Chapter 2: Problem formulation and scope

The purpose of this stage of EHRA is to formulate the problems to be considered by the risk assessment and to clarify the proposed scope. It corresponds with Phase I of the framework outlined in Figure 2 and with 'issue identification', the first stage of the original risk assessment framework depicted in Figure 1.

Essentially, this means addressing the following points:

- What is the concern?
- Why is it a concern?
- How urgent is the concern?
- How do stakeholders perceive the concern?

This will include identifying and describing:

- issues associated with existing environmental conditions
- susceptible and/or vulnerable populations likely to be exposed
- potential exposure pathways
- potential management options that may mitigate exposure
- the risk and other technical assessments necessary to evaluate risk and discriminate between potential risk management options.

2.1 IDENTIFYING AND DESCRIBING ISSUES WITHIN EXISTING ENVIRONMENTAL CONDITIONS

'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 or other industrial facility
- community outrage over the proposed development of a communications tower
- how contaminated sites are managed
- development of new standards for water quality, including use of a new water treatment chemical or new uses for recycled water
- changes to a food standard that permit higher levels of exposure or introduce new chemicals into the food chain.

'Hazards' relate to the capacity of a specific agent to produce a particular type of adverse health or environmental effect. The environmental agents of concern may include physical, chemical, biological or social factors.

- 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, unemployment cultural values and effects on access or amenity.

Examples of hazards include the capacity of:

- benzene to cause leukaemia
- solar radiation to cause skin cancer
- salmonella to cause vomiting and diarrhoea.

Hazardous agents may be identified from the 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
- information about analogous hazards.

2.1.1 Phases of issue identification

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.
2. Putting the hazards into their environmental health context (clarification and prioritising of problems and hazards).
3. Identifying all the chemicals of potential concern (COPC) (i.e. prioritising those chemicals that need to be fully considered in a quantitative risk assessment)
4. identification of potential interactions between agents.

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 – perhaps the contaminant affects multiple environmental media (e.g. lead smelter emissions contaminating soil, air, water and food)
- the hazard may have single or multiple sources (e.g. atrazine contamination of a drinking-water supply from a chemical spill versus particulates in ambient air arising from diesel engines, wood stoves and environmental tobacco smoke)
- 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 problem
- there is a context of public anxiety, anger and impatience
- different stakeholders may have different perceptions of the issues for example, a stakeholder group comprised of workers at a smelter who are also nearby residents may have complex perceptions
- the hazards may be compared with 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 (Presidential/ Congressional Commission on Risk Assessment and Risk Management – P/CCRARM 1997).

In relation to assessment of multiple exposure routes and sources, US regulations define two types of exposure that need to be considered in a risk assessment:

- **aggregate exposure:** the analysis of exposure to a chemical by multiple pathways and routes of exposure
- **cumulative exposure:** the combined risk estimate where exposure occurs simultaneously or consecutively to multiple chemicals that exert toxicity through a common mechanism.

In the case of 'aggregate' exposure, the requirement is no more than would be normally done in a conventional EHRA, where all potential exposure pathways should be considered in the risk assessment. The methodologies for 'aggregate' risk assessment are set out in Chapter 4.

In the case of 'cumulative' exposure, the methodologies are more complicated, particularly since cumulative exposure risk assessments are intended to address the interactions of multiple agents or stressors, not all of which are necessarily chemical agents. It could include biological or physical agents that could modify the toxicity of the environmental chemicals under consideration.

Further guidance on assessing multiple chemical exposures (i.e. mixtures of chemicals) is outlined in Chapter 12.

2.1.2 Identifying chemicals of potential concern

It is quite likely that the issue and/ or hazard identification stages will find a large number of chemicals whose presence in the environment and toxicity may give rise to adverse health outcomes. The issue then becomes which of them must be designated as chemicals of potential concern (COPC) (which must be addressed in the formal EHRA) or whether any of them can be readily eliminated from further consideration.

The tiered risk assessment screening process (see Section 1.9) may enable COPC to be discriminated from among a much larger number of environmental contaminants, and may point to the need for a more advanced (Tier 2 or 3) risk assessment.

