



# **Assessment of Effects of Hazardous Substances and New Organisms on Human Health**

**Written By Deborah Read  
ERMA New Zealand**

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## **Preface**

This guide is part of a series of technical guides produced by ERMA New Zealand to help people involved with the HSNO Act. It will be particularly helpful for those people who are reviewing applications (and that is the way it has been written), but it may also be useful for applicants and those interested in HSNO related risks more generally. People with a less technical interest in HSNO are advised to start with the other series of documents we publish, especially:

- the quick guides (aimed at a general audience or for those making a first acquaintance with HSNO)
- the user guides (aimed at those directly involved with HSNO but with less technical detail).

Publications in this technical series **are not** formally endorsed by ERMA New Zealand. They are intended to be a technical reference. A staff member will author most of the documents but in some cases there may be an external author.

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## **Introduction**

### ***How to use this guide***

The purpose of this guide is to provide a framework for reviewers to enable them to consistently appraise applications under the Hazardous Substances and New Organisms (HSNO) Act 1996, with respect to effects on human health.

The guide is based on a series of questions reviewers should ask about the information in an application and its implications for health. Part I covers hazardous substances and Part II new organisms. Each part is designed to stand alone and therefore contains some material that is also in the other part.

### **Scope**

This guide applies to applications to:

- import or manufacture hazardous substances
- import, field test in containment, or release from containment a new organism (including genetically modified organisms (GMOs))
- reassess approved hazardous substances.

It does not apply to applications to:

- import or manufacture hazardous substances in containment
- import or develop a new organism (including GMOs) in containment.

### **Background**

The purpose of the HSNO Act 1996 is to protect the environment and the health and safety of people and communities, by preventing or managing the adverse effects of hazardous substances and new organisms (Section 4).

To achieve this purpose section 6 (c) of the HSNO Act requires the Authority to take public health into account in its decision-making.

Decisions by the Authority must also recognise and provide for the principle of the maintenance and enhancement of the capacity of people and communities to provide for their own economic, social and cultural well-being and for the reasonably foreseeable needs of future generations (Section 5), and take into account the need for caution in managing adverse effects where there is scientific and technical uncertainty about those effects (Section 7), and the principles of the Treaty of Waitangi (Section 8).

## **Key terms**

Health means ‘a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity’ (World Health Organisation, 1947). This definition acknowledges the contribution of broad social, economic and physical factors to health.

Public health means the health of all of:

- the people of New Zealand; or
- a community or section of such people (Section 2, Health and Disability Services Act 1993).

It is concerned with total populations, or population groups (eg children, Māori, a specific occupational group) rather than individuals. The definition of public health as ‘the science and art of preventing disease, prolonging life, and promoting health through organised efforts of society’ (Acheson, 1988) was adopted by the former Public Health Commission and the Ministry of Health (Public Health Commission, 1994; Ministry of Health, 1997). Strategies that protect public health reduce the risk and impact of injury and disease, improve the quality of life, prolong life and may reduce the need for health care services.

Effects are defined outcomes (ERMA New Zealand, 1998) and include potential or probable, positive or adverse, past, present or future, acute or chronic, and cumulative effects (Section 2, HSNO Act).

## **Determinants of health**

The review procedure assesses whether the hazardous substance or new organism has any impact on those factors that influence health ie the determinants of health.

Māori models of health recognise the impact of broader socio-economic and cultural factors on health. There are four dimensions that collectively contribute to well-being (waiora): spiritual (wairua), mental (hinengaro), family (whānau) and physical aspects (tinana) (Durie, 1994). The extent to which an application satisfactorily addresses the Māori perspective on health will be assessed by Ngā Kaihautu Tikanga Taiao, the Authority’s Māori advisory committee.

The main determinants of health may be conceptualised as layers working out from an individual at the centre. The layers from the centre are:

- age, sex and genetic factors
- lifestyle factors
- social and community influences
- living and working conditions
- socio-economic, cultural and physical environmental conditions (Dahlgren and Whitehead, 1991).

Determinants interact in many ways and addressing one will therefore impact on other determinants.

## **Health impact assessment**

The objective of the review is to answer the question:

*What is the likelihood and the magnitude of the impact on public health from the hazardous substance or new organism?*

Health impact assessment involves checking that the substance or new organism does not have an adverse effect(s) on public health, or creates conditions that undermine the promotion of public health.

The amount of detail required in the application depends on the magnitude and likely significance of the actual or potential impact on public health. Impact can be measured in terms of mortality, morbidity, disability, quality of life, or potential years of life lost. In general, the more significant the effects the more information should be provided by the applicant.

The significance of any effects on public health is based on the:

- severity of the potential health effects
- number of people potentially affected
- nature of the potentially affected population(s)
- frequency and duration of the potential health effects
- extent to which the effects are reversible or irreversible
- likelihood that the health effects will occur
- extent to which the effects can be prevented or reduced, and
- level of uncertainty in the health risk assessment.

## Part I: hazardous substances

### Summary question chart

The objective of the review is to answer the question:

*What is the likelihood and the magnitude of the impact on public health from the hazardous substance?*

### Risk assessment

#### *Hazard identification*

The objective of this section is to answer the question:

*Is the substance a source of potential harm to public health?*

1. What intrinsic properties of the substance indicate that it is a source of potential harm to human health and safety?
2. What are the physico-chemical properties of the substance?
3. What are the toxicokinetics of the substance? What are the toxicodynamics of the substance?
4. What is the mechanism(s) of toxicity?
5. Are there health effects associated with the substance?
6. What are the known adverse human health effects?
7. What are the known adverse animal health effects?
8. What are the characteristics of the health effects?
9. What is the evidence that exposure may be associated with health effects?
10. Are there *in vitro* data?
11. Are there animal data?
  - What is the quality of the animal studies?
  - What is the relevance of the adverse effects in animals to human health?
  - Is the effect a result of mechanisms that are likely to occur in humans? Is the effect a result of mechanisms that are likely to occur at very high doses? Is the route of administration like human exposure?

- Are there data on more than one species? Are there data on both sexes?
- What are the data gaps?

12. Are there human data?

- What is the type of human data?
- What is the study design?
- What is the study's validity?
- What are the sources of bias? Has confounding been controlled for? eg age, cigarette smoking, alcohol
- Is the study population comparable to the risk population in terms of susceptibility?
- Are the characteristics of exposure in the study population comparable to those in the risk population?
- Is the statistical power of the study adequate?
- Is the statistical analysis of the study appropriate?
- What is the quality of the human studies?
- What are the data gaps?

13. Were the studies carried out by the applicant? If the studies were not carried out by the applicant, were they funded by the applicant?

14. Were *in vitro*/animal studies carried out in accordance with overseas regulatory agencies and/or following good laboratory practice?

15. Were the studies peer reviewed? Were the studies published, and where?

16. Have studies with negative or null results been considered?

17. Has the most recent evidence been included?

18. What is the overall credibility of the evidence?

19. Does the application contain the best available data? Has the applicant made appropriate use of the best available data?

20. Are there indirect health effects? What are the indirect health effects?

## ***Exposure assessment***

The objective of this section is to answer the question:

*What is the overall level and pattern of exposure in the population(s)?*

1. What exposure pathways are possible?
2. What are the conditions under which people could be exposed and the doses that could occur as a result of such scenarios?
3. Do different exposure pathways lead to the same or different effects? If the effects are the same, does one pathway dominate in magnitude or rate of effect?
4. What is the main exposure pathway(s)?
5. Who may be exposed? How many may be exposed?
6. What is the duration of exposure? Is exposure acute and/or chronic?
7. How often are populations exposed as a result of diet, drinking water, residential exposure, activity patterns or occupation?
8. What populations may be highly exposed as a result of occupation, age, geographical location, and social or cultural practices eg diet?
9. If highly exposed populations exist, have they been separately evaluated from the total population?
10. What populations may be highly susceptible as a result of genetic pre-disposition, age, lifestyle factors, or pre-existing medical conditions?
11. Is exposure cumulative?
12. What estimates of exposure have been used?
13. Are the exposure data used representative of the population under study?
14. Are the exposure data an over-estimate of average exposure? Are the exposure data an under-estimate of average exposure?
15. Are the exposure data derived from population exposure data or from source characteristics and models? If models have been used, how appropriate are they?
16. What assumptions have been made that have a significant impact on the results?

### ***Dose-response assessment***

The objective of this section is to answer the question:

*How do health effects vary with the level of exposure?*

1. Does the substance interact with other substances?

### ***Risk characterisation***

The objective of this section is to answer the question:

*What is the aggregate effect on health in the exposed population(s)?*

1. What are the quantitative aspects of the risk?
2. What are the qualitative aspects of the risk?
3. What are the sources of variability?
4. What are the sources of uncertainty?
5. Have sensitivity analyses been carried out eg using different exposure scenarios, alternative dose-response models, alternative inter-species adjustments?
6. What is the confidence that can be placed in any quantitative analysis of uncertainty and variability and its findings?
7. What are the information gaps?
8. Have all the relevant data been evaluated?
9. What are the weaknesses of the methods used?
10. What are the strengths of the methods used?
11. What are the critical assumptions? Are they reasonable? Are there plausible alternative assumptions? What is the effect of alternative assumptions on the conclusions?
12. What are the scientific controversies and their effect on the conclusions?
13. How reliable is the evidence? Are the conclusions justified by the evidence? Are the conclusions communicated in a way that reflects the weight of evidence?

14. Are there antagonistic or synergistic interactions that could lead to under- or over-estimation of the total risk?

### **Risk evaluation**

1. Who are the stakeholders?
2. What outcomes are important to the stakeholders and why?
3. What are the stakeholders' perceptions of the hazard?
4. What are the stakeholders' perceptions of the risk? Do different groups of stakeholders have different perceptions and concerns?
5. What is the larger real world context of the risk?
6. What contribution does the substance make to the overall risk of certain effects in the population or to the overall health of the population?
7. How is the risk distributed in relation to other health risks to the population?
8. Are there direct positive health effects?
9. What is the evidence that exposure may be associated with positive health effects?
10. What are the characteristics of the positive health effects?
11. Are there indirect positive health effects? What are the indirect positive health effects?
12. Have the relevant monetary costs and benefits been identified? Have the relevant non-monetary costs and benefits been identified?
13. What is the expected value of the costs and benefits and the uncertainty related to the expected value? How are the costs and benefits distributed over time, space, and groups in the population?
14. To what extent do the following risk characteristics apply?
  - exposure to the risk is involuntary
  - the risk will persist over time
  - the risk is subject to uncontrollable spread and is likely to extend its effects beyond the immediate location of incidence
  - potential adverse effects are irreversible
  - the risk is not known or understood by the public and there is little experience or understanding of possible measures for managing the potential adverse effects (HSNO (Methodology) Order 1998).

