	0.05	7.8
Loc 12										
0–150	100	3	2	85	6	15	80	28	0.25	8.4
150–300	940**	5	~	130	7	18	190	60	2.70*	8.4
300–450	46	1	~	110	12	24	46	26	0.20	7.8
HIL.	300	100	20	12%	100	600	7000	1000	15	<5 or >9

(1)HIL. = Health-based Investigation Levels

(2) All units are in mg/kg except where shown otherwise

(3) ~ indicates < Detection Level

* denotes \geq and $< 2 \times$ HIL^b, ** denotes ≥ 2 and $< 5 \times$ HIL, *** denotes ≥ 5 and $< 10 \times$ HIL.

****denotes $\geq 10 \times$ HIL. This is an arbitrary method of categorising data.

(adapted from South Australian Housing Trust/South Australian Health Commission format)

1.2.8 Content of data collection reports

Integration of reports

Where there is a series of reports, each succeeding report should summarise the important and relevant points from the preceding reports. This will assist in the rapid comprehension of new material by all parties involved.

Non-integrated reports result in far less efficient appraisals of data.

Accreditation of laboratories

Laboratories should be accredited by an appropriate body for the particular analyses being undertaken. A broad form of accreditation may not be applicable for the particular test.

Analytical techniques

The analytical techniques should comply with techniques described in NEPC (1999).

Environmental Health Risk Assessment for Air Pollutants

2.1 Introduction

Poor air quality can have a significant bearing on the causes and exacerbation of respiratory disease. For example, asthma may be exacerbated by air pollution and over two million or 11 per cent of Australians have asthma, including one in four primary school children, one in seven teenagers and one in ten adults (AIHW, 2000).

There are several issues that differentiate the risk assessment of air pollutants from pollutants found in other environmental media.

As individuals we have little control over the quality of the ambient air we breathe. Exposure to air pollutants occurs in all activities, whilst indoors, in motor vehicles, whilst at work and during recreation. It is important that all sources of air pollutants are considered, noting that for some pollutants, the indoor and occupational environments may contribute the most to exposure. In addition the surface area of the internal lining of the lungs is 50–70 square metres (about the size of a tennis court) compared to 1–2 square metres for the surface area of the skin). There are 300 million alveoli in adult human lungs and the air-blood barrier (consisting of the aqueous surface, epithelial lining and thin interstitial space) is 0.36 to 2.25mm thick indicating a much larger area for biological interaction to occur (Hrudey *et al*, 1996).

While the fundamental principles of risk assessment remain the same, different exposure assessment are available when assessing ambient air pollution from diffuse and point source regions or large areas, localised air pollution from point sources, and indoor air pollution such as may occur in the home or workplace. Where large populations are involved, different epidemiological methodologies such as time-series analysis may be able to be used. The risk assessment of a site-specific situation will differ from that for the development of a guideline as the former will usually relate to a specific, defined population while the latter will need to take into account a broader, more diverse population.

Ambient air is usually divided into two groups, the 'criteria' pollutants and 'other' (refer to Sections 2.5.1 and 2.5.2). Criteria pollutants are those that are common air pollutants, found in relatively high concentrations. The 'other' group is made up of hazardous air pollutants and other specific substances that are found in trace concentrations, are specific to a particular setting or activity and are monitored on a needs basis.

Irritant effects are often the critical health effect with criteria pollutants and the irritant effects may occur from short exposures with negligible systemic absorption. Other non-irritant health effects such as carcinogenicity (eg for benzene), mutagenicity and neurotoxicity are receiving increasing attention.

The criteria pollutants, carbon monoxide (CO), sulfur dioxide (SO₂), nitrogen dioxide (NO₂), Particulate Matter 10µm (PM₁₀), photochemical smog (measured as ozone) and lead (Pb) are typically monitored via a network of monitoring stations. These networks are usually located to meet environmental management objectives. Monitoring stations are selected for a range of reasons including monitoring of emissions from industrial facilities, major roadways or where high concentrations of secondary pollutants may be found. Ambient air exposures to pollutants are highly dependent on meteorological factors.

An extensive review of risk assessment related to the development of ambient air criteria for Australia has been published: *Report of the Risk Assessment Taskforce* (National Environment Protection Council, 2000). The Report reviews a range of risk assessment methodologies that could be applied to the development of ambient air criteria as well as detailed appendices covering epidemiological study design and data requirements, health effects of criteria air pollutants, ambient air monitoring programs in Australia and provides an example of the possible use of risk assessment related to the review of particle standards.

2.2 Identifying the Issues

The degree of air pollution from criteria pollutants and the identity of the pollutants present are obtained usually from the fixed site monitoring stations that are intended to provide information about the quality of air in an airshed and the population exposure to the pollutants. This takes into account diffuse source emissions such as vehicle emissions from motorways as well as point source emissions from industry. Specific information on air quality within a certain region that has major point source emissions, such as from a factory or a power station, that can have major impacts on the surrounding area, needs intensive local monitoring for pollutants that are known to be emitted from the local source. Such monitoring is often carried out by the jurisdictional environment agency or by the industry itself. New developments usually require Environment Impact Statements (EIS) to determine the contribution of the new source to the air quality in that area and the size of the population potentially exposed. EIS usually rely on air modelling data that are derived from known emissions and processes.

The levels of pollutants are compared with air quality standards that are usually health-based criteria, set either at levels below which adverse health effects are not expected to occur or at levels where the incidence of adverse health effects is considered acceptable. If the levels are found to exceed those in the standards, appropriate strategies and actions will need to be instigated to reduce the pollutants in the airshed.

2.3 Hazard Identification

For the criteria pollutants, most of the health effect data can be found in the epidemiological literature. For the hazardous air pollutants, both toxicological data and usually indoor or occupational studies are used during this stage.

2.3.1 Analytical methodologies

General references

- Manahan SE (1993). *Fundamental of Environmental Chemistry*. Lewis Publishers. Boca Raton.
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- United States Environmental Protection Agency (US EPA) (1999). *Compendium of Methods for the Determination of Toxic Organic Compounds in Ambient Air—2nd Edition*, EPA-625/R-96/010b, Center for Environmental Research Information, US EPA. January 1999. Cincinnati, Ohio.
- US EPA (1999). *Compendium of Methods for the Determination of Inorganic Compounds in Ambient Air*. EPA 625/R-96/010a, Office of Research and Development, US EPA. June 1999. Washington DC.
- US EPA (1994). *Quality Assurance Handbook for Air Pollution Measurement Systems*. US Environmental Protection Agency. EPA 600/R-94-038b, May 1994.

- US EPA (1990). *Compendium of Methods for the Determination of Air Pollutants in Indoor Air*. EPA 600/4-90-010, April 1990.
- US EPA (1983a). *Technical Assistance Document for Sampling and Analysis of Toxic Organic Compounds in Ambient Air*. US EPA, EPA 600/4-83-027, June 1983.

2.3.2 Dose–response assessment

Dose–response data for most classical air pollutants have been determined from human exposure data, (chamber studies), using a single compound at a time and various exposure durations and concentrations. Much of the dose–response data for PM₁₀ (and for ozone to a lesser extent) has been obtained from epidemiological studies. More recent chamber studies also use mixtures of compounds or sequential dosing with different compounds to try to model exposures in the ambient environment. Each pollutant is assessed against specific health endpoints characteristic to that pollutant.

Sensitive populations, such as children, have been identified and studied using chamber exposures.

Animal chamber exposure data are used to support human exposure data, often to identify physiological mechanisms of action.

Dose–response data will often be available from the documentation used in the development of criteria by organisation such as WHO.

2.3.3 Use of epidemiological data

Time-series epidemiological analyses are being used increasingly to examine public health effects of criteria pollutants. These may show short-term variations in air pollution levels within the usual range in the levels of hospital admissions, acute respiratory and cardiovascular disease or mortality. There are considerable problems of interpretation with these studies and the weak associations found are generally in conflict with the expected risk from the low concentrations of air pollutants present (IEH, 1999b). There is however, some coherence between different study types and designs to support the findings of time-series studies.

Times series studies require a population of sufficient number. NEPC (2000) also notes that time series studies require:

- daily estimates of population exposure for at least five years at constant locations;
- sufficient fixed sites in the monitoring network to characterise the spatial distribution of air pollutants in the study region, i.e. sub regions within the airshed contain at least one monitoring site;
- sub-regional monitoring sites provide a measure of the distribution of population exposure not peak data;
- daily data from each sub-regional monitoring site available for at least 75 per cent of days; and
- pollutants are not measured independently so that potential confounding can be assessed.

2.3.4 Sensitive sub-populations

For air pollutants, there are particular sub-populations that show increased sensitivity to some compounds. For example, 10 per cent of the population is particularly sensitive to ozone, severe asthmatics are sensitive to sulfur dioxide, people with angina and coronary heart disease are sensitive to the effects of carbon monoxide, and asthmatics and those with chronic lung disease are sensitive to nitrogen dioxide, and carbon monoxide (IEH, 1999c).

2.3.5 Use of occupational criteria

Worksafe Australia has developed a range of Exposure Standards for the occupational environment. The Exposure Standards should not be applied to ambient air quality as they are intended to protect healthy adult workers and do not take into account the very old, the very young and the infirm. In setting general environmental standards safety factors are applied to take these groups into account. Occupational Standards are often based around exposures for a 40 hour week (compared to the 168 hours that a person will be exposed to the general environment) and for a working lifetime, rather than a complete lifetime.

Worksafe exposure standards should not be applied without reference to the Guidance Note on the Interpretation of Exposure Standards for Atmospheric Contaminants in the Occupational Environment [NOHSC:3008(1995)], and to the related documentation which explains the rationale for the individual criteria.

2.3.6 Exposure assessment

Exposure assessment is the most problematic area in the risk assessment process for air pollutants and is the source of most of the uncertainty in the estimation of risk.

Some of the major difficulties are factors such as time and spatial variation of air pollutants and the fact that personal exposures are likely to rapidly vary and be affected by mobility and a range of other meteorological, physical and chemical processes. Exercise, for example, may substantially increase exposure at a given air concentration and exposure may also be affected by pre-existing lung disease (Samet, 1999).

2.3.7 Criteria pollutants

It is very difficult to determine from ambient air monitoring data from representative monitoring stations the number of people exposed, the duration of exposure and the actual level of exposure to air pollutants. Generally, worst case scenarios are used and exposure estimations are made using the highest daily or hourly concentrations. An assumption that most of the population in that region of the monitoring station airshed has been exposed is made. The data from several monitoring stations are usually averaged and considered representative of the population. In the case of some criteria pollutants, there are wide variations between concentration ranges due to meteorological factors and geography. Some methods are available to interpolate between monitoring stations and weight exposures according to population factors. Modelling techniques to improve exposure estimates are also available, however the models have not been validated for the Australian context.

If available, personal monitoring data would provide a much better indication on actual exposure, however this data is rarely available. Daily diaries of location and activities may also be used to identify where exposures have occurred. This method is costly and labour intensive so only small numbers of persons have been monitored by such ways in Australia.

2.3.8 Other pollutants

Exposures from point sources can be estimated using dispersion modelling techniques, but they depend on a considerable knowledge of factors such as processes and dispersion characteristics.

2.4 Exposure Defaults

2.4.1 The volume of exposure

The amount of air moved into and out of the human lungs is about 6 litres per minute at rest (8.6m³/day) but can increase up to about 60 litres per minute (86m³/day if this level of exertion could be sustained). For risk assessments a value of 22m³/day is used for adults and 15m³/day for a child (10 years). For further information refer to Section 7.16.3.

2.4.2 Dispersion modelling guidance

The use and interpretation of air modelling data is a specialised field.

Many models are available. Different models will be required to assess point source versus diffuse sources of contamination; for different types of contaminants (e.g. gases versus particles); and for different scenarios (e.g. a whole airshed versus properties neighbouring a factory).

For modelling data, the following minimum information is required:

- wind speed;
- wind direction;
- air temperature;
- mixing height (estimated or measured); and
- atmospheric stability.

Table 1 A2: Physicochemical properties of chemicals and the atmospheric environment important in transport-fate calculations

Properties of chemical	Properties of environment
<p>Physical properties:</p> <ul style="list-style-type: none"> • Molecular weight • Density • Vapour pressure (or boiling point) • Water solubility • Henry's constant (air-water distribution coefficient) • Lipid solubility (or octanol-water distribution coefficient) <p>Chemical properties</p> <ul style="list-style-type: none"> • Oxidation • Hydrolysis • Photolysis • Microbial decomposition • Other modes of decomposition <p>Particle properties</p> <ul style="list-style-type: none"> • Size • Surface area • Chemical composition • Solubility 	<p>Particulate load</p> <ul style="list-style-type: none"> • For dusts, other solids particulate mater • For liquids, aerosols <p>Oxidant level</p> <p>Temperature</p> <p>Relative humidity</p> <p>Amount and frequency of precipitation</p> <p>Meteorologic characteristics</p> <ul style="list-style-type: none"> • Ventilation • Inversion <p>Surface cover</p> <ul style="list-style-type: none"> • Water • Vegetation • Soil type

(adapted with permission from NAS, 1991)

Other information to be considered is:

- trapping of plumes in mixed layers of limited height;
- vertical plume dispersion in convective conditions;
- strength of capping inversions above mixed layers
- the standard deviation of the direction;
- relative humidity or a related parameter;
- surface layer heat flux, moisture flux and friction velocity; and
- fumigation of plumes.

(WA Department of Environmental Protection, 1999)

2.5 Risk Characterisation

2.5.1 Comparisons with criteria

The initial comparison should be with the National Environment Protection Measure (NEPM) for ambient air quality standards and goals, and the NHMRC indoor air quality goals.

The NEPM criteria are available for ambient air pollution for the substances listed in Table 3 A2.

Table 2 A2: Exposure modelling parameters for point sources.