It may also be possible to establish that chemical concentrations in the environment are so low that exposures are unlikely to exceed a generic threshold of toxicological concern (TTC) and can therefore be discounted. The application of a TTC approach to risk assessment is discussed in Section 5.13.

2.2 IDENTIFYING AND DESCRIBING SUSCEPTIBLE POPULATIONS

Within the general population there may be sub-groups potentially more susceptible to the effects of environmental chemicals than others in the population. Human variability (also called intra-species, i.e. inter-individual, variability) may arise through toxicokinetic or toxicodynamic variability (Dybing & Soderlund 1999). Both these areas of variability may be due to acquired and/or inherent factors that may make a person more susceptible to environmental pollution.

Sensitivity of individuals is also likely to be affected by age, sex, nutritional and pregnancy status, and combinations of these (IEH 1999c). It is therefore imperative that the issue identification stage considers whether any of these factors could influence the outcome of the EHRA.

A distinction needs to be drawn between the use of the terms 'susceptibility', 'vulnerability' and 'sensitive groups' within a population of 'receptors' under consideration in an EHRA.

Susceptibility: refers to intrinsic biological factors that can increase the health risk of an individual at a given exposure level. Examples of susceptibility factors include: genetic factors, late age and early life, and prior or existing disease.

Vulnerability: refers to human populations at higher risk due to environmental factors. Examples of vulnerability factors include poverty, malnutrition, poor sanitation, climate change and stress associated with mental health diseases.

Sensitive groups: refers to populations with both susceptibility and vulnerability factors.

2.2.1
Epidemiological principles

A sensitive sub-population is one where an adverse response to an environmental pollutant occurs at concentrations substantially lower than that affecting the majority of the population. Another sub-population that may be considered to be 'sensitive' is one where the consequences of exposure are more significant than in the majority of the population. For example, children may be considered a sensitive population because any irreversible adverse effects may influence their health throughout their life. The elderly, especially those with specific comorbid effects such as cardiac or respiratory failure, may also constitute a sensitive group because the secondary consequences (e.g. pneumonia, worsening cardiac failure) may be more serious than in the remainder of the population (NHMRC 2006).

The identification of sensitive sub-populations may be guided by:

- clinical history (e.g. the presence of diseases such as asthma, cardiac failure, chronic bronchitis or cystic fibrosis, which may exacerbate sensitivity to environmental pollutants)
- clinical evidence of hyper-responsiveness (e.g. using methacholine or more specific challenge tests to assess susceptibility to irritant air pollutants)
- demographic factors (e.g. the elderly or very young)
- genetic factors (e.g. cystic fibrosis).

From a physiological standpoint, any person who has decreased functional reserve in an organ system is theoretically less able to cope with additional environmental stressors, be they 'non-chemical' or 'chemical' in nature. As with other areas of medicine and toxicology, whether a particular individual will respond adversely to a certain environmental stressor depends upon the relative balance between the extent of physiological compromise (in some cases this is proportional to the degree of disease severity) and extent of exposure. In many situations, acquired susceptibility (e.g. illness or old age) shifts a person towards the 'sensitive' tail of the population dose–response curve for the pollutant. These individuals nonetheless remain part of the continuum of the overall population dose–response and experience effects similar to others but at lower exposures to pollutants, or more intense effects at equivalent exposures (NHMRC 2006).

Genetic variability can make an important contribution to human variability, such as in the form of polymorphic genes for metabolism or tissue repair from toxic insult. Although it has long been recognised that genetic polymorphism plays an important role in driving the variability in xenobiotic metabolism, and genetic polymorphisms have been used as biomarkers of potential effect (Scherer 2005), this awareness has typically not translated into quantitative use of the data in risk assessment or standard-setting (Haber et al. 2002; US EPA 2002a). This is likely due to data gaps in our understanding such as:

- prevalence of polymorphism
- lack of a defined link between genetic polymorphism and an adverse effect
- extent of induction/inhibition through co-exposure with other substances, lifestyle or diet
- relative contribution of multiple enzyme systems
- allelic frequencies for major ethnic groups
- large numbers of low-frequency alleles
- absence of chemical-specific phenotype data.