## **Risk management**

1. What are the key social, cultural and political factors that need to be taken into account when managing risks to public health?
2. Can the risk be prevented? Can the risk be reduced?
3. How can the risk be prevented? How can the risk be reduced?
4. What are the economic, social, cultural and ethical implications associated with implementing each option?
5. Does the action have a significant impact on the risk?
6. Does it reduce or prevent the risk in a way that is based on the best available scientific evidence? Is the action feasible?
7. Can the action be implemented effectively? Can the action be implemented with stakeholder support?
8. What is the impact of preventing or reducing the risk on overall public health?

## **Risk assessment**

The assessment of potential adverse health effects is based on a health risk assessment framework. Risk assessment is a central component of health impact assessment. It includes four stages: hazard identification, exposure assessment, dose-response assessment and risk characterisation.

Health risk assessment draws on the knowledge and methods of epidemiology, toxicology and exposure analysis. It aims to identify the adverse health effects that may be associated with exposure to a substance and to predict the likelihood that specific human populations will experience such effects at given exposure levels.

The amount of detail required at each stage of the risk assessment process depends on the magnitude and likely significance of the actual or potential health effects.

Though each stage has objective components, each also requires some decisions based on subjective judgements, which personal values may influence (Wartenberg and Simon, 1995).

In situations where a substance is a mixture each of the constituent compounds or elements is considered.

## **Hazard identification**

The objective of this section is to answer the question:

*Is the substance a source of potential harm to public health?*

Hazard identification involves the identification of a substance as a source of potential harm to humans. It is based on the type and quality of data on humans and/or laboratory animals and *in vitro* systems, other information such as toxicokinetics and quantitative structure-activity relationship (QSAR) analysis, and the weight of evidence from all of these data sources. The hazard may manifest itself in many ways including altered function and structural abnormalities.

*What intrinsic properties of the substance indicate that it is a source of potential harm to human health and safety?*

For the HSNO Act to apply the substance must have properties such as toxicity, flammability or explosiveness that exceed the threshold limits set in the HSNO regulations.

*What are the physico-chemical properties of the substance?*

Physico-chemical properties eg molecular weight, solubility influence a substance's transport through environmental media and fate after ingestion, inhalation or dermal contact. For example, low molecular weight, non-ionised, and lipid soluble substances generally show high skin permeability and extremes of pH (i.e.  $\leq 2$  and  $\geq 11.5$ ) may indicate dermal effects.

Comparisons of the chemical or physical properties with those of other substances known to cause particular toxic effects may give some indication of a potential for similar toxicity when little or no other data are available.

*What are the toxicokinetics of the substance? What are the toxicodynamics of the substance?*

*What is the mechanism(s) of toxicity?*

The general model of the toxic event is a sequence: absorption via ingestion, inhalation and/or dermal contact, modification, transport to an active site(s), and reaction at the active site(s) to produce a response that may in turn result in the adverse effect(s).

The active site may be the site of exposure making transport unnecessary and the efficiency of absorption may vary markedly with the route of exposure. Metabolism may decrease toxicity or in some instances produce a toxic metabolite.

Data on the absorption, distribution, metabolism and excretion of the substance can assist extrapolation of animal toxicity data to humans. These data may define the sequence of events leading to an adverse effect, identify changes in distribution and metabolism over a dose range, and compare different exposure pathways. Toxicokinetic models seek to account for differences between test animal species and humans by considering body weight, respiratory rate, fat content and other biological parameters.

Use of mathematical models to describe these processes allows prediction about body burdens and duration in the body after exposure has ended that may aid in assessing the hazard.

*Are there health effects associated with the substance?*

Potential adverse effects include injury, acute and chronic disease, psychological effects and death. Effects can be local such as skin, lungs, eye, or systemic. In cases of allergic effects, sometimes due to sensitisation resulting from previous exposure, a low dose may result in an inordinate local or systemic effect. Sometimes there may be idiosyncratic effects where there is an abnormal, often genetically predetermined, response.

*What are the known adverse human health effects?*

*What are the known adverse animal health effects?*

Effects can occur in any bodily system. Possible effects are:

- psychological eg depression
- sensory eg blurred vision, deafness
- neurological eg paraesthesia
- dermatological eg contact dermatitis, burns
- musculo-skeletal eg amputation
- haematological eg anaemia
- cardiovascular eg tachycardia
- respiratory eg asthma
- hepatic eg hepatitis
- gastro-intestinal eg diarrhoea
- genito-urinary eg renal failure

- endocrine eg hypothyroidism
- immunological eg anaphylaxis
- female reproductive
  - general reproductive effects eg amenorrhoea, infertility
  - teratogenicity eg cleft palate
  - other effects in pregnancy
  - effects during lactation
- male reproductive eg oligospermia
- carcinogenicity
- genotoxicity.

*What are the characteristics of the health effects?*

Characteristics of the effects include:

- severity
- latency
- ability to affect future generations
- whether it is irreversible or reversible
- transient
- fatal
- acute or chronic
- immediate or delayed
- progressive.

Health effects may be modified by factors such as immediacy or latency from weeks to decades, effects may be reversed eg regeneration of liver cells, or tolerance may develop.

*What is the evidence that exposure may be associated with health effects?*

Experimental and epidemiological methods are the two main approaches used in health risk assessment to identify, characterise and quantify risks to human health.

Experimental studies are often the only data available. *In vitro* systems and laboratory animals are more commonly used since it is usually unethical to deliberately expose humans. In these experiments, living cells or animals are exposed to a range of doses of the substance. The responses are usually compared to those in control *in vitro* systems or animals in which there is no exposure but all other factors are identical.

*Are there in vitro data?*

### **(1) In vitro studies**

*In vitro* systems generally do not take the route of administration, distribution, or metabolism of the substance into account. They are useful for screening of a substance and analysis of specific actions eg skin irritation. They need to be validated for their ability to predict the effect seen in intact animals. When *in vitro* data support *in vivo* data it enhances the reliability of the *in vivo* results.

Mutagenic activity of substances is an important pre-screening factor for potential carcinogenicity by using *in vitro* bacterial or mammalian cells. Not all mutagens are carcinogens and vice versa. However there is a strong correlation between substances that are mutagenic, carcinogenic and teratogenic in that the genotoxic effects of a substance may be expressed in a number of ways.

*Are there animal data?*

## **(2) Animal studies**

Animal studies are designed to evaluate potential adverse effects by different routes of exposure, duration of exposure and endpoints. They are generally classified as:

- acute – single exposure, then two weeks observation
- subacute – 14 days of repeated exposure
- subchronic – usually 90 days of repeated exposure in rodents
- chronic – 6-24 months of repeated exposure in rodents, or
- lifetime – 18-30 months of repeated exposure in rodents (Klaassen, 1996).

These studies include:

- toxicokinetics
- acute toxicity – oral, dermal, inhalation
- skin and eye irritation/corrosion
- skin sensitisation
- mutagenicity
- three month feeding
- long term feeding, including carcinogenicity
- developmental toxicity/teratogenicity
- reproductive toxicity
- neurotoxicity.

There are a number of advantages and disadvantages of animal studies compared to human epidemiological studies (Table 1).

**Table 1 Advantages and disadvantages of animal studies compared to human epidemiological studies**

Advantages	Disadvantages
Laboratory setting allows more control	Uncertainties associated with extrapolating from animals to humans
Reveal the mechanism(s) of toxicity through invasive monitoring and post mortem examination	Exposure is much greater than what humans would typically be exposed to
Provide information prior to human exposure	
Provide information on all target sites that may be adversely affected	

Exposure is often several orders of magnitude higher to increase the sensitivity of the experiment and to compensate for the limited number of animals used. As a result extrapolation of the findings to lower exposures is necessary.

*What is the quality of the animal studies?*

The quality of the information available from animal studies is influenced by:

- appropriateness of the study design and conduct
- consistency of results across studies
- biological plausibility of statistical associations
- similarity of results to effects in humans.

*What is the relevance of the adverse effects in animals to human health?*

Adverse effects in animals are not necessarily relevant to human health. For example, issues that need to be considered in assessing the relevance of animal cancer study results to human cancer risk include:

- quality of the experiment's design and conduct
- occurrence of common compared to rare tumours
- progression, or lack of progression from a benign to a malignant tumour
- latency until tumour induction
- dose-response relationships, and
- genetic toxicity (The Presidential/Congressional Commission on Risk Assessment and Risk Management, 1997).

*Is the effect a result of mechanisms that are likely to occur in humans? Is the effect a result of mechanisms that are likely to occur at very high doses? Is the route of administration like human exposure?*

Some toxic mechanisms and pathways that occur in animals may not occur in humans. It is also possible that the high doses used in animal studies induce effects that do not occur at lower doses.

*Are there data on more than one species? Are there data on both sexes?*

It is usual to provide information from tests in several species. This may indicate species differences in response.

*What are the data gaps?*

*Are there human data?*

### **(3) Human studies**

Human studies may include case reports and epidemiological studies, in particular of populations with occupational exposure. In some instances eg neurotoxicity assessment of substances that have short-lived and reversible effects, it may be ethically possible to carry out laboratory exposure studies on volunteers.

### *What is the type of human data?*

The first type of human data that is available is often a case report. Case reports are the result of medical assessment of an individual(s), usually in the workplace. They can generate hypotheses and may support associations suggested by other human or animal data. Case reports of acute high level exposure resulting from incidents can also be useful for identifying signs and symptoms that may also apply to lower exposures.

Although epidemiological studies have a number of limitations (Table 2) they provide directly relevant information about the effects of human exposure. The strength of a study is influenced by the study design.

**Table 2 Advantages and disadvantages of epidemiological studies**

Advantages	Disadvantages
Directly relevant information about the effects of human exposure	Limited control due to their observational nature Limited exposure data Cannot adjust for unrecognised bias and confounding Cannot provide information prior to human exposure

### *What is the study design?*

There is a hierarchy of study designs ranging from randomised controlled trials at the top to ecological studies at the bottom.

#### **1. Randomised controlled trial**

The randomised controlled trial is the strongest study design for establishing associations. It is rare in environmental epidemiology because it is usually neither ethical nor practical.

#### **2. Observational studies**

Observational studies such as cohort and case-control studies are the most common strong designs in environmental epidemiology.

##### *i. Cohort studies*

Cohort studies are potentially more reliable at establishing a causal association than case-control studies but are more expensive.

- If the incidence of the effect is rare, the study size has to be large or the study period long.
- If the study is prospective and the effect has a long induction period the study must be at least as long as the induction period to observe the effect.
- Is the comparison group similar to the exposed group eg observation time, geographical location?
- In an occupational cohort study, has the healthy worker effect (which presumes that workers face a lower risk for adverse health effects than the general population) been taken into

account? For example, risk will be under-estimated if an occupational group is compared to a general population group.