Input requirements/data needs	Output requirements
Release point locations	Concentrations at each receptor point
Mass emission rate of compounds to be studied	
Concentration of individual or aggregated compounds	
Stack height	
Stack velocity	
Stack temperature	
Stack diameter	
Geography	
Rural/urban site classification	
Local meteorological data	
Receptor locations for concentration predictions	
Frequency and duration of short-term (intermittent) releases	

(adapted with permission from NAS, 1991)

Table 3 A2: NEPM standards and goals

Pollutant	Averaging period	Maximum concentration	Goal within 10 years maximum allowable exceedances
Carbon monoxide	8 hours	9.0 ppm	1 day a year
Nitrogen dioxide	1 hour	0.12 ppm	1 day a year
	1 year	0.03 ppm	none
Photochemical oxidants (as ozone)	1 hour	0.10 ppm	1 day a year
	4 hours	0.08 ppm	1 day a year
Sulfur dioxide	1 hour	0.20 ppm	1 day a year
	1 day	0.08 ppm	1 day a year
	1 year	0.02 ppm	none
Lead	1 year	0.50 µg/m ³	none
Particles as PM ₁₀	1 day	50 µg/m ³	5 days a year

Further information is available at www.nepc.gov.au

Table 4 A2 details NHMRC criteria for a range of substances relevant to indoor air quality.

Table 4 A2: Indoor interim national air quality goals recommended by the National Health and Medical Research Council

Pollutant	Measurement ($\mu\text{g}/\text{m}^3$)*	Units (ppm)	Measurement criteria	Notes	NHMRC session at which recommended
Carbon monoxide (CO)	10,000	9	Eight hour average not to be exceeded more than once a year	This period of measurement is not to be confused with that for Threshold Limit Values.	98th (Oct 1984)
Formaldehyde #	120	0.1	Not to be exceeded	Within domestic premises and schools.	93rd (June 1982)
Lead	1.5	-	Three months average	-	88th (Oct 1979)
Ozone, photochemical oxidants	210	0.10	Maximum hourly average not to be exceeded more than once a year	A public warning to be given if ozone levels are expected to rise above $500 \text{ g}/\text{m}^3$ (0.25 ppm).	119th (June 1995)
	170	0.08	Four hour average	-	119th (June 1995)
Radon #	200 becquerels per cubic metre ($5.4 \text{ nCi}/\text{m}^3$)	-	Annual mean	Action level for simple remedial action in Australian homes. Where the concentration exceeds this level, householders should consult the appropriate State authority for advice.	109th (May 1990)
Sulfates	15	-	Annual mean	-	104th (Nov 1987)
Sulfur dioxide (SO_2)	700	0.25	Ten minute average	Caution: at these recommended levels, there still may be some people (for example, asthmatics and those suffering chronic lung disease) who will experience respiratory symptoms and may need further medical advice or medication.	120th (Nov 1995)
	570	0.20	One hour average		120th (Nov 1995)
	60	0.02	Annual mean		106th (Nov 1988)
Total Suspended Particulates (TSP)	90	-	Annual mean	TSP goal to be read in conjunction with annual SO_2 goal.	92nd (Oct 1981)
Total Volatile Organic Compounds	500	-	Hourly average	A single compound shall not contribute more than 50% of the total	115th (June 1993)

* Expressed at 0°C and 101.3 kPa , # Formaldehyde and Radon are final goals (NHMRC, May 1996)

For the non criteria pollutants for which there are no NEPM standards or NHMRC goals, the WHO Air Quality Guidelines for Europe (WHO, 1999a) may be used. The WHO guidelines are listed in Table 5 A2. The WHO guidelines are applicable to both ambient and indoor air.

The following text has been taken directly from the WHO (1999a) documentation.

'The WHO 'Guidelines for Air Quality' values are levels of air pollution below which lifetime exposure, or exposure for a given averaging time, does not constitute a significant health risk. If these limits are exceeded in the short-term it does not mean that adverse health effects automatically occur;

however the risk of such effects increases. Although the 'Guidelines for Air Quality' values are health- or environment-based levels they are not standards per se. Air quality standards are air quality guidelines promulgated by governments, for which additional factors may be considered. For example, the prevailing exposure levels, the natural background contamination, environmental conditions such as temperature, humidity and altitude, and socio-economic factors.'

The tables for health endpoint relationships for PM₁₀ and PM_{2.5} can be obtained from the WHO website: www.who.int/peh/air/Airqualitygd.htm

Table 5 A2: WHO air quality guidelines for Europe organic air pollutants

Compound	Guideline value (µg/m ³)	Averaging time
Acetaldehyde	2000	24 hours
Acrolein	50	30 minutes
Acrylic acid	54	1 year
2-Butoxyethanol	13,000	1 week
Carbon disulfide	100	24 hours
Chloroform	1.3	24 hours
1,2-Dichloroethane	700	24 hours
Dichloromethane	3,000	24 hours
Di-n-butyl phthalate	0.05	24 hours
Styrene	70 (odour)	30 minutes
Tetrachloroethylene	250	24 hours
Toluene	260	1 week
	1,000	30 minutes
Xylenes	4,800	24 hours
	4,400	30 minutes

(adapted from WHO, 1999a)

Table 6 A2: WHO air quality guidelines for Europe inorganic air pollutants

Compound	Guideline value ($\mu\text{g}/\text{m}^3$)	Averaging time
Cadmium	0.005	1 year
Carbon monoxide	100,000	15 minutes
	60,000	30 minutes
	30,000	1 hour
	10,000	8 hours
Fluorides	1	1 year
Hydrogen sulfide	7 (odour)	30 minutes
Lead	0.5	1 year
Manganese	0.15	1 year
Mercury (inorganic)	1	1 year
Nitrogen dioxide	200	1 hour
	40	1 year
Ozone	120	8 hours
Sulfur dioxide	500	10 minutes
	125	24 hours
	50	1 year

(adapted from WHO, 1999a)

Environmental Health Risk Assessment for Food

3.1 Introduction

The key reference is the 'Framework for the assessment and management of food-related health risks' (ANZFA, 1996) which is the source of most of the material in this Appendix. ANZFA is revising its risk management processes in 2001.

Food-related risks can occur because of a range of factors and in many cases, the interdependence of these factors needs to be considered when assessing risk.

Some of the risk factors associated with food (in alphabetical order)

- agricultural chemical residues;
 - biological agents;
 - cooking and process-related artefacts;
 - environmental contaminants;
 - food additives;
 - food processing aids;
 - marine toxins;
 - microbiological agents;
 - mycotoxins;
 - novel foods;
 - novel ingredients;
 - nutrient imbalance;
 - packaging migrants;
 - physical agents;
 - plant toxins;
 - radionuclides; and
 - veterinary chemical residues.
- (ANZFA, 1996)

3.2 Identifying the Issues

3.3 Hazard Identification

The hazards associated with an agent will be affected by:

- the structure and associated physicochemical properties;
- the metabolism and toxicokinetics of the substance; and
- the results of a series of toxicity tests conducted both in animal models and/or in *in vitro* systems.

For microbiological agents, hazard identification consists of identification of the microorganisms and/or microbiological toxins of concern. The International Commission of Microbiological Specifications for Food (ICMSF) has categorised the most serious and common of the microbiological hazards according to the severity of the hazard they present. Data for classifying microbiological hazards may come from animal studies, but more commonly from controlled human studies, epidemiological studies, or studies on outbreaks of food-borne diseases.

3.4 Chemical Risk Assessment

Chemicals in food can be categorised as either food ingredients, food additives or food contaminants.

3.4.1 Particular issues

Much of the chemical risk assessment is based around the development and use of Acceptable Daily Intakes (ADIs).

While the use of ADI approach is applicable for many chemicals specifically added to food, other classes of chemicals may sometimes require a different approach. These include traditionally used food additives and processing aids, nutrients, genotoxic carcinogens, some naturally occurring chemicals, and environmental contaminants.

For many traditionally used food additives and processing aids, there is little toxicity data upon which to base an assessment of risk. Many such chemicals have a long history of use in foods or are members of chemical classes known to be of low toxicity. For some chemical groups, standard toxicity tests may be inappropriate to assess hazard. Generally, acceptable levels of intake are determined using a combination of toxicity data, information on traditional food use, structure/activity relationships, metabolic data and toxicokinetic data.

Nutrients in food must also be considered separately since, regardless of the potential toxicity, there is a nutritional requirement that must be met. The appropriate total intake of a particular nutrient, therefore, must fall within a range, the upper bound of which should not be within the toxicity range. The margin of safety therefore varies for each nutrient, and may be influenced by age and sex of individuals or genetic differences between population groups. Epidemiological data are the most appropriate data for assessing risk in this instance but often lack the degree of sensitivity required to obtain meaningful conclusions. For essential trace elements there will be deficiency symptoms at low concentrations and toxic effects at high concentrations. For this reason, Acceptable Ranges of Oral Intake (AROI) are being determined which are the ranges between those concentrations causing deficiency and those causing toxicity.

Carcinogenic chemicals which are also genotoxic (i.e. capable of causing genetic damage) present a particular problem with regard to safety assessment. Because of their ability to produce DNA damage at very low dose levels, a NOEL cannot easily be established for such chemicals. In general, the approach has been to disallow the use of such chemicals in foods. When their occurrence in food is unavoidable, either because they are naturally occurring or are produced during processing or cooking, levels should be kept to a minimum. Carcinogenic chemicals for which the mechanism is likely to be other than through a genetic change (so-called non-genotoxic carcinogens) can generally be regulated

in a similar manner to other chemicals using a NOEL to establish an ADI.

Food intolerance, including allergic reactions, can occur to many foods and food components. Satisfactory animal models to predict food intolerance in humans have not yet been developed, and currently double-blind challenge feeding studies in humans following an elimination diet appear to be the only reasonably reliable way of identifying factors causing food intolerance. Food intolerance is restricted to small sub-populations or individuals and the usual remedy is to provide component labelling of food to enable sensitive individuals to avoid consuming foods containing a particular component.

3.5 Microbiological Risk Assessment

There are three models of action whereby pathogenic microorganisms cause disease: the first is a result of ingesting toxin which is present in the food as a result of microbiological growth (e.g. *Staphylococcus aureus* [enterotoxin], *Bacillus cereus* [emetic toxin]); the second is a result of toxin formation within the intestinal tract after ingestion of the organism (e.g. *Clostridium perfringens* [enterotoxin]); the third is an infection-type which includes more widespread systemic effects (e.g. *Listeria monocytogenes*).

The International Commission on Microbiological Specifications for Foods (ICMSF) has grouped the most common and serious of these microbiological hazards into three categories according to the severity of hazard or seriousness of disease they may cause. These categories include 'severe hazards'; 'moderate hazards, potentially extensive spread'; and 'moderate hazards, limited spread'. Foods may also be assigned categories of risk based upon the likelihood that the foodstuff will or will not be infected from source; whether or not it is able to support the growth of the pathogen concerned; whether there is substantial potential for abusive handling of the food; or whether the food will be subject to a terminal heat process after packaging or before consumption.

It is generally recognised that a minimum number of organisms is necessary to cause illness. This is referred to as the minimum infective dose or minimum intoxication dose (MID). The MID is influenced, however, by a wide variety of host and food vehicle factors and may vary for different population groups (such as the young, the elderly and the immunocompromised), different food types, and different microbiological strains. Only a limited amount of data is available on the relationship between the number of microorganisms, or amount of toxin, ingested and the human response so that attempts to quantify microbiological hazards are severely limited. Animal models have limited use for microbiological risk assessment due to the varying responses of different species. Human volunteer studies have some value but, for safety reasons, are limited to healthy young adults, who are not generally the most susceptible to food-borne pathogens. Volunteer studies are also limited by the variation among microbiological strains and the effect of food vehicles. Epidemiological studies considered in conjunction with volunteer studies can provide a more complete understanding of the quantitative relationship between exposure to microorganisms and human responses. Epidemiological studies generally involve the sub-populations, including high risk groups, and they involve real food vehicles. The limitation is that the number of microorganisms ingested by individuals can only be estimated. Outbreaks of food-borne illness can provide information on the number of microorganisms which caused disease in a particular situation, but do not provide information on the minimum dose necessary to cause illness.

3.6 Analytical Methodologies

3.6.1 Food

Food Standards Code. Latest edition. Australia New Zealand Food Authority. The FSC prescribes AOAC methods for many of its chemical tests and Australian Standard methods (mostly AS1766 Food Microbiology but also some AS dairy-specific standards) for most micro tests. Where neither is applicable the FSC mostly

describes its own methods. There are however some other external references quoted. For example there is an FDA method quoted for *Listeria* in poultry.

3.7 Assessment of Summary Statistic Data

A key source of information is the series of Australian Market Basket Survey publications which are published biannually by ANZFA. These provide information about certain substances in a range of foods across Australia.

3.8 Censored Data

For contaminants found to contain a concentration below the Level of Reporting (LOR), the laboratory assigns 'Not Detected' or 'Trace Results'. These are given a numerical value below the LOR which results in the 'calculation of contaminant exposure being overestimated, but it can be considered to be a worst-case scenario. Dietary exposures are also determined using a zero value so that a range can be reported for these contaminants.' (ANZFA, 1998, p. 15). In the 1996 Market Basket Survey, for example, for cadmium the values were (in mg/kg): limit of reporting, 0.005; trace result, 0.00375; and not detected, 0.0025.