Guideline values used in risk assessments should normally have been developed in such a way that most sensitive sub-populations are protected. Some older guideline values do not specifically address this issue. Risk assessors should check that sensitive sub-populations are covered in the guidelines being used. Particularly, each assessment should consider whether early childhood exposure to carcinogens is relevant for the site or activity being investigated and, if so, whether it is covered in the guideline proposed for use.

2.2.2
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:

- growth, development and maturational rates
- children's 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)
- placental transfer of contaminants and accumulation in breast milk can result in exposures which are unique to the prenatal and postnatal states
- behavioural factors, for example, children's play activities may put into more frequent contact with soil contaminants and they are also more likely to indulge in soil eating behaviours (pica)
- available parameters for toxicity assessment, for example, techniques for assessing dizziness, intelligence and hearing impairment are different between children and adults
- biochemical and physiological responses, for example, children have a higher metabolic rate, more limited ability to control body temperature, more rapid growth rate and a higher percentage of water in the lean body tissue
- disposition of the agent within the body, for example, 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
- 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
- exposure factors – the surface area to body mass ratio will change markedly with ageing. In the newborn, the ratio is typically 0.067 (m^2/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 3 m^2 in an infant to approximately 75 m^2 in an adult and the respiration rate drops from 40 breaths per minute to 15 breaths per minute (Snodgrass 1992).

A general discussion of the issues relating to risk assessment for children may be found in Calder (2008), Roberts (1992) and US EPA (2005b; 2006a), with a more extensive review of the physiological, pharmacokinetic, behavioural, genetic and exposure factors that may alter the sensitivity of children to environmental hazards (Hines et al. 2010).

The potential impact of these differences highlights the need for agent-by-agent appraisal. However, it should be recognised that the derivation of some types of toxicological reference doses (e.g. ADI or TDI) envisage whole-of-life exposure and may therefore be relevant for assessing risks associated with early-life exposure stages.

Special consideration has been advocated by the US EPA for assessing risks associated with early-life exposure to mutagenic carcinogens (see Section 5.8). US legislation mandates the application of an additional 10x safety/uncertainty factor in the derivation of an RfD for pesticides where studies indicate developmental neurotoxicity or other toxic effects that could be associated with early-life susceptibility.

While Australian environmental health authorities have not enunciated specific policies relating to applying these US early-life risk assessment strategies, additional precaution tends to be applied on a case-by-case basis when justified by relevant data. While the US early-life risk assessment policies are not automatically adopted in Australia, they have been incorporated into the development of health investigation levels (HILs) for benzo(a)pyrene (BaP) in the revision of the contaminated sites NEPM (see Section 16.1) and they should be considered where there is good evidence that such an approach is relevant.

2.2.3
Risk assessment and older persons

For the ageing, there is a decrease 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 ageing population from many drugs has been reported (Crome 1999). Changes will occur to the immunological system often resulting in reduced immunocompetence.

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 or those with age-related pathology (e.g. Alzheimer's) 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.

2.2.4
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 & Mattison 1994). Some of the factors that influence these processes are summarised in Tables 1–4.

Men and women differ in many lifestyle and occupational exposure factors (e.g. alcohol drinking and cigarette smoking) dietary patterns and how they spend their time. 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 analysis of animal studies suggest there are important differences between males and females in the expression of toxicity.

Table 1: Factors influencing the absorption of chemicals

Parameter	Physiological difference	Effects on toxicokinetics
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

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

Parameter	Physiological difference	Effects on toxicokinetics
Plasma volume	Pregnant F > M > F	Concentration increases 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

Table 3: Factors influencing the rate of metabolism of chemicals

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

BMR = Basal metabolic rate.

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

Parameter	Physiological difference	Effects on toxicokinetics
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
(Tables 1–4 adapted from Government/Research Councils Initiative on Risk Assessment and Toxicology, 1999)

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).

2.2.5 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 foetus.