- Was the procedure for detecting the health effect the same in the two groups? For example, if only the exposed group has periodic health examinations this could result in a greater proportion of diagnosed cases among the exposed than the comparison group.

*ii. Case-control studies*

- If exposure is rare the study size has to be large.
- Information bias may arise from incorrect exposure information being obtained from the cases and/or the controls eg recall may be greater among cases. For example, do the data collection methods used give reasonably accurate and unbiased information? Are the data collection methods the same for both cases and controls?
- Selection bias may arise as a result of the way in which the cases and/or the controls were selected. For example, are the cases a representative group of individuals with the health effect? Does the control group represent the exposure distribution in the population from which the cases derive?

### **3. Ecological studies**

An ecological study is the weakest study design for establishing an association. Ecological studies can only generate rather than test causal hypotheses because they use aggregate data for exposure and health effects.

*What is the study's validity?*

It is important to assess the internal and external validity of a study.

Internal validity refers to the validity of the results as they relate to the subjects in the study. Selection bias, information bias such as from the measurement of exposure and/or the health effect, and confounding affect internal validity.

*What are the sources of bias? Has confounding been controlled for? eg age, cigarette smoking, alcohol*

External validity refers to the extent to which results can be generalised outside the study population. Generalising beyond a study's observations requires a judgement about what features of the observations may be extrapolated.

*Is the study population comparable to the risk population in terms of susceptibility? Are the characteristics of exposure in the study population comparable to those in the risk population?*

Differences between the two populations in characteristics such as age and duration of exposure may have important effects on the dose-response relationship.

Inferring cause and effect relationships from epidemiological studies requires careful evaluation because associations may be the result of bias, confounding or random chance. Criteria for evaluating the evidence for causation are:

- temporality  
Exposure must precede the effect and take account of latency periods for effects such as cancer.
- strength of association

The stronger the observed association, which is usually measured by the relative risk, the more convincing the case for causation.

- consistency among studies

Several studies with similar findings support causality.

- biological plausibility

Toxicological evidence exists on the mechanisms of action of the substance.

- dose-response relationship

There is a clear relationship between exposure and response.

- reversibility

Removal of the exposure results in reduction or elimination of the effect.

- study design (Beaglehole et al, 1993).

The more criteria that are met the greater the evidence for causation. Failure to meet these criteria indicates failure to provide positive evidence in support of a hypothesised cause; it does not prove the absence of causation (Rizak et al, 1997).

*Is the statistical power of the study adequate?*

Even if an exposure-related effect exists, an epidemiological study may not show an effect because the sample size is too small. To detect risks of 1 in 10,000 or 1 in 100,000 or less studies often need at least several thousand subjects. Epidemiological studies should be considered only if the statistical power of each study is adequate (Shore, 1995; Wartenberg and Simon, 1995).

Statistical power is dependent on the size of the study group, the frequency of the outcome and the level of excess risk to be identified. It may be enhanced by combining populations from several studies using meta-analysis. Studies with lower power tend to have wider confidence intervals.

*Is the statistical analysis of the study appropriate?*

Significance testing provides information on whether observed differences are caused by random chance. It does not reflect the biological or practical significance nor confirm the existence of a cause-effect relationship. Statistical significance can be expressed in terms of a P-value or confidence interval. Both are influenced by sample size. For example, if the sample size is small the confidence interval is wide and testing the null hypothesis for a given P-value may result in a non-significant finding because of insufficient subjects to detect an effect that may have been evident in a larger sample.

*What is the quality of the human studies?*

*What are the data gaps?*

Other issues to consider with respect to the application are:

*Were the studies carried out by the applicant? If the studies were not carried out by the applicant, were they funded by the applicant?*

*Were in vitro/ animal studies carried out in accordance with overseas regulatory agencies and/ or following Good Laboratory Practice?*

*Were the studies peer reviewed? Were the studies published, and where?*

*Have studies with negative or null results been considered?*

*Has the most recent evidence been included?*

*What is the overall credibility of the evidence?*

*Does the application contain the best available data? Has the applicant made appropriate use of the best available data?*

The hazard can be defined by a weight of evidence approach for an endpoint (US EPA, 1996 and 1998) (Table 3).

**Table 3 Characterisation of the hazard to human health**

Category	
Sufficient evidence	There is collectively enough animal and human data to judge whether or not a hazard could exist.
Sufficient human evidence	There is enough evidence from epidemiological studies, or case reports in conjunction with other supporting evidence, to judge that a hazard could exist.
Sufficient animal evidence/limited human data	There is enough evidence from animal studies and/or limited human data to judge if a hazard could exist. The minimum evidence necessary to determine if a potential hazard exists is data showing an effect in an appropriate well-designed study in an animal species. The minimum evidence to judge that a potential hazard does not exist generally includes data from >1 well-designed study and 2 species showing no effect at adequate high doses. Information on toxicokinetics, mechanisms, or physico-chemical properties may strengthen the evidence.
Insufficient evidence	There is less than the minimum evidence necessary for assessing the potential for toxicity. For example, no data; data from studies that are have a limited design or conduct; data limited to <i>in vitro</i> tests, toxicokinetics, or QSAR analysis.

*Are there indirect health effects? What are the indirect health effects?*

Human and ecological health are closely connected. Ecosystems are essential to human survival and well-being. For example, changes in the quality and availability of food, water, air, land and soil may have health effects.

## Exposure assessment

The objective of this section is to answer the question:

*What is the overall level and pattern of exposure in the population(s)?*

Exposure assessment involves an assessment of the potential for human exposure to the substance. The recommended approach is to start as simply as possible and sequentially use more sophisticated analyses but only as warranted by the value added to the decision process (US EPA, 1997). The steps involved vary depending on how much is known about existing exposures and what information is available. The most reliable information is from personal, biological and/or ambient environmental monitoring of amounts of substances to which people are exposed over time. These data are usually not available and information is derived instead from simulation models and/or generalised assumptions about relevant physical parameters and human activities.

*What exposure pathways are possible?*

Exposure can be direct or indirect and as a result of inhalation, ingestion or direct contact with the skin or mucous membranes eg eye (Figure 1). Sources of exposure include occupational, consumer products and the ambient environment, in particular air and water.

Dose or effective exposure is the quantity of the substance actually taken up by an individual. In addition to the quantity of the substance present, it depends on the exposure pathway, chemical and physical properties of the substance, and an individual's physiology and activity. Models may be used to determine the uptake of a substance that take account of bioavailability, population characteristics and activities, and multiple exposure pathways. Use of biological markers may help to define the relationship between exposure and dose.

*What are the conditions under which people could be exposed and the doses that could occur as a result of such scenarios?*

*Do different exposure pathways lead to the same or different effects? If the effects are the same, does one pathway dominate in magnitude or rate of effect?*

*What is the main exposure pathway(s)?*

*Who may be exposed? How many may be exposed?*

*What is the duration of exposure? Is exposure acute and/or chronic?*

*How often are populations exposed as a result of diet, drinking water, residential exposure, activity patterns or occupation?*



*What populations may be highly exposed as a result of occupation, age, geographical location, and social or cultural practices eg diet?*

Variability results from differences in exposure levels in the environment or heterogeneity in characteristics such as dose-response within a population. Sources of variability arise from environmental, lifestyle and genetic differences among humans. For example, physiological variation such as body weight and inhalation rate, and weather variability. Individual exposure and risk can vary widely in a population.

Infants and children may be more exposed than adults as a result of their higher inhalation rate and higher consumption of certain foods.

*If highly exposed populations exist, have they been separately evaluated from the total population?*

*What populations may be highly susceptible as a result of genetic pre-disposition, age, lifestyle factors, or pre-existing medical conditions?*

Examples of susceptible populations are given in Table 4.

**Table 4 Susceptible populations and reasons for susceptibility**

Population group	Reason for susceptibility
Fetus	Sensitivity of developing organs to substances that cause birth defects
Infants and young children	Sensitivity of developing brain to neurotoxic substances
Children	Greater food intake on the basis of body weight
Elderly	Reduced detoxification and elimination mechanisms in the liver and kidneys
People with atopy or chronic disease	Eg asthmatics – increased airways responsiveness to respiratory irritants and allergens

Lifestyle factors such as diet and cigarette smoking may also influence susceptibility.

*Is exposure cumulative?*

*What estimates of exposure have been used?*

Exposure assessment should attempt to characterise the distribution of exposure levels in the population as accurately as possible. Exposure can be calculated using point estimate and/or probabilistic methods. Point exposure estimates include:

- a hypothetical maximally exposed individual – exposure is assumed to occur at the highest level possible throughout an individual's lifetime (assuming 70 years)
- a high-end exposure estimate – exposure is assumed to occur at the higher end (eg 90<sup>th</sup> or 95<sup>th</sup> percentile) of a range of actual or estimated individual exposures.

Worst-case analyses are often used so that true human risks are not under-estimated. The most exposed person's potential risk thus acts as a benchmark for the adequacy of a proposed strategy to control or restrict environmental concentrations of a substance.

Probabilistic analysis techniques such as the Monte Carlo technique result in a probability distribution of exposures that more accurately predicts exposures than does the approach using point estimates. Probability distributions are assumed for input variables eg concentration of a substance, ingestion rates, and output variables are defined eg total exposure. Random values are generated from the input distributions and output distributions derived. An arbitrary point in the distribution is selected eg 95<sup>th</sup> percentile to determine the maximum likely exposure for which the risk is then calculated. Such techniques are only needed when worst-case analyses suggest there may be a problem.

*Are the exposure data used representative of the population under study?*

If exposure data were collected overseas, population density, lifestyle and local industry may have had a significant effect on exposure concentrations and activity patterns.

*Are the exposure data an over-estimate of average exposure? Are the exposure data an under-estimate of average exposure?*

*Are the exposure data derived from population exposure data or from source characteristics and models? If models have been used, how appropriate are they?*

*What assumptions have been made that have a significant impact on the results?*

For example, assumptions may be made about how much of a substance will be ingested daily by those potentially exposed and over what time period this would occur.

## **Dose-response assessment**

The objective of this section is to answer the question:

*How do health effects vary with the level of exposure?*

Dose-response assessment determines the amount of the substance that causes adverse effects. It uses information on the effects associated with various levels of exposure (or dose) from the experimental and epidemiological studies and information on 'real world' exposure to develop estimates of the likelihood of effects in potentially exposed populations. The method chosen can considerably influence the risk assessment.

Dose-response assessment for developmental toxicity and other non-cancer health effects is usually done as part of hazard identification as the determination of whether there is a hazard or not often depends on whether a dose-response relationship exists.

In the absence of human data results from animal studies using high doses are often extrapolated to humans to give estimates of dose-response relationships. The dose-response estimates from animal studies are usually multiplied by uncertainty factors in an attempt to allow for quantitative differences in response between animals and humans and variation in individual susceptibility to exposure in humans.