3.9 Exposure Assessment

National food consumption data are used in dietary exposure assessments and are available from dietary surveys and market basket surveys. Dietary surveys estimate actual food intakes in various subgroups of the population, taking into account such factors as age and ethnic background. Market basket surveys measure the amount of pesticide residues and other selected contaminants in freshly prepared and ready-to-eat foodstuffs. Detailed theoretical daily intake calculations are carried out when there is a potential for high exposure levels in humans. The average daily food consumption values are used in predicting pesticide residue intake in comparison with the health guideline value (ADI, TDI or TWI). Theoretical daily intake calculations are performed based on the procedures as outlined in

e.g. the Guidelines for Predicting Dietary Intake of Pesticide Residues (revised) (1997) prepared by the Global Environment Monitoring - Food Contamination Monitoring and Assessment Programme in collaboration with the Codex Committee on Pesticide Residues, and published by the WHO (WHO, 1997). There are formal programs in Australia to assess human exposure to pesticides and certain contaminants - these are the National Residue Survey and the Australian Market Basket Survey.

3.10 Risk Characterisation

3.10.1 Sources of uncertainty

The principal sources of uncertainty are:

- **The host**

Some sections of the population are at greater risk from exposure to pathogens. These 'at risk' groups include the elderly, the young and the immunocompromised. Other host factors that may affect exposure to a microbiological agent include pregnancy, nutritional status, concurrent or recent infections, physiological factors, medication and stress. In most cases, host factors are more important in determining the severity or outcome of an infection than in determining the likelihood of infection.

- **The food vehicle**

The nature of the food vehicle may influence the amount of a microorganism needed to cause infection or disease. This includes its fat content, iron content, buffering capacity, presence of preservatives, physical state, storage temperature and storage history.

- **The level and distribution of microbiological contamination**

The number of microorganisms present in a product at the time of sampling for microbiological analysis may have little relation to the number of organisms present at the time of consumption. The number of microorganisms varies as a result of storage, handling, or preparation. In addition, the distribution of microbiological agents within a food product may vary due to factors such as surface contamination and colony

formation.

- **The potential for mishandling**

Many cases of microbiological food-borne illness result from mishandling in the home or food service establishment, associated with actions such as under-cooking of foods, allowing cross-contamination of cooked and uncooked food, and storage of foods at incorrect temperature or for excessive periods of time.

- **Terminal heat processes**

A food subjected to a heat process prior to consumption is generally regarded as having a lower risk although in certain circumstances such a food may harbour heat stable toxins. The risk associated with these foods may increase if subsequent cooking or handling procedures are inadequate.

- **Person-to-person transmission**

Secondary spread of microorganisms is an important factor in some types of microbiological food-borne diseases. Infected people may also unsuspectingly contribute to the spread of an outbreak by contamination through handling or serving food.

- **Variety of disease syndromes**

Some microbiological agents can cause a wide range of disease symptoms. In addition, while most microbiological agents involved short-term risks, some food-borne diseases can have long-term sequelae, such as reactive arthritis.

Environmental Health Risk Assessment for Water

4.1 Introduction

There is a wide range of water types, water uses and possible routes of transmission of waterborne hazards to humans. In undertaking health risk assessments the characteristics and potential uses of water bodies need to be determined. Water sources include fresh, estuarine, marine and waste waters. Water uses can include supply of potable water for drinking and bathing, recreation, aquaculture or irrigation of crops. Human exposure to waterborne contaminants can include:

- direct exposure through ingestion, dermal contact, inhalation of aerosols or sprays; or
- indirect exposure through foods contaminated by irrigation water or water used for aquaculture and seafoods contaminated by waste water discharges. Health risk associated with food contamination via a waterborne route is within the scope of Appendix 3 addressing the risk assessment of food.

4.2 Identifying the Issues

Health risks associated with various types of water are considered in a range of guidelines detailed in the following text.

Drinking water is generally the highest and most direct source of human exposure to waterborne contaminants and accordingly it usually receives the most attention in water-related health risk assessment. Drinking water quality issues are addressed in detail within the Australian Drinking Water Guidelines (NHMRC and ARMCANZ, 1996). These guidelines (ADWG) provide an excellent description of water quality management needs from source water to tap. They also provide detailed fact sheets describing the rationale and health risk evidence for setting of guideline numbers for all individual quality parameters currently covered.

The ADWG are undergoing rolling revisions and their current status and draft guidelines can be found at www.health.gov.au/nhmrc/advice/water.htm.

Health risks associated with recreational water are considered in published guidelines for recreational water quality (US EPA, 1999) and in guidelines being prepared by WHO and NHMRC. Health risks associated with use or reclaimed water are considered in draft guidelines for use of reclaimed water from sewerage systems (NHMRC, ARMCANZ and ANZECC) which should be published in early 2000. In addition annual reviews of health effects associated with waste water disposal and reuse are published in Water Environment Research (e.g. Froese and Bodo 1999)

4.2.1 Drinking water

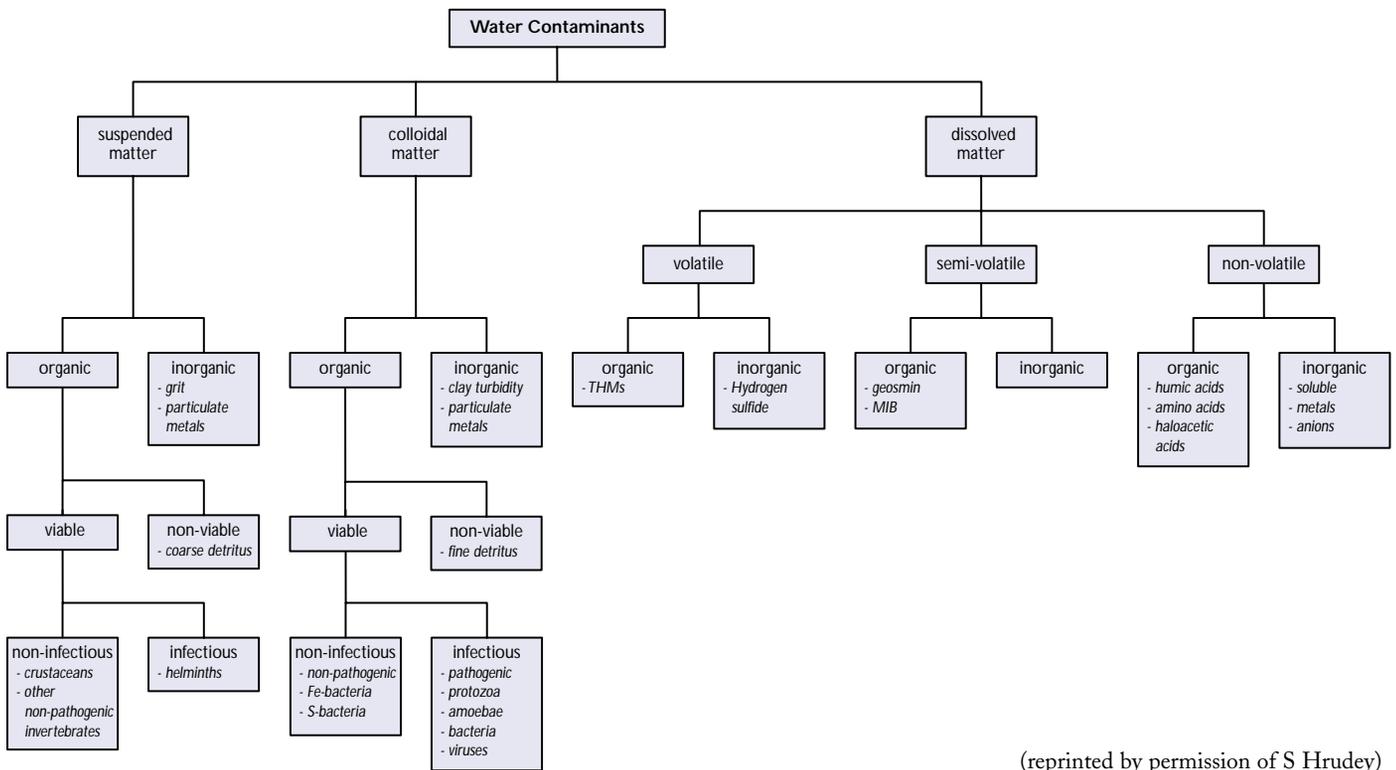
Drinking water quality is usually categorised in terms of physical, chemical or biological parameters. For drinking water, the health-related physical parameters are primarily radiological (NHMRC and ARMCANZ, 1996). Turbidity, as a physical parameter in its own right is an aesthetic concern. However, in drinking water produced by filtration plants, turbidity is also used as an indicator of treatment efficiency for the removal of pathogenic microorganisms (e.g. see US EPA, 1998). The chemical parameters of concern in drinking water are categorised into inorganic and organic chemicals. The latter are sub-categorised into disinfection by-products, pesticides and other organic compounds (NHMRC and ARMCANZ, 1996). The biological parameters are focused on pathogenic microorganisms which are categorised into bacteria, protozoa, toxic algae (cyanobacteria) and viruses. The water quality parameters currently covered by the ADWG are listed in Table 1 A4.

The overall relationship among common water quality parameters can be summarised in a variety of ways, with one approach presented in Table 2 A4 (Hrudey, 1999). This perspective shows how the physical characteristics of water contaminants (suspended vs. dissolved, volatile vs. non-volatile) relate to their chemical character as well as their classification as biological or chemical contaminants.

Table 1 A4: Parameters covered by the Australian Drinking Water Guidelines (NHMRC and ARMCANZ, 1996)

Micro-organisms	Physical characteristics	Inorganic chemicals	Organic chemicals
<p>Bacteria</p> <ul style="list-style-type: none"> • <i>Aeromonas</i> • <i>Campylobacter</i> • Coliforms • <i>Escherichia coli</i> • <i>Klebsiella</i> • <i>Legionella</i> • <i>Mycobacteria</i> • <i>Pseudomonas aeruginosa</i> • <i>Salmonella</i> • <i>Shigella</i> • <i>Vibrio</i> • <i>Yersinia</i> <p>Protozoa</p> <ul style="list-style-type: none"> • <i>Acanthamoeba</i> • <i>Cryptosporidium species</i> • <i>Giardia</i> • <i>Naegleria fowleri</i> <p>Toxic algae</p> <ul style="list-style-type: none"> • Cyanobacteria <p>Viruses</p> <ul style="list-style-type: none"> • Adenovirus • Enteroviruses • Hepatitis viruses • Norwalk virus • Rotavirus, para rotaviruses and reovirus 	<p>Radionuclides</p> <ul style="list-style-type: none"> • Radium-226, Radium-228 • Radon-222 • Uranium • Other beta-gamma-emitting radioisotopes <p>Physical parameters</p> <ul style="list-style-type: none"> • Dissolved oxygen • Hardness • pH • Taste and odour • Temperature • Total dissolved solids • True colour • Turbidity 	<ul style="list-style-type: none"> • Aluminium • Ammonia • Antimony • Arsenic • Barium • Beryllium • Boron • Bromate • Cadmium • Chloride • Chlorine • Chlorine dioxide, Chlorite • Chlorate • Chromium • Copper • Cyanide • Fluoride • Hydrogen sulfide, Sulfide • Iodine, iodide • Iron • Lead • Manganese • Mercury • Molybdenum • Monochloramine • Nickel • Nitrate and nitrite • Selenium • Silver • Sodium • Sulfate • Tin • Zinc 	<p>Disinfection by-products</p> <ul style="list-style-type: none"> • MX • Chloroacetic acids • Chloroacetones • Chlorophenols • Chloropicrin • Cyanogen chloride • Formaldehyde • Haloacetonitriles • Trichloroacetaldehyde • Trihalomethanes (THMs) <p>Other organics</p> <ul style="list-style-type: none"> • Acrylamide • Benzene • Carbon Tetrachloride • Chlorobenzene • Dichlorobenzenes • Dichloroethanes • Dichloroethenes • Dichloromethane • Epichlorohydrin • Ethylbenzene • EDTA • Hexachlorobutadiene • Nitritotriacetic acid • Organotins • Plasticisers • PAHs • Styrene • Tetrachloroethylene • Toluene • Trichlorobenzenes • 1,1,1-trichloroethane • Trichloroethylene • Vinyl chloride • Xylenes <p>Pesticides</p> <ul style="list-style-type: none"> • Aldrin and dieldrin • Atrazine • Chlordane • 2,4-D • DDT and derivatives • Heptachlor, heptachlor epoxide • Lindane • Plus 113 others

Table 2 A4: Classification of water quality parameters



(reprinted by permission of S Hrudey)

Comments:

- Exchange of contaminants between phases is governed by a dynamic equilibrium that is dependant on temperature and the relative concentration of contaminant in each phase

Operational definitions:

- *dissolved*—passes microfiltration but not reverse osmosis
- *colloidal*—not removed by sedimentation or direct granular filtration
- *volatile*—air strippable
- *semi-volatile*—steam strippable
- *viable*—can replicate under favourable conditions
- *infectious*—can infect a susceptible mammal representative of humans

Technology specification examples:

- *chlorination/ozonation*—converts organic matter into new organic compounds with some oxidised to inorganic products and disinfects by making viable organisms non-viable
- *coagulation*—converts colloidal and suspended matter so that sedimentation and granular filtration can remove suspended and colloidal matter
- *granular filtration*—removes some fraction of suspended and coagulated colloidal matter

(Hrudey, 1999)

The management of water quality requires attention ranging from sound management of land use and human activities in catchments through to the application of treatment technology to achieve safe drinking water. A variety of measures may be considered for the protection and enhancement of source water quality including (Reinert and Hroncich, 1990):

- assessment of safe yield in terms of water quantity;
- catchment land ownership;
- land use controls or management agreements;
- in situ treatment (mixing, aeration, algae control);
- wildlife control;
- forest or agricultural management practices;
- emergency response measures;
- routine sanitary surveys and catchment inspection;
- access control (e.g. fencing); and
- public education.

The application of risk management principles towards a total water quality management system for Australian drinking water systems is being evaluated under the rolling revisions to the ADWG program. The results of a series of pilot studies will be developed to include expanded advice on hazard identification and risk assessment for drinking water quality management systems, including principles derived from the Hazard Analysis Critical Control Point (HACCP) approach which has been widely adopted for risk management in the food industry.