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 foetus) is a risk for the foetus 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 foetus
- the onset and duration of exposure
- the level and duration of dosage
- the genetic constitution of the foetus
- the timing of the exposure in relation to the stage of foetal development.

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

Access of an agent to the foetus is determined by its lipophilicity, molecular weight or ionic nature. Generally the more lipophilic a chemical is the more likely it is to cross the placental barrier. For large molecules like polymers, size generally prevents their passage across 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 foetal 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.

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 breastfeeding 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).

2.2.6 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, where the influence of these factors can be distinguished, the potential influence of lifestyle factors should be clearly identified in risk assessments. Specific lifestyle factors that may have an effect on risk assessment include:

- tobacco smoking
- diet
- hobbies
- recreational drug use
- excessive use of prescribed medications.

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, such as 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. 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 kilogram 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).

Home-grown produce (e.g. vegetables) has been associated with contamination of heavy metals such as lead, arsenic and cadmium. This may be of particular concern when assessing contaminated sites. The NEPM processes used to develop health investigation levels (HILs) incorporate four different exposure scenarios, one of which includes potential for home-grown vegetables as an exposure source. The potential for lipophilic chemicals to be stored and/or bioaccumulate in meat and poultry tissue (e.g. meat, fat, skin) and eggs (egg yolk) is an important consideration in regulating pesticide residues and environmental contaminants in foods (see Chapter 17).

The type of diet can also influence the risk of 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 pyrolysis of fats and other food components during the cooking process. 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 a car, bus, aeroplane or 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 also result in an increased exposure to lead (Lead Safe 1997). House renovating can 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.

2.3 IDENTIFICATION OF POTENTIAL EXPOSURE PATHWAYS

When issues have been identified, a preliminary qualitative risk assessment may be carried out to prioritise issues for a 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. There may be multiple iterations of hazard appraisal as the risk assessment proceeds and new information and perspectives emerge.

The issue identification processes relating to exposure may be aided by the development of appropriate conceptual site models (CSMs), which delineate the exposure sources and potential pathways leading to human exposures. Identification of exposure pathways using CSMs and the modelling and quantitative description of them are discussed in more detail in Chapters 4 and 13.

Where multiple exposure pathways may include background exposure not specifically associated with the source under consideration in the EHRA, consideration needs to be given to allocating a permissible component of the exposure under consideration. Allocating specific proportions of the ADI/TDI to account for background or other sources of exposure is discussed in more detail in Section 5.11.1.

Other issues relating to identifying exposure pathways and quantitation of pathway inputs are discussed further in Chapter 4.

2.4 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's disease 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)
- antagonistic, where the combined effect of two or more agents is less than the sum of the individual effects – 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. Some contemporary approaches to the health risk assessment (HRA) of chemical mixtures are discussed in Chapter 12.

2.5 IDENTIFYING POTENTIAL MANAGEMENT OPTIONS THAT MAY MITIGATE EXPOSURE

While risk management should be considered to be a process separate from or dissociated from risk assessment, a formal EHRA is likely to identify those hazards and exposure pathways that make the greatest contributions to the overall risk. This may include assessment of possible future risks associated with continuing or expansion of existing operations. Information derived from an EHRA will be useful to risk managers in formulating and prioritising risk mitigation options. These may include:

- closing down/ceasing use of the hazard source altogether or substituting with a less hazardous material where minimisation of any further environmental contamination is required
- cleaning up a contaminated site using the EHRA outcomes and/or statutory instruments to guide the level of clean-up required – this may require a combination of *in situ* hazard treatment or containment, or removing the hazardous material to another site
- sealing off the contaminated environment to prevent further access by human receptors
- preventing ongoing release to the environment or denying development plans that could increase such release.

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 costs of undertaking a risk assessment to determine whether action is necessary are considerable. In other instances, risk assessment will be inappropriate because the solutions to the problem will not be based on addressing risk but on addressing other factors such as social and political concerns.

Risk management also needs to be understood within the inevitable constraints that it will operate when risks are found to be small. Risk management inevitably involves trying to steer a sensible course between making a Type 1 (false positive) or Type 2 (false negative) error (Hrudey & Leiss 2003). In other words, risk management for small and uncertain risks involves trying to decide between taking action when none is required or failing to take action when it is required.