Since systemic toxic substances are by definition distributed within an organism the concentration will bear some relationship to its size. Therefore as a first approximation the dose in milligrams per kilogram of body weight that has produced an effect is noted. Once sufficient data are available extrapolation gives the dose that will produce a given effect in 50 percent of an exposed population. The route of exposure and characteristics of the organism studied eg age, sex, nutritional status must be specified.

If human data are available the high to low dose extrapolation is still required since dose-response data from human studies usually applies to high exposure levels in the workplace whereas the exposure is low in the general population. At low levels of exposure it is difficult to detect effects in an epidemiological study unless the study population is very large. Nevertheless the health impact of low level exposure may be considerable if the exposed population is large. Other differences in exposure between the study population and risk population such as duration and pattern may also exist.

Mathematical models are used to extrapolate effects from high dose to low dose. The aim is to develop a potency value that represents the increase in health effect occurrence per unit of exposure. In animal studies occurrence is measured as lifetime risk and exposure is measured as daily concentration per unit of body weight. Potency then represents the increase in lifetime risk per unit of daily dose. In human studies occurrence is measured as rates and exposure may be measured by duration and concentration or in cumulative time at a concentration level. Potency is then in units of rates or ratios for a given exposure. Lifetime risk is derived by applying potency value to life tables or to proportional mortality data (Hertz-Picciotto, 1995).

Key issues in characterising a dose-response relationship are:

- the relationship between the selected extrapolation models and information about biological mechanisms
- how data were chosen from studies that demonstrated the range of possible potencies
- correspondence between the expected exposure pathway(s) and exposure pathway(s) used in the studies
- correspondence between the expected exposure duration and exposure duration in the studies used, and
- variation in susceptibility among different populations (US EPA, 1995).

For practical purposes toxic effects are considered to be of two types, threshold and non-threshold.

### **(1) *Threshold***

Non-genotoxic carcinogens and non-carcinogenic substances are assumed to exhibit a threshold dose below which no adverse effect may be expected. This uses the highest dose at which no adverse effect is observed (the no observed adverse effect level or NOAEL). The precision of the NOAEL is determined by the sensitivity of the toxic endpoint, the dose interval and to a lesser extent the size of the study group. The sensitivity of the toxic endpoint depends on the incidence of the effect in the control group and/or its inter-animal variability. For example, a low incidence of a rare effect can be detected but the same increase in incidence of a common effect may not be statistically different from the control group.

## (2) *Non-threshold*

Genotoxic carcinogens are assumed to exhibit no threshold for carcinogenesis and a linear no threshold model is used. The cancer potency factor expresses potency in terms of the increased risk of cancer predicted to result from continuous lifetime exposure to a specified dose in milligrams per kilogram of body weight per day of the substance. The same information may be expressed in terms of the dose (risk specific dose) which is predicted to give rise to a specified increase in individual lifetime risk eg 1 in 1,000,000 chance of death from cancer.

Mathematical models based on animal data are used to derive the concentration of a substance estimated to cause one additional case of cancer in a population of 100,000 or 1,000,000 exposed at this concentration for a lifetime of 70 years.

Models can be tested statistically in an attempt to determine which model best fits the observed data.

When studies of sufficient quality are available for both animals and humans the human data are preferable as a basis for extrapolation (Smith, 1988; Hertz-Picciotto, 1995). Advantages of using human data are:

- a lower magnitude of error than animal data
- Uncertainty from inter-species extrapolation is greater than uncertainty from bias or errors in exposure information in epidemiological studies.
- a smaller range of extrapolation ie from an occupational group to the general population
  - the context and patterns of exposure in animals poorly represent human exposure scenarios
  - the genetic diversity and variability in the human population are better represented in a human study.

Where human data are inadequate to derive a dose-response relationship, such as well-designed null studies, they can be used as a check on the plausibility of a risk assessment based on animal data and reduce the range of uncertainty. Other human studies that cannot contribute to dose-response assessment can contribute to the weight of evidence that determines whether the substance is a health hazard (Hertz-Picciotto, 1995).

*Does the substance interact with other substances?*

There is a possibility that different substances may have antagonistic effects eg zinc reduces the effects of cadmium exposure. Such examples are rare. Of public health concern are additive effects:

- synergistic effects when the combined effects are greater than the sum of effects (eg smoking and asbestos, ethanol and carbon tetrachloride) and
- potentiation when a substance which alone does not have a toxic effect in combination increases the toxicity of the latter (eg isopropanol increases the liver damage by carbon tetrachloride when combined with it).

## Risk characterisation

The objective of this section is to answer the question:

*What is the aggregate effect on health in the exposed population(s)?*

Risk characterisation results in an estimation of risk for the population from integrating the information from hazard identification, exposure and dose-response assessments. It describes risk in terms of the probability of its occurrence and the magnitude of the adverse effect (HSNO (Methodology) Order 1998). Risk assessment is a decision-making tool not a precise analysis of actual or measurable risk. The focus therefore should be on how best to inform decision-making. Plausible upper and lower estimates of risk can be calculated based on the plausible range of values for the exposure and dose-response estimates. Expression of risk in terms of both central tendencies and upper bound estimates broadens usefulness (Crouch et al, 1995). Assessment results may then be more effectively communicated as a series of risk options that are more relevant to real life.

In order to resolve some of the differing interpretations about risk it is important to recognise all of the major characteristics of risk. Risk can never be truly measured or verified. All knowledge about risk falls within a continuum that extends from a theoretical purely scientific quantitative end to a theoretical purely qualitative end. All aspects of risk, whether quantifiable or not, have some qualitative element to them (Light and Hruday, 1996).

For substances with known or suspected carcinogenic effects, in particular those that are genotoxic carcinogens, it may be possible to make a quantitative assessment of cancer risk at low exposures based on assumptions about the dose-response relationship.

For substances with non-carcinogenic effects, for which it is generally assumed that a threshold of effect exists, it may only be possible to state that estimated exposures are above or below a maximum 'permissible' level of exposure. This may also apply to non-genotoxic carcinogens.

Characterisation should address quantitative and qualitative features of the assessment and identify its important strengths and uncertainties (US EPA, 1995). Since there is always uncertainty associated with an assessment a single numerical presentation of risk alone is incomplete and may be misleading.

*What are the quantitative aspects of the risk?*

Quantitative aspects of the risk are the probability of various effects and their magnitude. They are best understood in the context of the background qualitative aspects of the data on which the calculations are based.

*What are the qualitative aspects of the risk?*

Qualitative aspects of the risk include the nature of the effects, who might experience the effects, any means to prevent or reverse the effects, and the strength and consistency of evidence.

Qualitative information is often more useful and understandable than quantitative estimates of risk.

*What are the sources of variability?*

Variability results from differences in the nature and extent of exposure and from variation in susceptibility.

*What are the sources of uncertainty?*

Health risk assessment is typically dominated by uncertainty, in particular about the health effects of low level exposure, rather than variability. Uncertainty results from information that is not known or only partly known.

Characterisation is incomplete without discussion of the uncertainty associated with each stage of the assessment that strongly influences confidence in the risk estimate. This should include issues such as quality and quantity of available data, assumptions, use of models, incomplete understanding of biological phenomena, and scientific judgements used to bridge information gaps.

*Have sensitivity analyses been carried out eg using different exposure scenarios, alternative dose-response models, alternative inter-species adjustments?*

Sensitivity analyses of important parameters are often desirable for deciding among options.

*What is the confidence that can be placed in any quantitative analysis of uncertainty and variability and its findings?*

Not every assessment requires or warrants a quantitative characterisation of variability and uncertainty such as Monte Carlo analysis. For example, when screening calculations using point estimates show exposures or risks to be clearly below levels of concern and the screening technique is known to significantly over-estimate exposure (US EPA, 1997).

*What are the information gaps?*

*Have all the relevant data been evaluated?*

*What are the weaknesses of the methods used?*

*What are the strengths of the methods used?*

*What are the critical assumptions? Are they reasonable? Are there plausible alternative assumptions? What is the effect of alternative assumptions on the conclusions?*

*What are the scientific controversies and their effect on the conclusions?*

*How reliable is the evidence? Are the conclusions justified by the evidence? Are the conclusions communicated in a way that reflects the weight of evidence?*

*Are there antagonistic or synergistic interactions that could lead to under- or over-estimation of the total risk?*

Although exposure is not synonymous with risk due to differences among individuals in susceptibility or other factors, information on the exposure levels experienced by different members of the population gives a picture of the range of risks that may occur and the overall

adverse impact on the population. Individual, population and subgroup population risks may be described.

### ***(1) Individual risk***

High-end and central tendency descriptions are used to give the variability in risk experienced by different individuals in the population. High-end risk estimates are based on exposures that are expected to occur in a small component of the population. Central tendency descriptions of risk may be based on either the arithmetic mean exposure or the median exposure. The arithmetic mean may differ markedly from the median estimate because of the skewness of typical exposure profiles.

### ***(2) Population risk***

Population risk may be described as a probabilistic number of cases of a health effect in the population over a specific time period or estimated proportion of the population with risk above some specified level eg 1 in 1,000,000 or within a range of some specified level eg acceptable daily exposure (ADE). The probabilistic number of cases can be obtained by summing the individual risks over all the individuals in the population or through the use of a risk model such as many carcinogenic models that assume a linear non-threshold response to exposure. In general when small populations are exposed population risk estimates may be very small. In these situations individual risk estimates will usually be more useful for decision-making.

### ***(3) Subgroup population risk***

Important subgroups such as highly exposed or highly susceptible people can be identified and where possible the risk quantified. This is useful when there is a subgroup that is experiencing significantly different exposures or has significantly different susceptibility to the effect from that of the larger population.

ADEs are designed to protect susceptible populations. If data on susceptible populations are available then the ADE is set using the NOAEL observed in the most susceptible population. If no such data are available then an additional 10-fold factor is used to account for variability between the average human response and the response of more susceptible individuals.

## **Risk evaluation**

Risk is a combination of scientific analysis and judgement and societal values. All judgements, expert and lay, are prone to bias. The key is to understand the bias each is putting on his/her judgement.

The public's conception of risk may include a number of ethical and social values such as equity, threats to future generations, uncertainty and potential for catastrophe that are excluded from technical assessments of risk.

*Who are the stakeholders?*

*What outcomes are important to the stakeholders and why?*

*What are the stakeholders' perceptions of the hazard?*

*What are the stakeholders' perceptions of the risk? Do different groups of stakeholders have different perceptions and concerns?*

*What is the larger real world context of the risk?*

For example, the substance under consideration may reduce the use of an already approved substance that is known to cause a greater health risk.