Water treatment has evolved from classical technology developed in the early 1900s that was originally based on coagulation, filtration and disinfection. These basic approaches have been refined and improved through the use of a number of technological alternatives so that a modern water treatment process scheme can be

developed that will satisfy specified finished water quality requirements given identified source water quality challenges. The menu of drinking water treatment process types that are available for consideration now generally includes (AWWA, 1990; Dezuane, 1997):

- air stripping / aeration;
- coagulation processes (destabilisation, mixing and flocculation);
- sedimentation and flotation;
- filtration;
- ion exchange and inorganic adsorption;
- chemical precipitation;
- membrane processes;
- chemical oxidation;
- adsorption of organic compounds; and
- disinfection.

Within each of these process categories there are an expanding range of technologies and operating strategies being developed. Research has been dedicated to improving the capability and reliability of these technologies to meet drinking water quality criteria that may be specified by health risk assessments.

4.2.2 Recreational water

Recreational water quality is usually categorised in terms of microbiological parameters although physical features that could represent a hazard to bathers are also considered in some guidelines (NHMRC, 1990) and will be included and probably expanded in those being prepared by WHO and NHMRC.

As for drinking water the management of water quality requires attention to sound management of potential sources of pathogens from adjoining drainage areas and catchments. Pathogens can be transported through point sources such as waste water outfalls or diffuse sources where contamination is related to rainfall events.

A practical guide to the design and implementation of assessments and monitoring programmes associated with recreational water is:

- Bartram J. and Rees G. (eds) (2000). *Monitoring Bathing Waters*. E&FN Spon, London.

4.2.3 Reclaimed water

Like drinking water, reclaimed water quality is usually categorised in terms of physical, chemical and biological parameters. The management of risk is usually based on a combination of treatment, controlled use and controlled exposure.

Treatment processes have not changed a great deal and are based on a combination of primary, secondary and tertiary treatment and disinfection. Detention in lagoons is a low technology but robust method of treating sewage and can be used to provide primary and/or secondary treatment. Tertiary treatment generally involves filtration and is required for uses with potential for higher exposures such as residential non-potable use.

4.3 Hazard Identification

Health risk assessment for chemical parameters was first documented in some detail in a series of publications of the National Research Council of the U.S. National Academy of Sciences (NAS, 1977; 1986; 1987; 1989). These expert panel reports, published as separate volumes in the series *Drinking Water and Health* addressed the emerging key issues underlying risk assessment of chemical contaminants in drinking water and provided a framework which has guided the evolution of health risk assessment of drinking water contaminants.

The most common and likely source of human health effects associated with water is through exposure to microbiological pathogens. The ability of a pathogen to cause illness is usually well established but in assessing water quality there is a tendency to ignore species variability. For example, while *Cryptosporidium* as a generic group has been identified as a cause of waterborne illness only one species *C. parvum* is regarded as causing human infections. In addition it is likely that only sub types of *C. parvum* are infectious for humans.

Water has been documented as a source of large disease outbreaks such as the 1993 Milwaukee outbreak of Cryptosporidiosis that was estimated to have infected over 400,000 people (Mackenzie *et al*, 1994). However, quantitative risk assessment for microorganisms has only recently developed in comparison with chemical risk assessment (Haas *et al*, 1999). Models for microbiological pathogens have been developed for a few organisms including *Cryptosporidium*, *Giardia* and some types of viruses but the models are limited. A range of factors that are generally not yet adequately considered include: human variability in the form of immune status and partial or total immunity through prior exposure, variations in virulence and variations in seriousness of illness outcomes. With a few exceptions (e.g. *Legionella*, *Naegleria fowleri*) water borne pathogens tend to be transient contaminants and not free-living organisms.

Limited quantitative microbiological risk assessment has also been undertaken for use of reclaimed water. As for drinking water, models have been developed for *Cryptosporidium*, *Giardia* and some types of viruses.

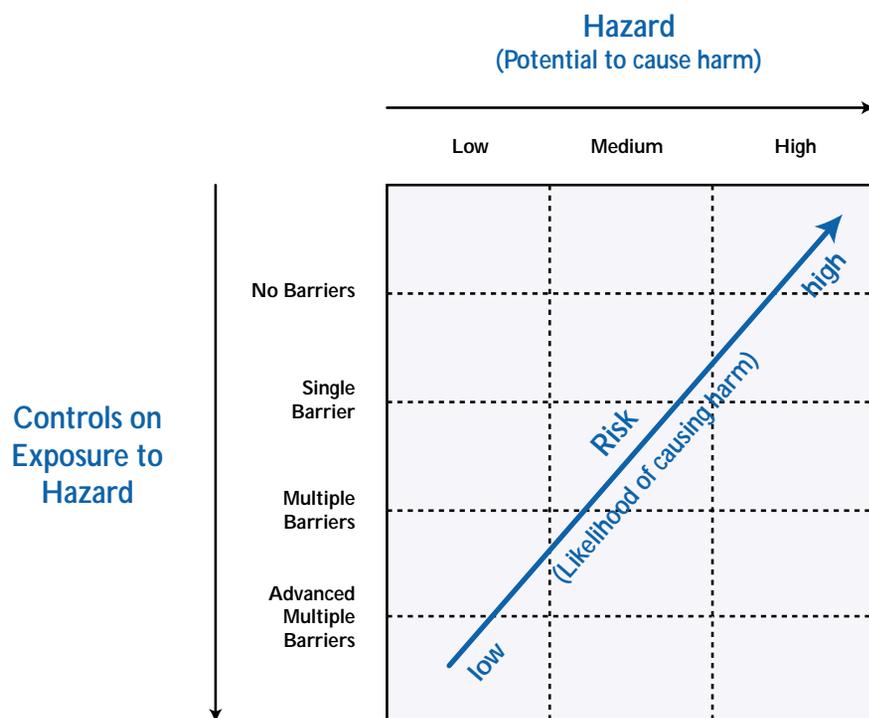
Drinking water health risk assessment provides a compelling example of risk tradeoffs because acute microbiological disease is almost certain to arise with surface water supplies that are not subjected to disinfection (Singer, 1999). However, since the discovery in 1974 that chloroform and other trihalomethanes are produced as by-products of chlorine disinfection, there has been a phenomenal growth in the identification of disinfection by-products (DBPs), as summarised in the organic DBP section of Table 1 A4. As a result there have been numerous epidemiological studies, some of which suggest possible links between DBPs and adverse health effects ranging from bladder cancer to adverse reproductive outcomes. Maintaining a sensible balance between the known infectious disease risks that can be controlled by disinfection and the hypothesised health effects associated with DBPs has presented the drinking water industry with a substantial challenge in the assessment and trade-off of competing risks (Craun, 1993). Issues associated with potential conflicts between

compliance with requirements for microbiological and DBP control are discussed in a US EPA Guidance Manual (1999).
 (www.epa.gov/safewater/mbp/mbptg.html)

Drinking water sources or recreational water are most likely to be polluted with human, animal, agricultural and industrial wastes. The hazards associated with human and animal wastes are predominantly microbiological while those associated with industrial wastes are generally chemical. Agricultural wastes can be microbiological (animal) or chemical (fertilisers,

pesticides). In addition pollution can exert secondary effects through the support of increased growth of naturally occurring organisms such as cyanobacteria which may pose health risks from both drinking water and recreational water use perspectives (Chorus and Bartram, 1999). This recent World Health Organization monograph, prepared with substantial input from Australian experts, provides an excellent illustration of a practical approach to hazard identification and preliminary risk assessment for cyanobacterial hazards to drinking water supplies. This is summarised as a generic approach in Figure 1 A4.

Figure 1 A4: A generic rationale for hazard identification and preliminary risk assessment for drinking water health risks



(adapted from Bartram *et al*, 1999)

A similar approach is likely to be included in guidelines being prepared by NHMRC and WHO for recreational water.

4.4 Multiple Barrier Approach to Reduce Contamination and Health Risks

The provision of barriers to the transmission of pathogens and contaminants is important in reducing health risks associated with water. The multiple barrier approach relies on the concept of using more than one type of protection or treatment in a series in a water treatment process to control contamination and provide overall process reliability, redundancy and performance.

An example of the multiple barrier approach to protect drinking water occurs in normal catchment-to-tap management. The barriers include the following:

- Protection of source water from contamination with an active catchment protection program;
- Long detention times within reservoirs (weeks to months);
- Water treatment e.g. coagulation, settling and filtration;
- Finished water to be disinfected before it enters the distribution system;
- Maintenance of an adequate disinfection residual throughout the distribution system; and
- Maintenance of the integrity of the distribution system i.e. no breaks in the pipes, roofs on water tanks etc.
- Monitoring for microbiological quality should be regarded as a check that the barriers are maintained.

4.5 Monitoring Methodologies

The most widely accessible comprehensive reference for techniques of water analysis and sampling is the publication, 'Standard Methods for the Examination of Water and Waste water'

(Clesceri *et al*, 1998). Explicit guidance on the frequency of monitoring for parameters that are covered by the ADWG has been provided in the ADWG document (NHMRC and ARMCANZ, 1996). Water quality monitoring has long been based on indicator or surrogate parameters to represent agents of health concern. For example, the presence of microbiological pathogens, which have been impractical to monitor directly, has been inferred by indicator bacteria such as the total or thermotolerant coliform bacteria. The presence of indicator organisms has been taken as a sign that water quality may have been compromised with the possible presence of enteric pathogens. Confidence in the reliability of these indicator organisms has been undermined by the finding of protozoan pathogens like *Cryptosporidium* and *Giardia* species that are substantially more resistant to chemical disinfection than the indicator organisms. This reality means that inactivating the indicator organisms by disinfection does not assure inactivation of the pathogens. These circumstances are further complicated by the lack of reliable methods to monitor for viable and infective strains of the resistant pathogens so that the relevance of non-specific monitoring data remains a challenge.

In the case of chemical contaminants, some parameters like the trihalomethanes (THMs) may be only indicator or surrogate measures for other chemical agents that may or may not pose health risks. There are also issues about the chemical species that are measured in water quality monitoring. For example, arsenic toxicity varies over a thousand fold depending on the chemical form of the arsenic. The more common inorganic forms of arsenate or arsenite that are most likely to be present in drinking water are believed to pose the greatest health concerns.

Guidance on sampling water has also been provided by Keith (1988; 1991; 1992). Water bodies are often not homogeneous mixtures and a number of issues need to be addressed in designing sampling programs including differences between stream flows and embayments, water depth, stratification and the impacts of silts and sediments as sources of microbiological and chemical contaminants.

4.6 Assessment of Summary Statistics and Presentation of Data

The appropriate format for presenting water quality data depends on the nature of the hazard. Microbiological hazards generally pose an acute risk so that short term monitoring is needed and transient excursions above guideline levels can pose the danger of waterborne disease transmission. Because real time (instantaneous) monitoring of microbiological parameters is currently not possible, factors which can be monitored frequently or continuously, like disinfectant residual and turbidity, are often used to document treatment performance and thereby infer acceptable microbiological control. Chemical parameters that pose a chronic risk, such as suspected carcinogens, are usually judged in relation to standards based on lifetime exposure. For these parameters, long-term average exposure is generally considered for dose, although it is usually expressed on a daily basis (i.e. as an average daily dose for a lifetime). The more recent interest in the possibility of adverse reproductive outcomes associated with various water quality parameters has changed this perspective making short-term (possibly even peak) exposures more relevant.

4.7 Censored Data and Levels of Reporting

As a general guide, reporting to a sensitivity of one tenth of the guideline level is preferred but may not be practicable for some substances, such as pesticides, where the guidelines have been set at a level of detection. Reporting levels need to be set sufficiently low so as to be able to distinguish parameter trends from background levels. Like most environmental data, water quality data are often highly skewed because sub-detection values cannot exist so that data sets are truncated at the detection limit. Often, log normal distributions may fit the data, unless a few extreme values skew the data more than a log normal distribution will readily accommodate.

4.8 Dose–Response Assessment

There are difficulties associated with dose–response assessments for both chemical and microbiological contaminants. Microbiological dose–response assessments are faced with the difficulty of considering human and microbiological variation. The likelihood of contracting an infection is influenced by factors such as immune status, immunity imparted by previous exposure and virulence of the specific type or strain of microorganism.

Measurement of chemical parameters in water is generally well developed. However, evaluating causal linkages and dose–response relationships between estimated doses and disease generally involves a great deal of uncertainty. Predictions are often based on extrapolation of high dose animal toxicology data to chronic low level exposures in humans. Thus, uncertainty arises from both interspecies extrapolation and high to low dose extrapolation. For chronic diseases like cancer, the causal linkages must be inferred from observational epidemiology studies for which drinking water contaminant exposures must usually be reconstructed from limited historical data. These realities raise considerable uncertainty about actual exposure levels, as well as the uncertainty arising from bias and confounding on the estimation of relative risk.

4.9 Exposure Assessment

There is a tendency to simplify exposure assessment by focusing on ingestion of standardised volumes of water. However, exposure to drinking water and recreational water contaminants can occur through ingestion, inhalation and dermal contact. For example, with volatile and lipophilic organic contaminants (e.g. THMs) doses from showering and bathing may be higher than via ingestion (Weisel and Jo, 1996). The scope and complexity of drinking water contaminant exposure assessment has recently been addressed in some detail (Olin, 1999) and is summarised in Figure 2 A4.

**Figure 2A4 removed from electronic version due to copyright restrictions.
If required, it is available in the hard copy of the document – page 181.**

In determining guideline values for drinking water a standard daily consumption is used which in Australia has been judged to be 2 litres per day for an adult. However, there is variation in consumption and individuals may derive drinking water from a number of sources including tap water at home and work, bottled water and rainwater. More detailed exposure evaluations must take into account the full range of contaminant exposure routes.