2.6 WHAT RISK AND OTHER TECHNICAL ASSESSMENTS ARE NECESSARY TO EVALUATE RISK AND DISCRIMINATE BETWEEN POTENTIAL RISK MANAGEMENT OPTIONS?

A formal EHRA will generally provide sufficient information to identify the major contributors to risk and enable the risk manager to prioritise the needs for risk mitigation. Having then identified technically feasible risk management options, the next phase would be to undertake an economic analysis of the costs and benefits associated with each of these risk management options. The economic assessment processes are beyond the scope of this enHealth document, but some guidance may be found in enHealth monographs on economic evaluation of environmental health issues (enHealth 2003).

Chapter 3: Hazard identification and dose–response assessment

3.1 INTRODUCTION

The two elements of risk assessment discussed in this chapter are:

- hazard identification (using toxicity test data)
- dose–response assessment.

These elements are identified as part of Phase II of the expanded framework for EHRA outlined in Figure 2.

There are essentially two levels of hazard identification commonly undertaken in risk assessments in Australia. For many risk assessments developed as part of environmental protection licensing, planning processes or contaminated sites assessments, the hazard identification component may simply identify the relevant national or international guideline values for each chemical that may be present. For risk assessments undertaken by national chemicals regulators or those setting national guidelines, the assessment will generally involve a full investigation of the international toxicity literature relevant to the chemical, including an appraisal of the dose–response relationships that underpin any derived guideline values. This chapter focuses on an understanding of dose–response relationships that provide insight into the development of health-based guideline values, while Chapter 5 outlines the sources of guideline values and other information that can be used in the risk characterisation process.

Additional detail on the design and interpretation of animal-based toxicity tests is included in Chapter 9, along with a discussion of some of the newer techniques for hazard assessment (*in vitro* and *in silico* techniques, genomics, structure–activity analysis and 'read-across' from comparable substances) where the toxicity database for a new industrial chemical may be less comprehensive than other types of regulated chemicals.

3.2 HAZARD IDENTIFICATION

Hazard identification examines the capacity of an agent to cause adverse health effects in humans and other animals (US EPA 1995a). 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.

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 (both qualitative and quantitative toxicity information is evaluated in assessing the incidence of adverse effects occurring in humans at different exposure levels)
- 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 (including cancer or pregnancy outcome data). In each instance, the quality of the study design and methodology, as well as the resulting data, will need to be rigorously assessed.

Section 5.12 provides guidance on sources of toxicological information and where to find health-based guideline values. There is also guidance on what to do when no suitable toxicological data appears to be available (see Section 5.13).

In the case of data derived from experimental studies in animals (see Chapter 9), a comprehensive data package will generally consist of:

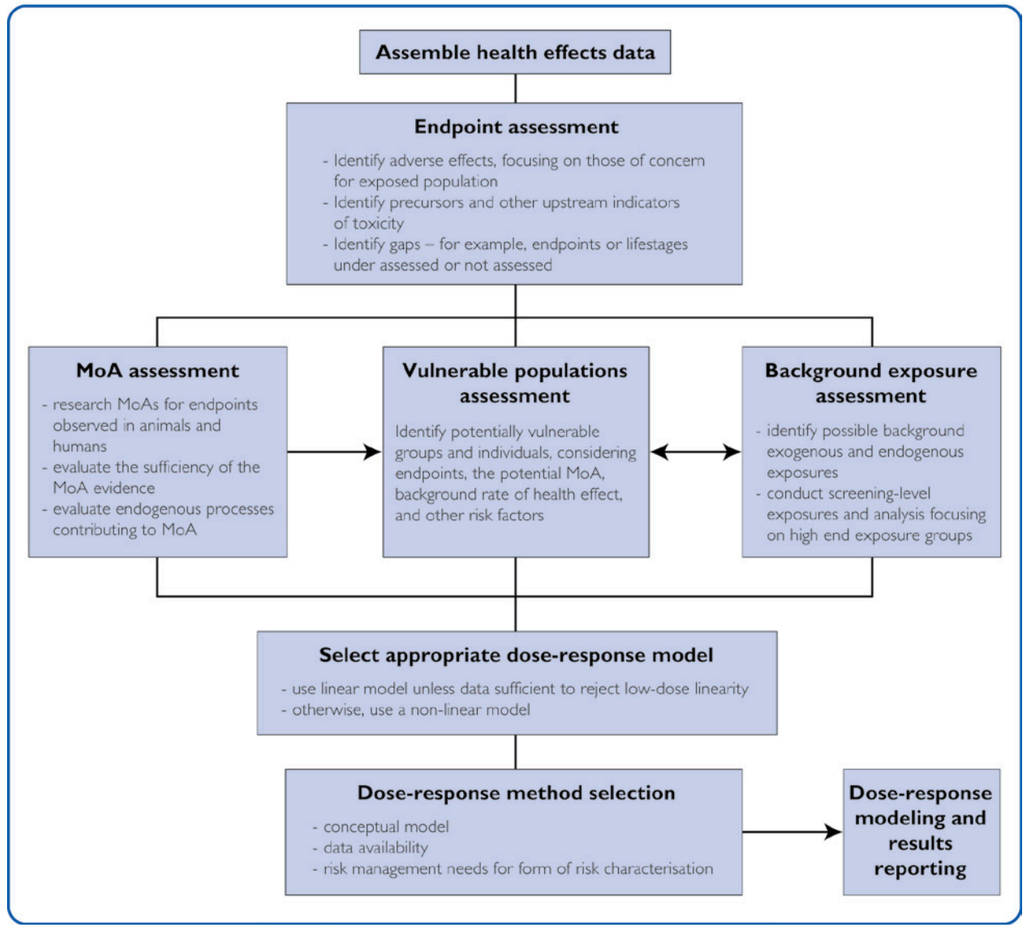
- **Acute toxicity:** Studies investigating the effects of single doses of a substance. The LD_{50} test, or medium lethal dose test are typical examples. The standard acute toxicity studies also include tests for: acute oral, dermal and inhalational toxicity; eye irritation; skin irritation; and skin sensitisation.
- **Sub-chronic toxicity:** Short-term, repeat-dose studies, generally having an exposure duration up to 90 days in rodents. 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 lasting for the greater part of the life span of the test animals, usually 18 months in mice and 2 years in rats. Chronic studies are particularly important for assessing potential carcinogenicity.
- **Reproductive toxicity:** Studies designed to provide general information about the effects of a test substance on reproductive performance in both male and female animals.
- **Developmental toxicity:** Studies in pregnant animals that examine the spectrum of possible *in utero* outcomes for the conceptus, including death, malformations, functional deficits and developmental delays. More recent developments extend the period of dosing and/or observation into the neonatal period, to assess potential neurobehavioural effects and other potential post-partum toxicity.
- **Genotoxicity:** Studies designed to determine whether test chemicals can perturb genetic material to cause gene or chromosomal mutations.
- **Other tests:** Specific tests developed for endpoints such as neurobehavioural toxicity, developmental neurotoxicity and various *in vitro* tests (e.g. skin absorption, irritancy potential and endocrine-related endpoints), which aim to reduce or eliminate the *in vivo* use of animals, on the grounds of addressing animal welfare issues.

Key issues include:

- nature, reliability and consistency of human and animal studies
- the availability of information about the mechanistic basis for activity
- the relevance of the selected animal studies to humans
- whether the mode of toxic action is well understood – knowledge of the mode of action (MoA) is becoming increasingly important in interpreting carcinogenic responses (see Chapter 11) and assessing the risk of chemical mixtures (see Chapter 12).

Various sources of information are needed to identify and characterise environmental hazards (Figure 6). Integrating information on MoA, exposures (including background exposures) and identifying susceptible populations are all important factors in determining the correct use of dose–response information.

Figure 6: Potential sources of information used to identify and characterise environmental hazards, leading to characterisation of mode of action (MoA), dose–response models and susceptible populations



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