*What contribution does the substance make to the overall risk of certain effects in the population or to the overall health of the population?*

*How is the risk distributed in relation to other health risks to the population?*

*Are there direct positive health effects?*

*What is the evidence that exposure may be associated with positive health effects?*

*What are the characteristics of the positive health effects?*

For example, are the effects irreversible, acute or chronic, immediate or delayed, or affect future generations?

*Are there indirect positive health effects? What are the indirect positive health effects?*

Indirect positive health effects include employment and food supply.

*Have the relevant monetary costs and benefits been identified? Have the relevant non-monetary costs and benefits been identified?*

Examples of monetary health costs and benefits are the cost of healthcare and the value of a life. A reduced or enhanced sense of well-being is an example of a non-monetary health cost or benefit.

*What is the expected value of the costs and benefits and the uncertainty related to the expected value? How are the costs and benefits distributed over time, space, and groups in the population?*

*To what extent do the following risk characteristics apply?*

- *exposure to the risk is involuntary*
- *the risk will persist over time*
- *the risk is subject to uncontrollable spread and is likely to extend its effects beyond the immediate location of incidence*
- *potential adverse effects are irreversible*
- *the risk is not known or understood by the public and there is little experience or understanding of possible measures for managing the potential adverse effects (HSNO (Methodology) Order 1998).*

## **Risk management**

Risk management can be defined as the process of identifying, evaluating and implementing actions to reduce or prevent risks to human health. Communication among stakeholders is important so that public values can inform and influence the development of risk management strategies. The nature and extent of stakeholder involvement should be appropriate to the scope and impact of an application and the potential of the application to generate controversy (The Presidential /Congressional Commission on Risk Assessment and Risk Management, 1997). Broader participation improves the information base of risk management and may also be argued to bring different scientific perspectives to bear (The Royal Society, 1992).

The distribution of people involved in public participation may not necessarily reflect the distribution of the burden of risk. Those with a disproportionate burden of risk are often those with the least access to public participation.

*What are the key social, cultural and political factors that need to be taken into account when managing risks to public health?*

*Can the risk be prevented? Can the risk be reduced?*

*How can the risk be prevented? How can the risk be reduced?*

'What if ..?' questions can be used to look at risk management options eg What if a worker uses this substance without using protective equipment?

The HSN0 regulations include controls on substances related to their hazardous properties and pan-life cycle controls such as identification/labelling and packaging to manage adverse effects.

To protect public health, health-based exposure limits must be set by the Authority in certain circumstances. These limits are:

### **(1) Acceptable daily exposure (ADE)**

The ADE is an estimate of the overall daily dose, measured in milligrams per kilogram of body weight, below which an adverse effect is unlikely to occur following a lifetime of exposure. It is derived from the NOAEL divided by uncertainty factors. The toxic endpoint used is the one that shows the lowest NOAEL in the most sensitive mammalian species for which there is data. In the absence of a NOAEL the lowest observed adverse effect level (LOAEL) is used.

Uncertainty factors are used to take account of inter-species differences in susceptibility, susceptible human population subgroups, and data quality eg reliability, measurement uncertainty. An uncertainty factor of 10 is generally used to account for extrapolation from animals to humans, and further uncertainty factors of 10 for susceptible human populations, when a NOAEL is extrapolated from a LOAEL, and when only acute animal data are available. If human data are available a lower total uncertainty factor eg 10 may be applied than if only animal data are available eg a factor of 100 to 1,000. The total uncertainty factor should not exceed 10,000 as the resulting value would be too imprecise (World Health Organisation, 1994).

### **(2) Reference dose (RfD)**

The RfD is an estimate of a daily exposure, measured in milligrams per kilogram of body weight, below which an adverse effect is unlikely to occur following a lifetime or limited time interval of exposure. It is derived from the NOAEL (or LOAEL) divided by uncertainty factors. The NOAEL used is from a study that shows a specific endpoint of concern eg teratogenicity. More than one RfD may be established for the substance.

### **(3) Potential daily exposure (PDE)**

The PDE is a measure of the likelihood of an individual being exposed to the substance through a medium given daily consumption and use patterns. It is expressed as a percentage of the ADE or RfD in milligrams per kilogram of body weight per day. Media include air, water, soil, deposition on plants, food, and non-food products eg graphic materials. All potential routes of exposure are considered for each medium that is likely to expose humans to the substance. For example, the contribution of dermal absorption and ingestion through food as a result of the substance in air. The sum of all PDEs for the substance is generally less than 100 percent of the ADE to provide a margin of safety in addition to that already provided in the ADE. This accounts for cross-route exposure and exposure that has not been characterised.

### **(4) Tolerable exposure limit (TEL)**

Exposure standards ie a TEL must be set based on the ADE, RfD and/or PDE for the substance. The TEL is the level below which there is a low risk of an adverse effect occurring following exposure. It is the exposure limit that is enforced under the HSNO Act.

The calculation of the TEL for each medium takes into account the following factors:

- potential exposure or consumption eg volume of intake or surface area for uptake
- body weight
- toxicokinetic and/or toxicodynamic data
- frequency and duration of exposure
- nature of exposure eg acute or chronic
- medical, accident or epidemiological evidence.

The distribution of individuals in a potentially exposed population, in terms of age, sex and health status is also considered (Ministry for the Environment, 1999).

In the case of a mixture there may be more than one TEL based on its constituent compounds or elements.

Workplaces require separate exposure limits since exposures occur over a limited time frame and involve less susceptible individuals than in the general population. A Workplace Exposure Standard (WES) is expressed in milligrams per cubic metre or parts per million of air.

Some substances eg agricultural compounds also have a Maximum Residue Limit (MRL) set under the Food Act 1981.

*What are the economic, social, cultural and ethical implications associated with implementing each option?*

*Does the action have a significant impact on the risk?*

*Does it reduce or prevent the risk in a way that is based on the best available scientific evidence? Is the action feasible?*

*Can the action be implemented effectively? Can the action be implemented with stakeholder support?*

*What is the impact of preventing or reducing the risk on overall public health?*

## Part II: new organisms

### Summary question chart

The objective of the review is to answer the question:

*What is the likelihood and the magnitude of the impact on public health from the new organism?*

#### Risk assessment

##### *Hazard identification*

The objective of this section is to answer the question:

*Is the organism a source of potential harm to public health?*

1. How is the organism classified?
2. What is the organism's life cycle?
3. What are the biological characteristics of the organism?
4. Is the organism genetically modified? If so, what is the origin of the gene?
5. What does the gene code for?
6. How was the gene put into the plant, animal or micro-organism? What is the evidence of the stability of the GMO?
7. Have any unintentional or secondary changes arisen from the genetic modification? If so, what are these changes?
8. What are the physico-chemical properties of the protein the gene codes for?
9. Is the organism pathogenic? Is it an opportunistic pathogen? Is it a parasite?
10. Is the organism toxigenic?
11. What is the mechanism(s) of toxicity?
12. What is the organism's virulence? What factors influence virulence?
13. What is the reservoir(s)?
14. What is the host range? Are there vectors? What are the vectors?

15. Are there health effects associated with the organism?
16. What are the known adverse human health effects?
17. What are the known adverse animal health effects?
18. What are the characteristics of the health effects?
19. What is its potential to mutate and have an adverse effect on human health?
20. What is the evidence that exposure may be associated with health effects?
21. Are there *in vitro* data?
22. Are there animal data?
  - What is the quality of the animal studies?
  - What is the relevance of the adverse effects in animals to human health?
  - Is the effect a result of mechanisms that are likely to occur in humans? Is the effect a result of mechanisms that are likely to occur at very high doses? Is the route of administration like human exposure?
  - Are there data on more than one species? Are there data on both sexes?
  - What are the data gaps?
23. Are there human data?
  - What is the type of human data?
  - What is the study design?
  - What is the study's validity?
  - What are the sources of bias? Has confounding been controlled for? eg age, cigarette smoking, alcohol
  - Is the study population comparable to the risk population in terms of susceptibility?
  - Are the characteristics of exposure in the study population comparable to those in the risk population?
  - Is the statistical power of the study adequate?
  - Is the statistical analysis of the study appropriate?
  - What is the quality of the human studies?

- What are the data gaps?

24. Were the studies carried out by the applicant? If the studies were not carried out by the applicant, were they funded by the applicant?
25. Were *in vitro*/animal studies carried out in accordance with overseas regulatory agencies and/or following Good Laboratory Practice?
26. Were the studies peer reviewed? Were the studies published, and where?
27. Have studies with negative or null results been considered?
28. Has the most recent evidence been included?
29. What is the overall credibility of the evidence?
30. Does the application contain the best available data? Has the applicant made appropriate use of the best available data?
31. Are there indirect health effects? What are the indirect health effects?

#### *Exposure assessment*

The objective of this section is to answer the question:

*What is the overall level and pattern of exposure in the population(s)?*

1. What exposure pathways are possible?
2. What are the conditions under which people could be exposed and the doses that could occur as a result of such scenarios?
3. Do different exposure pathways lead to the same or different effects? If the effects are the same, does one pathway dominate in magnitude or rate of effect?
4. What is the main exposure pathway(s)?
5. Who may be exposed? How many may be exposed?
6. What is the duration of exposure? Is exposure acute and/or chronic?
7. How often are populations exposed as a result of diet, drinking water, residential exposure, activity patterns or occupation?
8. What populations may be highly exposed as a result of occupation, age, geographical location, and social or cultural practices eg diet?

9. If highly exposed populations exist, have they been separately evaluated from the total population?
10. What populations may be highly susceptible as a result of genetic pre-disposition, age, lifestyle factors, or pre-existing medical conditions?
11. Is there secondary spread of the organism?
12. In the case of a GMO, is there a possibility of horizontal gene transfer to consumers or to their gut micro-organisms?
13. Does exposure result in immunity? Is immunity full or partial? Does immunity wane over time or is it lifelong?
14. What estimates of exposure have been used?
15. Are the exposure data used representative of the population under study?
16. Are the exposure data an over-estimate of average exposure? Are the exposure data an under-estimate of average exposure?
17. Are the exposure data derived from population exposure data or from source characteristics and models? If models have been used, how appropriate are they?
18. What assumptions have been made that have a significant impact on the results?

*Dose-response assessment*

The objective of this section is to answer:

*How do health effects vary with the level of exposure?*

1. What is the infectious or toxic dose?
2. Is there a relationship between dose and the severity of effect?
3. Does exposure always result in infection and disease?

*Risk characterisation*

The objective of this section is to answer:

*What is the aggregate effect on health in the exposed population(s)?*

1. What are the quantitative aspects of the risk?

2. What are the qualitative aspects of the risk?
3. What are the sources of variability?
4. What are the sources of uncertainty?
5. Have sensitivity analyses been carried out eg using different exposure scenarios, alternative dose-response models?
6. What is the confidence that can be placed in any quantitative analysis of uncertainty and variability and its findings?
7. What are the information gaps?
8. Have all the relevant data been evaluated?
9. What are the weaknesses of the methods used?
10. What are the strengths of the methods used?
11. What are the critical assumptions? Are they reasonable? Are there plausible alternative assumptions? What is the effect of alternative assumptions on the conclusions?
12. What are the scientific controversies and their effect on the conclusions?
13. How reliable is the evidence? Are the conclusions justified by the evidence? Are the conclusions communicated in a way that reflects the weight of evidence?
14. Are there antagonistic or synergistic interactions that could lead to under- or over-estimation of the total risk?