In recreational guidelines an estimated maximum ingestion of 100 mL per recreational session is used for both marine and fresh waters (NHMRC, 1990).

In regard to reclaimed water maximum exposures have been calculated for a number of uses including irrigation of edible crops (10mL), irrigation of public areas, golf courses etc (1mL) (Asano *et al*, 1992).

Determination of potential doses in terms of the concentration of contaminants in water is better developed for chemicals than for pathogens. For some chemicals (e.g. some pesticides), there may be health concerns at concentrations near routine detection limits. It is possible that these limits are higher than for other chemicals which can be detected in parts per billion or even lower concentrations. However, for many microorganisms there are no reliable or sensitive quantification methods and in some cases methods have not been developed to identify species or strains that can cause human infections.

4.10 Risk Characterisation

The characterisation of risk that is inherent in setting drinking water guideline levels can be generally summarised according to:

$$\text{Guideline Level} = \frac{\text{RL} \times \text{BM} \times \text{AF} \times \text{ED}}{\text{IR} \times \text{UF} \times \text{AT}}$$

Where:

Guideline Level = the guideline concentration of contaminant in water

RL = the reference toxicity level (often a no effect level)

BM = the body mass, often 70 kg for an adult

AF = what proportion of total exposure can be attributed to drinking water

ED = exposure duration (if exposure is less than continuous)

IR = an ingestion rate, often taken as 2L per day

UF = uncertainty factors applied to reduce the RL

AT = an averaging time of exposure, will equal ED if exposure is continuous

Health-related criteria have been established for a wide range of chemical contaminants in water and initial comparison of estimated exposure levels should be with the ADWG (NHMRC and ARMCANZ, 1996). An additional source of information is provided by the US EPA Drinking Water Health Advisories within the Integrated Risk Information System (IRIS) which can be found at: www.epa.gov/ngispgm3/iris/dwater.html. These Health Advisories provide data for drinking water exposures for up to one day, 14 days, 7 years and lifetime exposures.

Australian Models of Risk Assessment

A range of models are used by State, Territory and Federal agencies in Australia for regulatory, administrative and investigation purposes. Approaches dealing with contaminated soil, air, food and water have been identified in Appendices 1–4.

5.1 Chemical risk assessment

Several bodies are involved in the process for assessing chemical risk assessment. National chemicals legislation and responsible authorities are outlined in Table 1 A5.

Table 1 A5: Chemical risk assessment in Australia

	Industrial chemicals	Agricultural and veterinary	Medicine and medical chemicals	Food additives, contaminants, products processing and toxins
Agency	National Industrial Chemicals Notification and Assessment Scheme (NICNAS) within TGA	National Registration Authority (NRA) for Agricultural and Veterinary Chemicals	Therapeutic Goods Administration (TGA)	Australia New Zealand Food Authority
Ministry	Health and Ageing	Agriculture, Fisheries and Forestry	Health and Ageing	Health and Ageing
Scope	Assessment only, not registration based	Assessment and Product Registration	Assessment and Product Registration	Assessment and Product Registration
Relevant legislation	Industrial Chemicals (Notification and Assessment) Act 1989	Agricultural and Veterinary Chemicals (Code) Act 1994, Agricultural and Veterinary Chemicals Administration Act 1994	Therapeutic Goods Act 1989	Australia New Zealand Food Authority Act 1994 Food Standards Code
About the chemicals	Industrial chemicals are varied and cover, for example, dyes, solvents, adhesives, plastics, laboratory chemicals, paints, as well as chemicals used in cleaning products and cosmetics and toiletries	Agricultural products include chemicals which generally destroy/repel pests or plants. Veterinary products are used to prevent, diagnose or treat disease in animals (Toxicology and public health OH&S and environmental assessments conducted for the NRA by the Chemicals Unit of the TGA, NOHSC, and Environment Australia respectively).	Therapeutic goods included prescription and non-prescription (OTC) medicines. OTCs included complementary medicines (herbal, vitamins, minerals and homeopathic preparations), and some sterilants and disinfectants.	Chemicals are added to food for a number of reasons, for instance as a processing agent, preservation or as a flavouring or colouring. These are known as food additives.

5.2 Occupational⁶ Risk Assessment

The following processes are adopted by the Chemical Assessment Division of NOHSC.

5.2.1 NICNAS (existing chemicals)

Data requirements

For existing industrial chemicals, the data requirements depend on the assessment type. A standard dataset for a **full** Priority Existing Chemical (PEC) comprises information confirming the identity of the chemical, the physicochemical properties and use of the chemical (including import/manufacture volumes), all available toxicological/epidemiological data, detailed exposure information for workers, the public and the environment and risk management initiatives. The toxicological package includes available human, animal and *in vitro* data and ecotoxicity and biodegradability/fate data for the environmental assessment.

The dataset for a **preliminary** PEC may or may not include a detailed toxicological package or detailed exposure data. Risk assessment, in terms of a formal risk characterisation for specific uses is not carried out for preliminary assessments.

The dataset for a **secondary notification** assessment is determined in accordance with a set of circumstances (criteria) as set out in the ICNA Act. Should these circumstances require a re-evaluation of the risk(s) assessed in the original PEC report, then a formal risk characterisation is usually carried out.

Exposure data

Occupational exposure data is provided as statutory obligation (under the ICNA Act) from applicants (for assessment). This information is supplemented from literature review, site visits, international reports (e.g. OECD SIARs) and where data is lacking from modelling. The model

that has been used to date is the UK HSE EASE model, which provides estimates of airborne and dermal exposure for different occupational scenarios.

Where exposure by inhalation is the major route of exposure, and the toxicological database includes good quality inhalation data (human or animal), the common practice is to use 'external' exposure data (i.e. not to attempt to extrapolate to 'internal' dose) in the risk characterisation process (see below). When 'external' exposure data are used/determined, no adjustment is made to account for reduced personal exposures resulting from the use of personal protective equipment (e.g. respiratory protection, gloves etc.). However, where mechanical ventilation is installed, this can be factored into the EASE model, should suitable monitoring data (i.e. measured when ventilation has been installed and is operational) not be available. The quality of the monitoring data should also be a factor considered in the risk characterisation and exposure standard setting processes (see below).

Where dermal exposure is an important route of exposure and/or where the toxicological database does not provide an inhalation study, internal (dose) exposure may be estimated, utilising the available pharmacokinetic data, and used in the risk characterisation process.

5.2.2 Toxicological data

Toxicological and epidemiological/case study/clinical data is also provided as statutory obligation (under the ICNA Act) from applicants (for assessment). This data is supplemented from literature review and international reports (e.g. OECD SIARs, IPCS, IARC, ECETOC).

Currently, available toxicological and epidemiological data are evaluated in conjunction with available pharmacokinetic data, to estimate the critical NOAEL or, if not determined, the LOAEL for both acute and chronic exposures for each relevant route of exposure (i.e. oral, dermal

⁶ Under NICNAS, environmental and public health risk assessment (RA) is carried out by EA and TGA, respectively. Although there are differences in exposure calculation methods, the methodologies currently adopted for public health and environmental risk characterisations (i.e. NOAEL/Estimated human exposure ratio and PNEC/PEC ratio) are consistent with the margin of exposure (MOE)—also referred to as margin of safety (MOS)—approach adopted for OHS risk characterisation.

and inhalation). The health hazards for each endpoint are classified in accordance with the NOHSC Approved Criteria for Classifying Hazardous Substances.

The quality of the toxicological database should be a factor considered in the risk characterisation and exposure standard setting processes (see below).

5.2.3 Risk characterisation

The current methodology utilised by NICNAS is the 'margin of exposure' (MOE) approach.

In deriving the MOE, direct comparison is made of the critical NOAEL with the measured/estimated exposures for each occupational scenario of relevance to manufacture and use in Australia. This is carried out separately for inhalation and dermal exposure (where relevant) i.e. by using NOAELs derived specifically from each route of exposure.

Where exposures may be significant by both routes, the combined estimated internal dose may be used. In this case, the oral NOAEL (for the critical effect) is usually considered more appropriate NOAEL for deriving the MOE.

The resulting MOE, is then evaluated (for each route), taking into account the quality of the available database (e.g. whether derived from human data, uncertainties in the database etc.) and nature/severity of effect (e.g. carcinogen, sensitiser etc.). No specific values are assigned to component uncertainty factors (this is usually part of the exposure standard setting process carried out by NOHSC—see below). However, the risk characterisation process takes these uncertainties (NB these are identified in the report) into account in evaluating the adequacy of the MOE.

Based on the magnitude of the MOE, current risk management initiatives are assessed and where found inadequate, recommendations for additional exposure reduction measures (controls) or other risk management initiatives are promulgated. Recommendations may include regulatory action by NOHSC or other Agencies (e.g. TGA and EA, where public health and

environmental risks have been identified).

Recommendations to NOHSC may include: the setting of an occupational exposure standard (see below), review of an existing exposure standard (see below), scheduling of a substance in accordance with the model regulations for control of workplace hazardous substances and, as a last resort, phase out of use and manufacture.

5.2.4 NICNAS (new chemicals)

For new industrial chemicals, the data requirements depend on the notification category and are stipulated under the ICNA Act. A standard dataset comprises information confirming the identity of the chemical, the physicochemical properties and use of the chemical, detailed exposure information about how workers, the public and the environment are exposed to the chemical, and a standard toxicological package. The toxicological package includes animal and *in vitro* data for the human health assessment and ecotoxicity and biodegradability data for the environmental assessment.

Exposure assessment

The occupational exposure assessment is conducted by establishing the use pattern of the chemical and identifying the sources of occupational exposure. Exposure is then estimated by taking into account the routes of exposure, the frequency and duration of exposure, and measured worker data, for example, atmospheric and/or biological monitoring results. Information is needed for each of the scenarios where workers are potentially exposed to the chemical.

For new industrial chemicals, the occupational exposure assessment is usually qualitative, as measured data is unlikely to be available and there is insufficient information available to predict reliable quantitative estimates. Modelling, for example, using EASE, is occasionally used.

Toxicological assessment

Both human and experimental animal data are assessed in accordance with international guidelines to identify the critical health effects of

the chemical and to determine the dose–response relationship, with no observed adverse effect levels (NOAELs) established wherever possible. For new industrial chemicals, human data is usually not available. The health hazards of the chemical are classified in accordance with the NOHSC Approved Criteria for Classifying Hazardous Substances.

For new chemicals, the toxicological database may consist of studies which have been performed with a structural analogue of the notified chemical, or with a formulation. Adequacy and applicability of the data will be taken into account when performing the assessment. Where data gaps exist, or where toxicological data have not been provided, as with some classes of polymer, the toxicological hazard may be predicted from the chemical's physical properties or the characteristics of structurally related chemicals, given that factors such as volatility, solubility and molecular weight can indicate the likely extent of absorption across biological membranes.

Risk characterisation

The health risk to workers is characterised by integrating the occupational exposure and toxicological assessments. For brief or short-term exposures, human data and information from acute toxicity studies in animals are taken into account to determine the risk of adverse health effects such as acute respiratory effects and skin irritation. For longer term and repeated exposures, the health risk to workers is characterised by firstly comparing exposure estimates with NOAELs to give a margin of exposure (MOE), and then deciding whether there is cause for concern.

Matters taken into account when characterising the risk, include the uncertainty arising from the variability in the experimental data and inter- and intra-species variation, the nature and severity of the health effect and its relevance to humans and the reliability of the exposure information.

Where it is not possible to determine a NOAEL or LOAEL, for example, from lack of suitable data, the risk is evaluated on the basis of qualitative or

quantitative exposure relevant to the group of workers being considered. For new chemicals, a more qualitative characterisation takes place as exposures are often unknown or more difficult to predict.

5.2.5 NOHSC (agricultural and veterinary chemicals)

The Agvet Section conducts OHS risk assessments on behalf of the NRA, under two assessment programs, namely 'Product Registration, and 'Chemicals Review'.

Data requirements

The Agricultural and Veterinary Chemicals Code Act (1994) makes provision for the evaluation, registration and control of Agvet chemical products. Data required for the OHS assessment of Agvet chemical products include:

- use pattern of the product;
- formulation composition of product;
- physicochemical properties of the active constituent and product;
- toxicology of the active constituent and product; and
- exposure data.

Exposure data

It is a requirement under the Act that all available exposure data and adverse incident reports must be provided to the NRA by applicants (for assessment). Exposure data may cover manufacture/formulation of Agvet products and end use situations. Exposure data provided by applicants is supplemented from literature review, international reports (e.g. US EPA, UK MAFF), field/site visits and modelling. The model used to date is the UK Predictive Operator Exposure Model (POEM). Occasionally, exposure data from the US Pesticide Handlers Exposure Database (PHED) has been used where applicants provide subset exposure data.

The exposure assessment constitutes consideration of the use pattern of the product,

identification of potential exposure scenarios and predominant route(s) of exposure in each case. For Agvet chemicals, it is generally accepted that skin contamination is the predominant route of exposure. In general, inhalation exposure comprises only a small proportion of total exposure, except when the product is applied in an enclosed space (e.g. fumigants). Therefore, where the toxicological database includes dermal dosing studies of appropriate quality and duration, 'external' exposure data are used in the risk characterisation process.

In the absence of appropriate dermal studies, internal dose is estimated using external dermal exposure data corrected for dermal absorption. Absorption is estimated using *in vitro* and/or *in vivo* percutaneous absorption data. In the absence of chemical specific data, analogue data may be used, where available. Total body burden is determined by integrating exposure from inhalation and dermal routes and comparing the result with systemic effects data to ascertain potential health risk.

Where biomonitoring data are available, a biological monitoring approach may be used, as absorbed dose data interpreted with the aid of pharmacokinetic data are likely to be more accurate than the estimation of internal dose given by exposure data corrected for dermal and respiratory penetration.