### **Risk evaluation**

1. Who are the stakeholders?
2. What outcomes are important to the stakeholders and why?
3. What are the stakeholders' perceptions of the hazard?
4. What are the stakeholders' perceptions of the risk? Do different groups of stakeholders have different perceptions and concerns?
5. What is the larger real world context of the risk?
6. What contribution does the organism make to the overall risk of certain effects in the population or to the overall health of the population?
7. How is the risk distributed in relation to other health risks to the population?

8. Are there direct positive health effects?
9. What is the evidence that exposure may be associated with positive health effects?
10. What are the characteristics of the positive health effects?
11. Are there indirect positive health effects? What are the indirect positive health effects?
12. Have the relevant monetary costs and benefits been identified? Have the relevant non-monetary costs and benefits been identified?
13. What is the expected value of the costs and benefits and the uncertainty related to the expected value? How are the costs and benefits distributed over time, space, and groups in the population?
14. To what extent do the following risk characteristics apply?
  - exposure to the risk is involuntary
  - the risk will persist over time
  - the risk is subject to uncontrollable spread and is likely to extend its effects beyond the immediate location of incidence
  - potential adverse effects are irreversible
  - the risk is not known or understood by the public and there is little experience or understanding of possible measures for managing the potential adverse effects (HSNO (Methodology) Order 1998).

### **Risk management**

1. What are the key social, cultural and political factors that need to be taken into account when managing risks to public health?
2. Can the risk be prevented? Can the risk be reduced?
3. How can the risk be prevented? How can the risk be reduced?
4. What are the economic, social, cultural and ethical implications associated with implementing each option?
5. Does the action have a significant impact on the risk?
6. Does it reduce or prevent the risk in a way that is based on the best available scientific evidence? Is the action feasible?
7. Can the action be implemented effectively? Can the action be implemented with stakeholder support?
8. What is the impact of preventing or reducing the risk on overall public health?

## **Risk assessment**

The assessment of potential adverse health effects is based on a health risk assessment framework. Risk assessment is a central component of health impact assessment. It includes four stages: hazard identification, exposure assessment, dose-response assessment and risk characterisation.

Health risk assessment draws on the knowledge and methods of epidemiology, toxicology and exposure analysis. It aims to identify the adverse health effects that may be associated with exposure to a new organism and to predict the likelihood that specific human populations will experience such effects at given exposure levels.

The amount of detail required at each stage of the risk assessment process depends on the magnitude and likely significance of the actual or potential health effects.

Though each stage has objective components, each also requires some decisions based on subjective judgements which personal values may influence (Wartenberg and Simon, 1995).

## **Hazard identification**

The objective of this section is to answer the question:

*Is the organism a source of potential harm to public health?*

This involves the identification of an organism as a source of potential harm to humans. It is based on the type and quality of data on humans and/or laboratory animals and cell systems, and the weight of evidence from all of these data sources.

*How is the organism classified?*

*What is the organism's life cycle?*

*What are the biological characteristics of the organism? For example, is the organism tolerant to heat, cold, or desiccation?*

*Is the organism genetically modified? If so, what is the origin of the gene?*

*What does the gene code for?*

*How was the gene put into the plant, animal or micro-organism? What is the evidence of the stability of the GMO?*

*Have any unintentional or secondary changes arisen from the genetic modification? If so, what are these changes?*

*What are the physico-chemical properties of the protein the gene codes for?*

Physico-chemical properties influence a protein's fate after exposure and may indicate allergenicity. For example, many food allergens are resistant to digestion.

Comparisons of the chemical or physical properties with those of other proteins known to cause particular toxic or allergenic effects may give some indication of a potential for similar toxicity or allergenicity when little or no other data are available. For example, databases such as Genbank can be searched to identify amino acid sequence homologies between known toxins or allergens and the protein.

*Is the organism pathogenic? Is it an opportunistic pathogen? Is it a parasite?*

*Is the organism toxigenic?*

*What is the mechanism(s) of toxicity?*

*What is the organism's virulence? What factors influence virulence?*

*What is the reservoir(s)?*

*What is the host range? Are there vectors? What are the vectors?*

*Are there health effects associated with the organism?*

Potential adverse effects include acute and chronic infection or disease, psychological effects and death. Effects can be local such as skin, lungs, eye, or systemic. In cases of allergic effects, sometimes due to sensitisation resulting from previous exposure, a low dose may result in an inordinate local or systemic effect. Sometimes there may be idiosyncratic effects where there is an abnormal, often genetically predetermined, response.

*What are the known adverse human health effects?*

*What are the known adverse animal health effects?*

Effects can occur in any bodily system. Possible effects are:

- psychological eg depression
- sensory eg deafness
- neurological eg neuritis
- dermatological eg contact dermatitis
- musculo-skeletal eg myalgia
- haematological eg anaemia
- cardiovascular eg tachycardia
- respiratory eg asthma
- hepatic eg hepatitis
- gastro-intestinal eg diarrhoea
- genito-urinary eg renal failure
- endocrine eg hypothyroidism
- immunological eg anaphylaxis
- female reproductive
  - general reproductive effects eg infertility
  - teratogenicity eg anophthalmia
  - other effects in pregnancy

- effects during lactation
- male reproductive eg orchitis.

*What are the characteristics of the health effects?*

Characteristics of the effects include:

- severity
- latency
- ability to affect future generations
- whether it is irreversible or reversible
- transient
- fatal
- acute or chronic
- immediate or delayed, or
- progressive.

Health effects may be modified by factors such as immediacy or latency from weeks to decades, effects may be reversed eg regeneration of liver cells, or tolerance may develop.

*What is its potential to mutate and have an adverse effect on human health?*

*What is the evidence that exposure may be associated with health effects?*

Experimental and epidemiological methods are the two main approaches used in health risk assessment to identify, characterise and quantify risks to human health. The methods vary depending on the nature of the organism.

Experimental studies are often the only data available. They include *in vitro* and animal studies on the nature of toxins and their mode of action and the associated acute and chronic effects. In some instances it may be ethically possible to carry out human studies that expose volunteers, for example, to a potential allergen or to a range of doses of a pathogenic organism.

*Are there in vitro data?*

### **(1) In vitro studies**

*In vitro* tests (eg for specific immunoglobulin (IgE) antibodies) are useful for screening a protein expressed in a GMO for allergenicity.

*Are there animal data?*

### **(2) Animal studies**

Animal studies are designed to evaluate potential adverse effects of toxins by different routes of exposure, duration of exposure and endpoints.

There are a number of advantages and disadvantages of animal studies compared to human epidemiological studies (Table 5).

**Table 5 Advantages and disadvantages of animal studies compared to human epidemiological studies**

Advantages	Disadvantages
Laboratory setting allows more control	Uncertainties associated with extrapolating from animals to humans
Reveal the mechanism(s) of toxicity through invasive monitoring and post mortem examination	Exposure is much greater than what humans would typically be exposed to
Provide information prior to human exposure	
Provide information on all target sites that may be adversely affected	

Exposure is often several orders of magnitude higher to increase the sensitivity of the experiment and to compensate for the limited number of animals used. As a result extrapolation of the findings to lower exposures is necessary.

*What is the quality of the animal studies?*

The quality of the information available from animal studies is influenced by:

- appropriateness of the study design and conduct
- consistency of results across studies
- biological plausibility of statistical associations, and
- similarity of results to effects in humans.

*What is the relevance of the adverse effects in animals to human health?*

Adverse effects in animals are not necessarily relevant to human health.

*Is the effect a result of mechanisms that are likely to occur in humans? Is the effect a result of mechanisms that are likely to occur at very high doses? Is the route of administration like human exposure?*

Some toxic mechanisms and pathways that occur in animals may not occur in humans. It is also possible that the high doses used in animal studies induce effects that do not occur at lower doses.

*Are there data on more than one species? Are there data on both sexes?*

It is usual to provide information from tests in several species. This may indicate species differences in response.

*What are the data gaps?*

*Are there human data?*

### (3) *Human studies*

Human studies may include *in vivo* tests (eg skin prick tests for assessing allergenicity of a GMO that is a food), case reports and epidemiological studies.

*What is the type of human data?*

The first type of human data that is available is often a case report. Case reports are the result of medical assessment of an individual(s). They can generate hypotheses and may support associations suggested by other human or animal data. Case reports of acute high level exposure can be useful for identifying signs and symptoms that may also apply to lower exposures.

Although epidemiological studies have a number of limitations (Table 6) they provide directly relevant information about the effects of human exposure. The strength of a study is influenced by the study design.

**Table 6 Advantages and disadvantages of epidemiological studies**

Advantages	Disadvantages
Directly relevant information about the effects of human exposure	Limited control due to their observational nature Limited exposure data Cannot adjust for unrecognised bias and confounding Cannot provide information prior to human exposure

*What is the study design?*

There is a hierarchy of study designs ranging from randomised controlled trials at the top to ecological studies at the bottom.

#### **1. *Randomised controlled trial***

The randomised controlled trial is the strongest study design for establishing associations. It is rare in environmental epidemiology because it is usually neither ethical nor practical.

#### **2. *Observational studies***

Observational studies such as cohort and case-control studies are the most common strong designs in environmental epidemiology.

##### *i. Cohort studies*

Cohort studies are potentially more reliable at establishing a causal association than case-control studies but are more expensive.

- If the incidence of the effect is rare, the study size has to be large or the study period long.
- If the study is prospective and the effect has a long induction period the study must be at least as long as the induction period to observe the effect.
- Is the comparison group similar to the exposed group eg observation time, geographical location?

- Was the procedure for detecting the health effect the same in the two groups? For example, if only the exposed group has periodic health examinations this could result in a greater proportion of diagnosed cases among the exposed than the comparison group.

*ii. Case-control studies*

- If exposure is rare the study size has to be large.
- Information bias may arise from incorrect exposure information being obtained from the cases and/or the controls eg recall may be greater among cases. For example, do the data collection methods used give reasonably accurate and unbiased information? Are the data collection methods the same for both cases and controls?
- Selection bias may arise as a result of the way in which the cases and/or the controls were selected. For example, are the cases a representative group of individuals with the health effect? Does the control group represent the exposure distribution in the population from which the cases derive?

### **3. Ecological studies**

An ecological study is the weakest study design for establishing an association. Ecological studies can only generate rather than test causal hypotheses because they use aggregate data for exposure and health effects.

*What is the study's validity?*

It is important to assess the internal and external validity of a study.

Internal validity refers to the validity of the results as they relate to the subjects in the study. Selection bias, information bias such as from the measurement of exposure and/or the health effect, and confounding affect internal validity.

*What are the sources of bias? Has confounding been controlled for? eg age, cigarette smoking, alcohol*

External validity refers to the extent to which results can be generalised outside the study population. Generalising beyond a study's observations requires a judgement about what features of the observations may be extrapolated.

*Is the study population comparable to the risk population in terms of susceptibility? Are the characteristics of exposure in the study population comparable to those in the risk population?*

Differences between the two populations in characteristics such as age and duration of exposure may have important effects on the dose-response relationship.

Inferring cause and effect relationships from epidemiological studies requires careful evaluation because associations may be the result of bias, confounding or random chance. Criteria for evaluating the evidence for causation are:

- temporality

Exposure must precede the effect and take account of latency or incubation periods for effects such as cancer and transmissible spongiform encephalopathies.

- strength of association

The stronger the observed association, which is usually measured by the relative risk, the more convincing the case for causation.

- consistency among studies

Several studies with similar findings support causality.

- biological plausibility

Evidence exists on the biological mechanisms of action.

- dose-response relationship

There is a clear relationship between exposure and response.

- reversibility

Removal of the exposure results in reduction or elimination of the effect.

- study design (Beaglehole et al, 1993).

The more criteria that are met the greater the evidence for causation. Failure to meet these criteria indicates failure to provide positive evidence in support of a hypothesised cause; it does not prove the absence of causation (Rizak et al, 1997).

*Is the statistical power of the study adequate?*

Even if an exposure-related effect exists, an epidemiological study may not show an effect because the sample size is too small. To detect risks of 1 in 10,000 or 1 in 100,000 or less studies often need at least several thousand subjects. Epidemiological studies should be considered only if the statistical power of each study is adequate (Shore, 1995; Wartenberg and Simon, 1995).

Statistical power is dependent on the size of the study group, the frequency of the outcome and the level of excess risk to be identified. It may be enhanced by combining populations from several studies using meta-analysis. Studies with lower power tend to have wider confidence intervals.

*Is the statistical analysis of the study appropriate?*

Significance testing provides information on whether observed differences are caused by random chance. It does not reflect the biological or practical significance nor confirm the existence of a cause-effect relationship. Statistical significance can be expressed in terms of a P-value or confidence interval. Both are influenced by sample size. For example, if the sample size is small the confidence interval is wide and testing the null hypothesis for a given P-value may result in a non-significant finding because of insufficient subjects to detect an effect that may have been evident in a larger sample.

*What is the quality of the human studies?*

*What are the data gaps?*

Other issues to consider with respect to the application are:

*Were the studies carried out by the applicant? If the studies were not carried out by the applicant, were they funded by the applicant?*

*Were in vitro/animal studies carried out in accordance with overseas regulatory agencies and/or following Good Laboratory Practice?*

*Were the studies peer reviewed? Were the studies published, and where?*

*Have studies with negative or null results been considered?*

*Has the most recent evidence been included?*

*What is the overall credibility of the evidence?*

*Does the application contain the best available data? Has the applicant made appropriate use of the best available data?*

The hazard can be defined by a weight of evidence approach for an endpoint (US EPA, 1996 and 1998) (Table 7).

**Table 7 Characterisation of the hazard to human health**

Category	
Sufficient evidence	There is collectively enough animal and human data to judge whether or not a hazard could exist.
Sufficient human evidence	There is enough evidence from epidemiological studies, or case reports in conjunction with other supporting evidence, to judge that a hazard could exist.
Sufficient animal evidence/limited human data	There is enough evidence from animal studies and/or limited human data to judge if a hazard could exist. The minimum evidence necessary to determine if a potential hazard exists is data showing an effect in an appropriate well-designed study in an animal species. The minimum evidence to judge that a potential hazard does not exist generally includes data from >1 well-designed study and 2 species showing no effect at adequate high doses. Information on toxicokinetics, mechanisms, or physico-chemical properties may strengthen the evidence.
Insufficient evidence	There is less than the minimum evidence necessary for assessing the potential for toxicity. For example, no data; data from studies that are have a limited design or conduct; data limited to <i>in vitro</i> tests, toxicokinetics, or QSAR analysis.

*Are there indirect health effects?*

Human and ecological health are closely connected. Ecosystems are essential to human survival and well-being. For example, changes in the quality and availability of food, water, air, land and soil may have health effects.

There may also be significant effects for Māori health related to organisms because of their impact on taonga and the values attached to taonga.

*What are the indirect health effects?*

## Exposure assessment

The objective of this section is to answer the question:

*What is the overall level and pattern of exposure in the population(s)?*

Exposure assessment involves an assessment of the potential for human exposure to the organism. The recommended approach is to start as simply as possible and sequentially use more sophisticated analyses but only as warranted by the value added to the decision process (US EPA, 1997). The steps involved vary depending on how much is known about existing exposures and what information is available. The most reliable information is from personal, biological and/or ambient environmental monitoring of concentrations of organisms to which people are exposed over time. These data are usually not available and information is derived instead from simulation models and/or generalised assumptions about relevant physical parameters and human activities.

*What exposure pathways are possible?*

Pathways of human exposure to organisms vary according to the nature of the organism. They include inhalation, direct contact with the skin or mucous membranes eg eye, and ingestion (Figure 2). Sources of exposure include food and the ambient environment, in particular air and water.

Dose or effective exposure is the quantity of the organism actually taken up by an individual. In addition to the quantity of the organism present, it depends on the exposure pathway, chemical and physical properties of the toxin or protein coded by the gene in a GMO, and an individual's physiology and activity. Models may be used to determine uptake that take account of bioavailability, population characteristics and activities, and multiple exposure pathways. Use of biological markers may help to define the relationship between exposure and dose.

*What are the conditions under which people could be exposed and the doses that could occur as a result of such scenarios?*

*Do different exposure pathways lead to the same or different effects? If the effects are the same, does one pathway dominate in magnitude or rate of effect?*

*What is the main exposure pathway(s)?*

*Who may be exposed? How many may be exposed?*

*What is the duration of exposure? Is exposure acute and/or chronic?*

*How often are populations exposed as a result of diet, drinking water, residential exposure, activity patterns or occupation?*

Variability results from difference in exposure levels in the environment or heterogeneity in characteristics such as dose-response within a population. For example, there may be natural variation in the density of the organism as a result of seasonality.



Individual exposure and risk can vary widely in a population. For example, infants and children may be more exposed than adults as a result of their higher consumption of certain foods.

*What populations may be highly exposed as a result of occupation, age, geographical location, and social or cultural practices eg diet?*

*If highly exposed populations exist, have they been separately evaluated from the total population?*

*What populations may be highly susceptible as a result of genetic pre-disposition, age, lifestyle factors, or pre-existing medical conditions?*

Susceptible populations such as immunocompromised people eg those with HIV/AIDS or on high dose corticosteroids are likely to be infected or intoxicated by a lower dose of a pathogenic or toxigenic organism. They may also be affected by organisms that normally do not infect or intoxicate humans and may suffer from more severe illness.

Examples of susceptible populations are given in Table 8.

**Table 8 Susceptible populations and reasons for susceptibility**

Population group	Reason for susceptibility
Fetus	Sensitivity of developing organs to organisms that cause birth defects
Children	Greater food intake on the basis of body weight
People with food allergy	Hypersensitivity response to food allergens
People with chronic disease	Impaired immune mechanisms

Lifestyle factors such as diet and cigarette smoking may also influence susceptibility.

*Is there secondary spread of the organism?*

*In the case of a GMO, is there a possibility of horizontal gene transfer to consumers or to their gut micro-organisms?*

Secondary spread of infectious diseases is a unique feature of microbial risk that requires special attention in modelling. Information on the virulence or toxicity potential of the microbe and the susceptibility or health status of the host is needed to reduce the uncertainty in modelling microbial risks.

*Does exposure result in immunity? Is immunity full or partial? Does immunity wane over time or is it lifelong?*

*What estimates of exposure have been used?*

Exposure assessment should attempt to characterise the distribution of exposure levels in the population as accurately as possible. Exposure can be calculated using point estimate and/or probabilistic methods. Point exposure estimates include:

- a hypothetical maximally exposed individual – exposure is assumed to occur at the highest level possible throughout an individual’s lifetime (assuming 70 years)
- a high-end exposure estimate – exposure is assumed to occur at the higher end (eg 90<sup>th</sup> or 95<sup>th</sup> percentile) of a range of actual or estimated individual exposures.

Worst-case analyses are often used so that true human risks are not under-estimated. Probabilistic analysis techniques such as the Monte Carlo technique result in a probability distribution of exposures that more accurately predicts exposures than does the approach using point estimates. Probability distributions are assumed for input variables eg concentration of a toxin, ingestion rates, and output variables are defined eg total exposure. Random values are generated from the input distributions and output distributions derived. An arbitrary point in the distribution is selected eg 95<sup>th</sup> percentile to determine the maximum likely exposure for which the risk is then calculated. Such techniques are only needed when worst-case analyses suggest there may be a problem.

*Are the exposure data used representative of the population under study?*

If exposure data were collected overseas, population density and lifestyle may have had a significant effect on exposure concentrations and activity patterns.

*Are the exposure data an over-estimate of average exposure? Are the exposure data an under-estimate of average exposure?*

*Are the exposure data derived from population exposure data or from source characteristics and models? If models have been used, how appropriate are they?*

*What assumptions have been made that have a significant impact on the results?*

For example, assumptions may be made about the amount of the organism that will be ingested daily by those potentially exposed and over what time period this would occur.

## **Dose-response assessment**

The objective of this section is to answer the question:

*How do health effects vary with the level of exposure?*

Dose-response assessment determines the amount of the organism that causes adverse effects. It uses information on the effects associated with various levels of exposure (or dose) from the experimental and epidemiological studies and information on “real world” exposure to develop estimates of the likelihood of effects in potentially exposed populations. The method chosen can considerably influence the risk assessment.

*What is the infectious or toxic dose?*

In the case of microbes the number of organisms that produces an effect may be known from volunteer studies.

*Is there a relationship between dose and the severity of effect?*

Dose-response curves for microbes are often developed using human volunteers.

*Does exposure always result in infection and disease?*

In the absence of human data results from animal studies using high doses are often extrapolated to humans to give estimates of dose-response relationships. The dose-response estimates from animal studies are usually multiplied by uncertainty factors in an attempt to allow for quantitative differences in response between animals and humans and variation in individual susceptibility to exposure in humans.

As a first approximation the dose in milligrams per kilogram of body weight that has produced an effect is noted. Once sufficient data are available extrapolation gives the dose that will produce a given effect in 50 percent of an exposed population.