Pesticide exposure assessments also take into consideration the protection afforded by label specified protective equipment. Default protection factors are utilised in the absence of specific data.

Toxicological data

Toxicological and epidemiological/case study data provided by applicants are evaluated by the Therapeutic Goods Administration (TGA). The TGA evaluation is considered in order to determine relevant endpoint(s) and NOEL/LOEL(s) for use in the OHS risk assessment. The selection is based on factors including: quality of the database, frequency of use of the product, health significance of the

endpoint(s) and predominant route of exposure.

For new Agvet chemicals, the health hazards of the chemical are classified in accordance with the NOHSC Approved Criteria for Classifying Hazardous Substances.

Risk characterisation

The risk assessment takes into consideration the hazard of the chemical and the potential for occupational exposure. In general, an end use risk assessment is conducted for Agvet products. Potential exposure is determined by the use pattern of the product and current agricultural/animal husbandry practices (including existing exposure mitigation methods such as protective equipment and engineering controls).

As for industrial chemicals (NICNAS—Existing Chemicals), Agvet assessments currently utilise the 'margin of exposure' (MOE) approach. The benchmark MOE is determined on a case by case basis, following consideration of the quality of the database, nature and severity of the health effect and known variability in human metabolism of the chemical. In general, a 10 fold factor is considered appropriate to account for interspecies extrapolation and a similar factor (10x) for intraspecies variability.

Current exposure mitigation methods are evaluated quantitatively, where possible. In the absence of data or models, qualitative assessments are conducted based on generalised information about the use pattern and 'scientific judgement'. Where current exposure assessment methods are found to result in unacceptable risk, additional exposure and risk reduction methods may be recommended.

OHS recommendations on regulatory action may include: restrictions on use of the chemical, exposure mitigation methods in accordance with the hierarchy of controls under Hazardous Substances legislation or review of an existing exposure standard.

5.3 Exposure Standards (NOHSC)

5.3.1 Statutory process outline

National exposure standards for atmospheric contaminants in the occupational environment are declared by the National Occupational Health and Safety Commission (NOHSC) as guidelines to be used in the control of occupational health hazards [NOHSC:1003 (1995)].

The national exposure standards are not dividing lines between safe and dangerous concentrations of chemicals, neither are they a measure of relative toxicity. Appropriately qualified and experienced persons should undertake interpretation of the national exposure standards.

The national exposure standards are referenced in the NOHSC National Model Regulations for the Control of Workplace Substances [NOHSC:1005 (1994)], under regulation 12(4) related to employers' duties and the control of exposure provisions.

Enactment by the Commonwealth, State and Territory governments of uniform hazardous substance legislation, based on the national model regulations, places the national exposure standards in a regulatory context across all jurisdictions of Australia.

5.3.2 Data requirements

In 1999, the National Commission approved a new methodology for reviewing and updating the national exposure standards which maximises the use and acceptance of overseas standards from government and non-government sources, and minimises the need to develop standards in Australia.

Primary sources include the United Kingdom Health and Safety Executive HSE 'Occupational Exposure Limits', the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values, the German Government 'MAK' values and European Union standards.

These sources were selected after an assessment against several factors including quality and

availability of supporting documentation, integrity of the development process and consistency with the NOHSC philosophy of transparency, development through consultation, and scientific robustness.

5.4 Use of Toxicological/Exposure Database

Process is designed to minimise reassessment of toxicological data, rather relying on integrity of development process and inherent sound science of overseas systems.

Systems chosen represent an appropriate evaluation of available toxicological and epidemiological data sources by acknowledged agencies.

Where *de novo* standards are to be developed, the NOHSC Hazardous Substances Subcommittee will determine the broad parameters of the data requirements for any review, without limiting the range of toxicological data to be used by, for example, a consultant reviewing a national exposure standard.

NICNAS PEC Reports, supporting documentation from HSE, ACGIH and MAK, overseas scientific publications (ECETOC Reports, IPCS Environmental Health Criteria, CICAD reports, IARC Monographs, Criteria Documents from the Nordic Expert Group), are regarded as appropriate sources for risk assessment consideration in any review, and will continue to be employed in this regard.

5.5 Factors Considered in Standard Setting

Health-based standards are set on the basis of one or more critical endpoints (e.g. carcinogenicity, irritation). Where available, NOAEL levels for the critical effect can be used as the basis of the standard. Arbitrary safety factors (margins of safety) may be applied to the standard, and examples of 33–50 per cent of the value of an observable effect level (animal or human data) have been recommended on occasion.

All national exposure standards are subject to an impact analysis, the depth of which varies with the estimated impact of the proposed change to the standard, following a review. From a qualitative impact analysis of identifying where additional costs and benefits would be borne as a result of a change in the standard, through to a full economic impact analysis, NOHSC requires all changes to include this consideration.

5.6 Role of the Chemicals Unit of the TGA in Public Health Risk Assessment

The 'Chemicals Unit' which is part of the Chemicals and Non-Prescription Medicines Branch (CNPMB) of the TGA, exists as a professional scientific group to provide advice to the Minister, to the Scientific Director of the Unit, to appropriate Committees of State and Commonwealth Government agencies, and to the public, on possible risks to health associated with exposure to chemicals in the environment. These include agricultural chemicals, veterinary drugs, industrial chemicals and other chemicals which may have an impact on public health. The Unit is made up of two sections, the Chemical Products Assessment Section (CPAS) and the Chemical Review and International Harmonisation Section (CRIHS), together with the Scientific Director of the Branch and the secretariat of the Advisory Committee on Pesticides and Health (ACPH).

5.6.1 Chemical products assessment

The main function of CPAS is to assess the toxicology and public health aspects of applications for registration of new agricultural and veterinary chemicals. It also has an important role in assessing the public health aspects of notifications for new industrial chemicals and of re-assessment of existing industrial chemicals identified for priority reviews.

CPAS traces its origin back to 1984 when the then Toxicology Evaluation Section (TES) was created following a Senate enquiry into hazardous chemicals, which noted the increasing use of chemicals in the environment. Increasing public concern and media attention to chemical exposure

demanded greater accountability from the chemical industry and from government regulators. In addition, chemical residues in export produce (e.g. beef, wheat, dairy goods) have important implications for trade; Australia must be able to ensure standards of chemical regulation acceptable to international markets, as well as to domestic consumers. In acknowledgment of public health and trade concerns, chemicals regulation as an area of public policy has developed, recognising that the numbers of chemicals requiring assessment and the complexity of the assessment process have increased. The TES formed an integral part of this process, providing scientific advice to enable appropriate regulation of chemicals in order to safeguard public health. In 1996, the role of the section was broadened and the TES was renamed the Chemical Products Assessment Section (CPAS), with a particular focus on assessing agricultural and veterinary chemicals, as part of the National Registration Scheme (NRS) which is managed by the National Registration Authority for Agricultural and Veterinary Chemicals (the NRA).

Through the Scientific Director, recommendations on individual chemicals are provided to the NRA and form an important component of the decisions by the NRA in the registration of chemicals. Reports include scheduling recommendations made by the National Drugs and Poisons Schedule Committee (NDPSC) and may include additional toxicology advice provided by the Advisory Committee on Pesticides and Health (ACPH). (The recommendations of NDPSC are formally incorporated into the 'Standard for the Uniform Scheduling of Drugs and Poisons' (SUSDP) which forms the basis for national uniformity in drugs and poisons scheduling.)

The public health implications associated with the use of industrial chemicals are also assessed by CPAS staff, in accordance with the provisions of the National Industrial Chemicals (Notification and Assessment) Act. Advice is provided to NICNAS for eventual incorporation into a consolidated assessment report on occupational health, human health, and environmental effects.

Additionally, CPAS may be requested to assess the toxicological hazards associated with a range of natural and synthetic chemicals. Examples of these include vitamins, herbs, cosmetic ingredients, certain consumer products, and some environmental contaminants.

Evaluation Reports: Reports are structured to allow for ready access to the main points arising from the assessment. They are written to provide sufficiently detailed information for the reader to form an independent conclusion and aim to obviate the need, during a subsequent review of the chemical (or product), to refer back to the original study data.

Reports include:

- **Submission Summary**—briefly outlines the results from all studies accompanying the application/submission and includes a discussion of the important findings and appropriate recommendations.
- **Main Body of the Report**—contains detailed outlines of the studies conducted with the chemical, including methodology, the extent of monitoring for biological changes, all treatment-related effects and any other observations or information which may be pertinent to the assessment of the significance of the findings.
- **Consolidated Summary**—contains the integrated summaries of study results from previous submissions relating to the particular active ingredient, plus the newly evaluated data.
- **Confidential Business Information**—impurity profiles, product ingredients and information on additives in formulations etc are included in removable appendices at the end of the report.

In the Main Body of assessment reports on agricultural and veterinary chemicals, the following study types are assessed:

- **Toxicokinetics and Metabolism**—studies on the fate of the chemical in laboratory animals.

- **Acute Studies**—single dose toxicity studies, irritation and sensitisation studies on the active ingredient and on formulated products containing the active ingredient.
- **Short-Term Studies**—administration of multiple doses to test species for less than 90 days.
- **Subchronic Studies**—duration of dosing at least 90 days and less than 12 months.
- **Chronic/Carcinogenicity Studies**—administration for 12 months or longer. Carcinogenicity studies involve administration for the major portion of the animal's lifespan.
- **Reproduction Studies**—administration prior to, during, and following mating and pregnancy for one or more generations.
- **Developmental Studies**—administration to pregnant animals during the period of major organogenesis.
- **Genotoxicity Studies**—studies of the effects on genetic material.
- **Other Studies**—includes neurotoxicity, immunotoxicity, studies on humans, and toxicity studies on degradation products and impurities.

5.6.2 Chemical review and international harmonisation (CRIHS)

Until the mid-1990s, there was no formal program to review 'old' pesticides and veterinary drugs in Australia. However, two programs provided an informal mechanism for reviewing a number of aspects of chemicals safety. Firstly, a review process for individual chemicals occurred on the suspicion of human health and/or environmental concerns, or following international regulatory action(s); in practice this usually involved reviewing limited extra data related to the particular issue of concern rather than conducting a comprehensive review. Secondly, the Technical Grade Active Constituent

(TGAC) Scheme introduced in 1985, while designed primarily to identify the source and ascertain the quality of technical grade materials used for formulating end-use-products (EUPs) used in Australia, had significant elements of a review program in that mammalian toxicology data and environmental data were collected and reviewed. As a result of the TGAC scheme, toxicology data on over 400 pesticides were reviewed with respect to public health considerations over a 6–7 year period. As a consequence of the above two programs, Australia was well placed to develop further more formal review arrangements.

Australia introduced a formal program to review existing agricultural and veterinary chemicals in 1994 under the title of the Existing Chemicals Review Program (ECRP), managed by the NRA. The program carries out systematic reviews of existing agricultural and veterinary chemicals on a priority basis. This program is one of a number of initiatives arising from a 1990 senate enquiry into aspects of the legislative, administrative and regulatory procedures for agricultural and veterinary chemicals. The ECRP stemmed largely from the fact that many registered chemicals entered the market place based on criteria now recognised as outdated by today's regulatory standards. The ECRP involves cooperative arrangements between the Chemicals Unit (public health), Environment Australia (EA—environment), the National Occupational Health and Safety Commission (NOHSC—occupational health and safety) and the NRA (chemistry, efficacy and agricultural issues, residues, and registration).

The goal of the ECRP is to ensure that agricultural and veterinary chemicals in use in Australia can be used safely and effectively. The program operates according to the principles of openness, fairness and consistency with regard to public consultation, selection of chemicals for review, and standards of assessment. All aspects of a chemical (public health, OH&S, environmental, efficacy, and animal and crop safety) are considered in a review. Thus, the ECRP has been implemented to:

- ensure that the chemicals remain safe and effective when used according to label instructions by specifically considering toxicity and exposure patterns in relation to public health, occupational health and safety (OH&S); and environmental control mechanisms; known and potential environmental impacts; efficacy; safety issues in relation to target species (animal and crop); management options to reduce identified risks;
- maintain the protection of Australian trade and commerce in agricultural produce and livestock;
- address community concerns and general interest in agricultural and veterinary chemicals by providing information to the public on the use of chemicals and their environmental, public health and OH&S aspects; and
- consider public nomination of chemicals for review.

Agricultural and veterinary chemicals are selected for review on the basis of agreed criteria including their potential health and environment hazard(s), exposure potential, age and adequacy of the database, efficacy, international regulatory actions, and trade and other agricultural implications. The ECRP chemical selection process also incorporates a mechanism for public nominations of chemicals.

The toxicology and public health aspects of ECRP reviews are assessed by staff of the CRIHS. The Section provides toxicological and chemicals policy advice, as required, to the Scientific Director of the CNPMB, appropriate Committees of State and Commonwealth Government agencies, and to the public. It also provides scientific secretariat support to the Advisory Committee on Pesticides and Health (ACPH), an independent expert advisory committee to the Department and to the National Registration Authority for Agricultural and Veterinary Chemicals (the NRA).

The Section also undertakes technical policy development and provides health advice on international chemicals treaty negotiations. It interacts with the Population Health Division of the Department of Health and Ageing on a range of environmental health issues.

An important role of CRIHS is to encourage, and where practical, to extend, international harmonisation of chemicals regulation including toxicological reviews and re-registration programs. Another important function of the Section is to ensure public access to information relevant to the use of chemicals and the hazards they pose, especially pesticides.

5.6.3 Assessment processes within the chemicals unit

Toxicologists within the Chemicals Unit assess mammalian toxicology and toxicokinetic data and prepare written assessment reports which carry sufficient detail of the studies and findings to allow an independent assessment of the data. As the primary emphasis is on independent assessment, limited regulatory status is given to company summaries and company sponsored 'expert reports'; it is important that all toxicity data and the methods by which they are obtained be subjected to critical and independent scientific assessment.