At low levels of exposure it is difficult to detect effects in an epidemiological study unless the study population is very large, or in the case of pathogenic organisms the infectious dose is very low. Nevertheless the health impact of low level exposure may be considerable if the exposed population is large. Other differences in exposure between the study population and risk population such as duration and pattern may also exist.

Mathematical models are used to extrapolate effects from high dose to low dose.

Key issues in characterising a dose-response relationship are:

- the relationship between the selected extrapolation models and information about biological mechanisms
- how data were chosen from studies that demonstrated the range of possible potencies
- correspondence between the expected exposure pathway(s) and exposure pathway(s) used in the studies
- correspondence between the expected exposure duration and exposure duration in the studies used, and
- variation in susceptibility among different populations (US EPA, 1995).

For practical purposes toxic effects are considered to be of two types, threshold and non-threshold.

### **(1) *Threshold***

Non-genotoxic carcinogens and non-carcinogenic substances are assumed to exhibit a threshold dose below which no adverse effect may be expected. This uses the highest dose at which no adverse effect is observed (the no observed adverse effect level or NOAEL). The precision of the NOAEL is determined by the sensitivity of the toxic endpoint, the dose interval and to a lesser extent the size of the study group. The sensitivity of the toxic endpoint depends on the incidence of the effect in the control group and/or its inter-animal variability. For example, a low incidence of a rare effect can be detected but the same increase in incidence of a common effect may not be statistically different from the control group.

### **(2) *Non-threshold***

Genotoxic carcinogens are assumed to exhibit no threshold for carcinogenesis and a linear no threshold model is used.

Models can be tested statistically in an attempt to determine which model best fits the observed data.

When studies of sufficient quality are available for both animals and humans the human data are preferable as a basis for extrapolation (Smith, 1988; Hertz-Picciotto, 1995). Advantages of using human data are:

- a lower magnitude of error than animal data

Uncertainty from inter-species extrapolation is greater than uncertainty from bias or errors in exposure information in epidemiological studies.

- the context and patterns of exposure in animals poorly represent human exposure scenarios, and
- the genetic diversity and variability in the human population are better represented in a human study.

Where human data are inadequate to derive a dose-response relationship, such as well-designed null studies, they can be used as a check on the plausibility of a risk assessment based on animal data and reduce the range of uncertainty. Other human studies that cannot contribute to dose-response assessment can contribute to the weight of evidence that determines whether the organism is a health hazard.

### **Risk characterisation**

The objective of this section is to answer the question:

*What is the aggregate effect on health in the exposed population(s)?*

Risk characterisation results in an estimation of risk for the population from integrating the information from hazard identification, exposure and dose-response assessments. It describes risk in terms of the probability of its occurrence and the magnitude of the adverse effect (HSNO (Methodology) Order 1998). Risk assessment is a decision-making tool not a precise analysis of actual or measurable risk. The focus therefore should be on how best to inform decision-making.

Plausible upper and lower estimates of risk can be calculated based on the plausible range of values for the exposure and dose-response estimates. Expression of risk in terms of both central tendencies and upper bound estimates broadens usefulness (Crouch et al, 1995). Assessment results may then be more effectively communicated as a series of risk options that are more relevant to real life.

In order to resolve some of the differing interpretations about risk it is important to recognise all of the major characteristics of risk. Risk can never be truly measured or verified. All knowledge about risk falls within a continuum that extends from a theoretical purely scientific quantitative end to a theoretical purely qualitative end. All aspects of risk, whether quantifiable or not, have some qualitative element to them (Light and Hrudey, 1996).

For organisms with known or suspected carcinogenic effects, in particular those that are genotoxic carcinogens, it may be possible to make a quantitative assessment of cancer risk at low exposures based on assumptions about the dose-response relationship.

For toxins with non-carcinogenic effects, for which it is generally assumed that a threshold of effect exists, it may only be possible to state that estimated exposures are above or below a maximum “permissible” level of exposure. This may also apply to non-genotoxic carcinogens. Characterisation should address quantitative and qualitative features of the assessment and identify its important strengths and uncertainties (US EPA, 1995). Since there is always uncertainty associated with an assessment a single numerical presentation of risk alone is incomplete and may be misleading.

*What are the quantitative aspects of the risk?*

Quantitative aspects of the risk are the probability of various effects and their magnitude. They are best understood in the context of the background qualitative aspects of the data on which the calculations are based.

*What are the qualitative aspects of the risk?*

Qualitative aspects of the risk include the nature of the effects, who might experience the effects, any means to prevent the effects (eg secure containment of the organism), and the strength and consistency of evidence.

Qualitative information is often more useful and understandable than quantitative estimates of risk.

*What are the sources of variability?*

Variability results from differences in the nature and extent of exposure and from variation in susceptibility.

*What are the sources of uncertainty?*

Health risk assessment is typically dominated by uncertainty, in particular about the health effects of low level exposure, rather than variability. Uncertainty results from information that is not known or only partly known.

Characterisation is incomplete without discussion of the uncertainty associated with each stage of the assessment that strongly influences confidence in the risk estimate. This should include issues such as quality and quantity of available data, assumptions, use of models, incomplete understanding of biological phenomena, and scientific judgements used to bridge information gaps.

Microbial risk assessment models make a number of assumptions. For example, random dispersion is assumed whereas in reality microbes may be clustered.

*Have sensitivity analyses been carried out eg using different exposure scenarios, alternative dose-response models?*

*What is the confidence that can be placed in any quantitative analysis of uncertainty and variability and its findings?*

Not every assessment requires or warrants a quantitative characterisation of variability and uncertainty such as Monte Carlo analysis. For example, when screening calculations using point

estimates show exposures or risks to be clearly below levels of concern and the screening technique is known to significantly over-estimate exposure (US EPA, 1997).

*What are the information gaps?*

*Have all the relevant data been evaluated?*

*What are the weaknesses of the methods used?*

*What are the strengths of the methods used?*

*What are the critical assumptions? Are they reasonable? Are there plausible alternative assumptions? What is the effect of alternative assumptions on the conclusions?*

*What are the scientific controversies and their effect on the conclusions?*

*How reliable is the evidence? Are the conclusions justified by the evidence? Are the conclusions communicated in a way that reflects the weight of evidence?*

Although exposure is not synonymous with risk due to differences among individuals in susceptibility or other factors, information on the exposure levels experienced by different members of the population gives a picture of the range of risks that may occur and the overall adverse impact on the population. Individual, population and subgroup population risks may be described.

### ***(1) Individual risk***

High-end and central tendency descriptions are used to give the variability in risk experienced by different individuals in the population. High-end risk estimates are based on exposures that are expected to occur in a small component of the population. Central tendency descriptions of risk may be based on either the arithmetic mean exposure or the median (50<sup>th</sup> percentile) exposure. The arithmetic mean may differ markedly from the median estimate because of the skewness of typical exposure profiles.

### ***(2) Population risk***

Population risk may be described as a probabilistic number of cases of a health effect in the population over a specific time period or estimated proportion of the population with risk above some specified level eg 1 in 1,000,000 or within a range of some specified level. The probabilistic number of cases can be obtained by summing the individual risks over all the individuals in the population or through the use of a risk model such as many carcinogenic models that assume a linear non-threshold response to exposure. In general when small populations are exposed population risk estimates may be very small. In these situations individual risk estimates will usually be more useful for decision-making.

### ***(3) Subgroup population risk***

Important subgroups such as highly exposed or highly susceptible people can be identified and where possible the risk quantified. This is useful when there is a subgroup that is experiencing significantly different exposures or has significantly different susceptibility to the effect from that of the larger population.

## **Risk evaluation**

Risk is a combination of scientific analysis and judgement and societal values. All judgements, expert and lay, are prone to bias. The key is to understand the bias each is putting on his/her judgement.

The public's conception of risk may include a number of ethical and social values such as equity, threats to future generations, uncertainty and potential for catastrophe that are excluded from technical assessments of risk.

*Who are the stakeholders?*

*What outcomes are important to the stakeholders and why?*

*What are the stakeholders' perceptions of the hazard?*

*What are the stakeholders' perceptions of the risk? Do different groups of stakeholders have different perceptions and concerns?*

*What is the larger real world context of the risk?*

*What contribution does the organism make to the overall risk of certain effects in the population or to the overall health of the population?*

*How is the risk distributed in relation to other health risks to the population?*

*Are there direct positive health effects?*

For example, are they irreversible, acute or chronic, immediate or delayed, or affect future generations?

*What is the evidence that exposure may be associated with positive health effects?*

*What are the characteristics of the positive health effects?*

*Are there indirect positive health effects? What are the indirect positive health effects?*

Indirect positive health effects include employment and food supply.

*Have the relevant monetary costs and benefits been identified? Have the relevant non-monetary costs and benefits been identified?*

Examples of monetary health costs and benefits are the cost of healthcare and the value of a life. A reduced or enhanced sense of well-being is an example of a non-monetary health cost or benefit.

*What is the expected value of the costs and benefits and the uncertainty related to the expected value? How are the costs and benefits distributed over time, space, and groups in the population?*

*To what extent to the following risk characteristics apply?*

- *exposure to the risk is involuntary*
- *the risk will persist over time*
- *the risk is subject to uncontrollable spread and is likely to extend its effects beyond the immediate location of incidence*
- *potential adverse effects are irreversible*
- *the risk is not known or understood by the public and there is little experience or understanding of possible measures for managing the potential adverse effects (HSNO (Methodology) Order 1998).*

## **Risk management**

Risk management can be defined as the process of identifying, evaluating and implementing actions to reduce or prevent risks to human health. Communication among stakeholders is important so that public values can inform and influence the development of risk management strategies. The nature and extent of stakeholder involvement should be appropriate to the scope and impact of an application and the potential of the application to generate controversy (The Presidential /Congressional Commission on Risk Assessment and Risk Management, 1997). Broader participation improves the information base of risk management and may also be argued to bring different scientific perspectives to bear (The Royal Society, 1992).

The distribution of people involved in public participation may not necessarily reflect the distribution of the burden of risk. Those with a disproportionate burden of risk are often those with the least access to public participation.

*What are the key social, cultural and political factors that need to be taken into account when managing risks to public health?*

*Can the risk be prevented? Can the risk be reduced?*

*How can the risk be prevented? How can the risk be reduced?*

The HSNO Act does not allow for an organism to be released with controls. Controls for the development of GMOs or field testing of organisms, including GMOs, relate to containment.

*What are the economic, social, cultural and ethical implications associated with implementing each option?*

*Does the action have a significant impact on the risk?*

*Does it reduce or prevent the risk in a way that is based on the best available scientific evidence? Is the action feasible?*

*Can the action be implemented effectively? Can the action be implemented with stakeholder support?*

*What is the impact of preventing or reducing the risk on overall public health?*

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