Hazard/Risk Assessment: Given the complexity of biological data interpretation and the need for professional judgement and a flexible approach when assessing the public health risk of chemicals, it has not been the policy to establish prescriptive methodologies for hazard and risk assessment, although several guidance documents for evaluators have been drafted. In general, a qualitative approach is used to assess chemical risk. The approach taken to derive an Acceptable Daily Intake (ADI) follows the principles outlined in Environmental Health Criteria Monographs no's 104 and 210 prepared by the WHO/UNEP/ILO International Programme on Chemical Safety (IPCS). (A notable exception to the use of principles proposed in the EHC 104 is the endpoint for cholinesterase inhibition by organophosphorus compounds and carbamates, in

which case Australia has continued to use more conservative estimates based on inhibition of plasma cholinesterase rather than inhibition of red cell or brain acetylcholinesterase.)

Whilst the main focus of agricultural and veterinary chemical assessments is a consideration of human exposure to pesticides through ingestion of residues in food and/or drinking water, the direct dermal or inhalational exposure of the public, as users of chemicals (in the home garden/domestic setting) or as bystanders to agricultural or licensed Pest Control Operator (PCO) use, is also taken into account. (Risk assessments for workers exposed in the occupational setting are performed by the NOHSC—see Section 5.2)

In general, a classification system for public health aspects is not used when regulating chemicals with potential carcinogenicity. The potential human carcinogenicity of chemicals is assessed using a weight-of-evidence approach which takes into account epidemiological data, carcinogenic potency in animals, biological relevance and potential human exposure. Australia, in this regard, supports the general approach outlined by IPCS. Until there is a better understanding of the factors which influence carcinogenicity, the basis for a classification scheme remain unclear and thus the benefits of using such a scheme to regulate chemicals in the area of public health are limited. Indeed, whilst existing classification schemes for carcinogens are based on assessment of carcinogenic hazard, there is a danger that these may be misinterpreted as a classification of carcinogenic risk.

Exposure Assessment: Calculations of likely daily intakes of pesticide residues [either National Theoretical Maximum Daily Intakes (NTMDIs) or National Estimated Dietary Intakes (NEDIs) are based on the procedures as outlined in the 'Guidelines for Predicting Dietary Intake of Pesticide Residues' (1989) published by the UNEP/FAO/WHO Food Contamination Monitoring Programme in collaboration with the Codex Committee on Pesticide Residues.

Food consumption data is used in dietary risk assessment and is available from the Australian Dietary Survey (ADS) and the Market Basket Survey (MBS). The ADS estimates actual food intakes in various subgroups of the population, taking into account such factors as age and ethnic background. The MBS measures the amount of pesticide residue in ready-to-eat food based on a typical diet for different age groups. Estimated daily food residue intake can be compared with the ADI.

Whilst there is no formal program to assess human exposure to pesticides in the domestic setting, pesticides for domestic use are restricted to those of low toxicity and they have appropriate controls on availability, packaging and labelling. Additional exposure assessment may be carried out where a particular concern arises.

Risk management: Toxicological issues may raise concerns with respect to supply, availability, and use of agricultural or veterinary chemicals. The supply and availability of chemicals can be managed through NRA's registration process; that is, approval for pesticide Technical Grade Active Constituents (TGACs) may not be granted (or be withdrawn), approval for particular uses of a pesticide or veterinary chemical may not be granted (or be withdrawn), or registrations for particular products may not be granted (or be withdrawn), in order to eliminate or reduce potential public exposure.

The use of registered agvet products on the market can be regulated through poisons scheduling and appropriate labelling. The Commonwealth Government, acting on the advice of its National Drugs and Poisons Schedule Committee (a committee now established under the TGA Act), recommends classification of drugs and poisons which are published in the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP); these federal recommendations are adopted by State legislation. The more restrictive schedules prescribe restrictions on supply and use, as well as the use of appropriate signal headings on labels.

The poisons schedule classification of a chemical and its formulated products, together with product labelling instructions (first aid and safety directions), help control the availability of products and help minimise the exposure of users.

5.7 Standards Australia Model of Risk Management

A risk management Standard has been published by Standards Australia (1999). This is directed towards 'as wide a range of risk and risk management disciplines as possible' for application to 'a very wide range of activities or operations of any public, private or community enterprise, or group' so as to establish 'a systematic risk management program'. The Standard provides 'a generic guide for the establishment and implementation of the risk management process involving establishing the context and the identification, analysis, evaluation, treatment, communication and ongoing monitoring of risks'

The risk management process outlined in the Standard contains a model of risk assessment and uses the term 'risk analysis' to describe the process. 'Risk analysis' is defined as 'a systematic use of available information to determine how often specified events may occur and the magnitude of their consequences'.

The risk management Standard has been followed by a further Standard 'Environmental risk management—Principles and process. HB 203: 2000 (Standards Australia, 2000). This gives more extensive detail on environmental risk management using the framework established in AS/NZS 4360: 1999.

Both Standards provide qualitative measures of consequence and likelihood. Appendices in HB 203: 2000 detail sustainability principles, links between environmental risk and environmental management systems, discussion of how the acceptability of risk may be considered, sources of information for risk identification and cost-benefit analysis.

International Models of Risk Assessment

6.1 Risk Assessment in Canada

In 1993, Canada published a formal Risk Determination framework that defined and described the risk assessment and risk management process in a structured way. The framework reflected practices that had been occurring for a number of years. A process of review began in 1997 and the term 'risk determination' was replaced with 'risk management'.

The revised risk management process:

- has risk assessment as an inherent part of risk management rather than as a separate process;
- has a focus on adverse health effects but examines how information from sources such as the biophysical sciences, social sciences and economics can contribute to an understanding of risk;
- clarifies the risk management process, decisions and related information, and the roles of all parties involved in the risk management process; and
- provides broader participation in the risk management process.

After a step that identifies the problem and its context, a step for assessing potential risks and benefits occurs. The risk assessment component is a four stage process comprising:

- **Identify hazards.** The methods used vary depending on the type of agent involved and whether it is being reviewed prior to or after entering the market or environment;
- **Characterise hazards.** This involves the qualitative and/or quantitative evaluation of the nature of the adverse health effect(s) that humans may experience under expected levels of exposure. The preferred source of data is well-designed and conducted epidemiology studies, combined with documented exposure assessments;

- **Assess exposures.** Deterministic exposure assessments using generated single-point estimates of exposure are most common. Probabilistic assessments are used for more extensive assessments aimed at long term management of a risk e.g. fish and wildlife contaminants, food-borne microorganisms and consumer products. High exposure scenarios are used occasionally, particularly for exposure assessments involving chemical hazards such as environmental and food borne chemicals and consumer products for which extensive laboratory-exposure, epidemiological monitoring and surveillance data are available. This is becoming less common because a decline in available data e.g. from reduced animal experimentation; and
- **Characterise risks** using scientific data.

6.2 Risk Assessment in the United States of America

The development of regulatory risk assessment approaches became prominent in the USA in the 1980s but quantitative risk assessment dates to 1976 when the brief and generic EPA guidelines for cancer risk assessment were published (Hrudey, 1998).

One important landmark was a Supreme Court decision in 1980 when an Occupational Safety and Health Administration (OSHA) standard for exposure to benzene in the workplace was struck down. The policy had been aimed at reducing exposure as far as technologically possible but did not consider whether the existing concentration posed a significant risk to health. The majority of the court concluded that under their legislation, OSHA could only regulate if benzene posed a significant risk of harm. While 'Whose significant risk of harm' was not defined, the decision highlighted that some form of quantitative risk assessment was required as the basis for deciding whether the risk was large enough to warrant regulation (NRC, 1994).

Following from this judgement, Congress instructed FDA to have the National Research Council (NRC) appraise federal efforts to use risk assessment in 1981.

Drawing on work done previously by the Environmental Protection Agency, the Food And Drug Administration, the Occupation Safety And Health Administration, International Agency for Research on Cancer and the National Cancer Institute, the NRC report (1983) recommended a risk assessment on specific definitions of risk without recommending specific methods for the conduct of risk assessment.

Two key recommendations of the 1983 report were:

- A clear conceptual distinction between risk assessment and risk management should be maintained. However it was recognised it was not necessary nor advisable for a physical separation of the two activities.
- The scientific basis for risk assessment should be detailed along with default options. It was intended that the guidelines should be flexible and allow departures from the defaults if there was appropriate data to indicate that the default option was not appropriate.

The NRC committee did not recommend a specific methodology for risk assessment but noted that there should be opportunities for continuing review of the science underlying the guidelines and of the associated default options (NRC, 1994). The report acknowledged the critical role of science policy judgements and that these must be distinguished from scientific facts.

The Office of Science and Technology Policy brought together scientists from regulatory agencies, the National Institutes of Health and other federal agencies. This body reviewed the scientific basis of risk assessment of chemical carcinogens and adopted the framework for risk assessment proposed by the NRC. Only the Environment Protection Agency adopted a specific set of guidelines for carcinogen risk assessment (in 1986). The Environment

Protection Agency has gone on to issue guidelines for other adverse health effects (mutagenicity, developmental toxicity, effects of chemical mixtures, reproductive risk)

An important step in the application of these methodologies is to regulatory decision making was the EPA's adoption of risk assessment to guide decisions at major contaminated sites. It went on to apply risk assessment methodologies to decisions regarding pesticide residues in food, carcinogenic contaminants of drinking water supplies, industrial emissions of carcinogens to surface waters, and specified industrial chemicals (NRC, 1994).

The linearised multistage model using upper bound estimates has underpinned US regulatory risk assessment of carcinogens. It has been labelled as 'one of the most conservative models used in QRA' (IEH, 1999b). The US EPA has proposed changing from the linearised multi stage approach to a benchmark dose approach as their default model (US EPA, 1996) but the outcome of the proposal is not yet determined. The proposal remains in draft form and a recent attempt by the US EPA to recognise a threshold for carcinogenic effects from chloroform was withdrawn.

6.3 Risk Assessment in the United Kingdom

In 1996 the Government/Research Councils Initiative on Risk Assessment and Toxicology was established to review current practices for managing risks to health from chemical and to promote improved risk assessment decision-making. The agencies involved covered a wide variety of risks including those from food contaminants and additives, agricultural pesticides, biocides, veterinary products, occupational exposures, consumer products, air quality, water quality, land quality, and human medicines. As a result of the deliberations of the Initiative, a four stage process of risk assessment has been proposed consisting of:

1. identifying the properties of chemicals that can lead to adverse (toxic) health effects (hazard identification);

2. obtaining quantitative information about the hazard including, where possible, information on dose–response relationships (hazard characterisation);
3. assessing exposure to the chemical (exposure assessment); and
4. comparing exposure and hazard information (risk characterisation).

The Initiative has described the variety of risk assessment practices used in different government departments as a step towards establishing a common framework for the procedures used, identifying the major areas of uncertainty and weakness in current risk assessment processes, and establishing where these risk assessment processes might benefit from harmonisation across departments.

There are substantial differences between departments and agencies in the degree of caution incorporated into risk assessment for factors such as:

- the size of uncertainty factors applied when there are thresholds for toxic effects;
- the use of mathematical approaches for effects with or without a threshold. Mathematical modelling (using Probit analysis of the best available data set) may be used as one component of the risk assessment;
- the approaches to the assessment of genotoxic carcinogens. The UK has tended to use a qualitative weight of evidence approach to the evaluation of carcinogenic risk and has tended to avoid the use of mathematical approaches for quantitatively assessing risks from genotoxic carcinogens and they are rarely, if ever, carried out by UK regulatory agencies. The UK Department of Health's Committee on Carcinogenicity does not support the routine use of QRA for chemical carcinogens (IEH, 1999b);

- the treatment of data gaps and efficiency;
- the degree of protection for general population exposures compared to occupational exposures; and
- the degree of conservatism built into worse case exposure estimates (IEH, 1999b).

Particular interest has been taken in strategies for dealing with variability within the human population as a result of factors such as age, sex, pregnancy status, health status, lifestyle, and genetic factors. Physiologically-based pharmacokinetic modelling is considered to help to highlight and reduce the uncertainties of estimating the dose of an agent the body or parts of the body may receive after exposure.

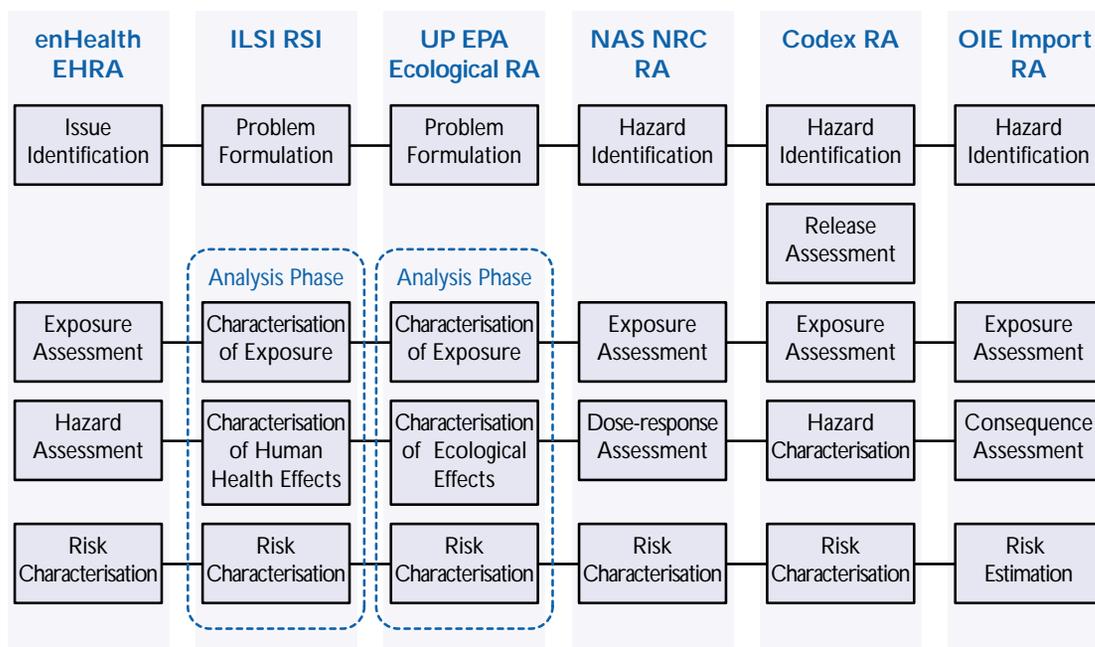
A Procedure for Microbiological Risk Assessment (ACDP, 1996) has detailed several stages for the process of microbiological risk assessment which is undertaken after the cause for concern is determined:

- Identification of the source(s) of the hazard(s) and the conditions under which adverse consequences could occur; and
- Reviewing and quantifying the risk consequent upon each hazard.

6.4 Terminologies used in Risk Assessment

While the fundamental processes are usually similar, slightly different terminologies are used internationally to describe components of the risk assessment process. ILSI (2000) has produced a comparison table of proposed models and how they fit in with the NAS paradigm. (See Figure 1 A6).

Figure 1 A6: Terminologies used in risk assessment



(adapted from ILSI, 1996 with permission)

WHO/IPCS Conceptual Framework for Cancer Risk Assessment

7.1 Introduction

This section describes the cancer endpoint or endpoints that have been observed and identifies which of these is addressed in the analysis. (The nature of the framework is such that only one mode of action is analysed at a time; hence, for example, tumour types associated with a different mode of action, even if recorded in the same animals, will require separate framework analyses). However, where different tumours are induced by related mode of action, they are best addressed in a single analysis. It should also be noted that some modes of action will involve multiple contributing components.

7.2 Postulated Mode of Action (theory of the case)

This section comprises a brief description of the sequence of events on the path to cancer for the postulated mode of action of the test substance. This explanation of the sequence of events leads into the next section which identifies the events considered 'key' (i.e. measurable) given the data base available for the analysis.

7.3 Key Events

This section briefly describes the 'key events'—i.e. measurable events that are critical to the induction of tumours as hypothesised in the postulated mode of action. To support an association, a body of experiments needs to define and measure an event consistently.

Pertinent observations: e.g. tumour response and key events in same cell type, sites of action logically relate to event(s), increased cell growth, specific biochemical events, organ weight, histology, proliferation assays, hormone or other protein perturbations, receptor-ligand changes, DNA or chromosome effects, cell cycle effects. For example, key events for tumours hypothesised to be associated with prolonged regenerative proliferation might be cytotoxicity in as measured histopathologically and an increase in labelling index. Key events for induction of urinary bladder tumours hypothesised to be due to formation of bladder stones composed primarily of calcium

phosphate might include elevated urinary calcium, phosphate and pH, and formation of bladder stones followed by irritation and regenerative hyperplasia of the urothelium

7.4 Dose-Response Relationship

This section should detail the observed dose-response relationships and discuss whether the dose-response for the key events parallels the dose-response relationship for tumours. Ideally, one should be able to correlate increases in incidence of a key event with increases in incidence or severity (e.g. lesion progression) of other key events occurring later in the process, and with the ultimate tumour incidence. Comparative tabular presentation of incidence of key events and tumours is often helpful in examining dose-response.

7.5 Temporal Association

This section should detail the observed temporal relationships or sequence of events and discuss whether the key events precede the tumour response. One should see the key events before tumour appearance; this is essential in deciding whether the data support the postulated mode of action. Observations of key events at the same time as the tumours (e.g. at the end of a bioassay) do not contribute to temporal association, but can contribute to analysis in the next section. Most often, complete data sets to address the criterion of temporality are not available.

7.6 Strength, Consistency and Specificity of Association of Tumour Response with Key Events

This section should discuss the weight of evidence linking the key events, precursor lesions and the tumour response. Stop/recovery studies showing absence or reduction of subsequent events or tumour when a key event is blocked or diminished are particularly important tests of the association. Consistent observations in a number of such studies, with differing experimental designs increases that support since different designs may

reduce unknown biases or confounding. Consistency, which addresses repeatability of key events in the postulated mode of action for cancer in different studies is distinguished from coherence, however, which addresses relation of the postulated mode of action with observations in the broader database (see point 7.7). Pertinent observations: e.g. tumour response and key events in same cell type, sites of action logically relate to event(s), initiation- promotion studies, stop/recovery studies.

7.7 Biological Plausibility and Coherence

The postulated mode of action and the events that are part of it need to be based on current understanding of the biology of cancer to be accepted, though the extent to which biological plausibility as a criterion against which weight of evidence is assessed is necessarily limited, due to considerable gaps in our knowledge in this regard. One should consider whether the mode of action is consistent with what is known about carcinogenesis in general (biological plausibility) and in relation to what is also known for the substance specifically (coherence). For the former, likeness of the case to others for structural analogues may be informative (i.e. structure activity analysis). Additionally, this section should consider whether the database on the agent is internally consistent in supporting the purported mode of action, including that for relevant non-cancer toxicities. Some modes of action can be anticipated to evoke effects other than cancer, e.g. reproductive effects of certain hormonal disturbances that are carcinogenic. Moreover, some modes of action are consistent with observed lack of genotoxicity. Coherence, which addresses relation of the postulated mode of action with observations in the broader database—for example, association of mode of action for tumours with that for other endpoints—needs to be distinguished from consistency (addressed in Section 6 above) which addresses repeatability of key events in the postulated mode of action for cancer in different studies.

7.8 Other Modes of Action

This section discusses alternative modes of action that logically present themselves in the case. If alternative modes of action are supported, they need their own framework analysis. These should be distinguished from additional components of a single mode of action which likely contribute to the observed effect, since these would be addressed in the analysis of the principal mode of action.

7.9 Assessment of Postulated Mode of Action

This section should include a clear statement of the outcome with an indication of the level of confidence in the postulated mode of action e.g. high, moderate or low.

7.10 Uncertainties, Inconsistencies and Data Gaps

Uncertainties should include those related to both the biology of tumour development and those for the database on the compound of interest. Inconsistencies should be flagged and data gaps identified. For the identified data gaps, there should be some indication of whether they are critical as support for the postulated mode of action or simply serve to increase confidence therein.

This version of the Framework is current at April 2001 but may be subject to further development.

Microbiological Risk Assessment

8.1 Introduction

The aim of microbiological risk assessment is to estimate the level of disease associated with a particular pathogen in a given population under a specific set of conditions and for a certain time frame.

There is much support for the application and development of microbiological risk assessment (MRA) (ACDP, 1996). To date, MRA has predominantly been applied to two exposure sources, food and water, and much of the conceptual development of MRA has resulted from the application of MRA to these media.

When compared with the chemical risk assessment, microbiological risk assessment (MRA), and particularly quantitative microbiological risk assessment (QMRA), can best be described as being in their infancy. For example, with QMRA, vast data sets need to be developed, modelling needs to be improved (e.g. secondary transmission) and analytical techniques need to be refined etc. The framework for MRA is still being developed with different approaches being proposed. Terminology specific to MRA and many other issues such as how to extrapolate from animal models to human models are yet to be resolved.

Nevertheless, Haas *et al.*, (1999) have successfully developed a MRA process which follows on from the influential US National Academy of Sciences (NAS) 1983 framework.

MRA is a developing field undergoing much transformation. With this in mind, the aim of this Appendix is to provide a brief description of the principles of MRA and to outline the MRA process. A more detailed description of MRA can be obtained by referring to the documents in the Bibliography.

8.2 Definitions

Microbiological risk assessment (MRA) has been defined by various scientific organisations/committees as follows.

The Codex Alimentarius commission (for microbiological hazards in foods):

- *A scientifically-based process consisting of the following steps; hazard identification, exposure assessment, hazard characterisation and risk characterisation (Codex, CAC/GL-30 (1999))*

The International Life Sciences Institute—Risk Science Institute (in conjunction with the US EPA):

- *A process that evaluates the likelihood of human health effects occurring after exposure to a pathogenic microorganism or to a medium in which pathogens exist (ILSI, 2000).*

The Advisory Committee on Dangerous Pathogens (UK)

- *A formal structured procedure for identifying and characterising microbiological hazard and determining the risk associated with it (ACDP, 1996).*

Quantitative microbiological risk assessment (QMRA) has been defined as follows:

- *The application of principles of risk assessment to the estimate of consequences from a planned or actual exposure to infectious microorganisms (Hass *et al.*, 1999).*

8.3 General Principles

The estimation of risk is sometimes expressed in numerical notation. However, risk can also be expressed qualitatively by using terms such as low/medium/high. Risk may also be characterised by a narrative description of the risk, or whether it breaches standards or guidelines. In practice, however, a continuum exists from a fully quantitative through to a wholly narrative expression of risk.

At present, MRA cannot always practically achieve numerical expression of microbiological risk (ACDP, 1996). This can be due to, for example, lack of dose–response data or a lack of understanding of the route of entry of a pathogen. Semi-quantitative or qualitative MRA can be applied in these situations.

The Codex principles of MRA, as applied to food, are listed below. These principles can also be generalised to the other media—water, air, soil and the surfaces of inanimate objects. Most of the principles listed are similar to established risk assessment principles, except for item 9 which is unique to MRA.

1. Microbiological Risk Assessment should be soundly based upon science
2. There should be a functional separation between Risk Assessment and Risk Management
3. Microbiological Risk Assessment should be conducted according to a structured approach that includes Hazard Identification, Hazard Characterisation, Exposure Assessment, and Risk Characterisation.
4. A Microbiological Risk Assessment should clearly state the purpose of the exercise, including the form of Risk Estimate that will be the output.
5. The conduct of a Microbiological Risk Assessment should be transparent.
6. Any constraints that impact on the Risk Assessment such as cost, resources or time, should be identified and their possible consequences described.
7. The Risk Estimate should contain a description of uncertainty and where the uncertainty arose during the Risk Assessment process.
8. Data should be such that uncertainty in the Risk Estimate can be determined; data and data collection systems should, as far as possible, be of sufficient quality and precision that uncertainty in the Risk Estimate is minimised (sic).
9. A Microbiological Risk Assessment should explicitly consider the dynamics of microbiological growth, survival and death in foods and the complexity of the interaction (including sequelae) between human and agent following consumption as well as the potential for further spread.

10. Wherever possible, Risk Estimates should be reassessed over time by comparison with independent human illness data.
11. A Microbiological Risk Assessment may need reevaluation, as new relevant information becomes available.

(Codex, CAV/GL-30; 1999, p.2–3).

8.4 Microbiological Risk Assessment—Paradigms and Frameworks

Microorganisms are living entities and are very different to chemicals and physical hazards by their nature. Some believe that MRA requires additional methods and terminology which are particular to microbiological risks (e.g. methods of estimating secondary transmission, and infective doses need to be developed. However, the enHealth model can, in general, be applied to MRA.

Haas *et al* (1999) have produced the most comprehensive attempt at describing the methods used in QMRA and the particular needs of MRA. However, they have not developed a modified framework that attempts to encompass these different needs. Instead, their approach to (Q) MRA loosely follows the National Academy of Sciences framework proposed for chemical risk assessment (NAS, 1983) which broadly includes the following steps: hazard assessment (comprising of hazard identification and dose–response analysis), exposure assessment, and risk characterisation.

By contrast, the International Life Sciences Institute and the US EPA (ILSI, 1996, 2000) have explicitly adapted the NAS framework to suit the unique challenges presented by MRA. Like the QRMA process described by Haas *et al*, it essentially follows the standard description provided by the National Academy of Sciences paradigm but uses synonymous terms for each part of the process.

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enHealth Council Membership and Terms of Reference

The enHealth Council is the premier advisory body on environmental health in Australia. It provides national leadership on environmental health issues, sets priorities, coordinates national policies and programs and provides a pivotal link between international fora and environmental health stakeholders in Australia. It is also responsible for the implementation of the National Environmental Health Strategy.

Membership

Chair—agreed by the Australian Health Ministers Conference

State and Territory Health Department representatives:

- Australian Capital Territory—Manager Health Protection Service
- New South Wales—Director Environmental Health
- Northern Territory—Program Director Environmental Health
- Queensland—Manager Environmental Health
- South Australia—Director Environmental Health
- Tasmania—Director Environmental and Public Health
- Victoria—Manager Environmental Health
- Western Australia—Director Environmental Health Service
- New Zealand—New Zealand Health Ministry

Commonwealth Department of Health and Ageing representative—Director of Environmental Health

Aboriginal and Torres Strait Islander Commission

Australian Consumers' Association

Australian Institute of Environmental Health—National President

Environment Australia

National Indigenous Environmental Health Forum—Chair

Public Health Association of Australia

Secretariat services provided by the Environmental Health Section of the Commonwealth Department of Health and Ageing.

Terms of Reference

1. Provide national leadership on environmental health issues by:
 - i) coordinating and facilitating environmental health policies and programs
 - ii) establishing strategic partnerships between environmental health stakeholders
 - iii) setting priorities for national environmental health policies and programs
 - iv) providing an open consultative system for policy development
 - v) facilitating cost effective use of environmental health resources
2. Drive the implementation of National Environmental Health Strategy
3. Advise the Commonwealth, States and Territories, Local government and other stakeholders on national environmental health issues
4. Coordinate the development of environmental health action plans at local, state and national levels.
5. Promote and develop model environmental health legislation, standards, codes of practice, guidelines and publications.
6. Strengthen the national capacity to meet current and emerging environmental health challenges.
7. Provide a pivotal link between international fora and environmental health stakeholders in Australia and strengthening Australia's collaboration with countries in the Asia-Pacific region