NHMRC Health Investigation Levels Review

Cancer Risk Assessment Methodology: A Review and Recommendations

Contents
Cancer Risk Assessment Methodology
A Review and Recommendations

1 Introduction

Cancer risk assessment can be considered a two-step procedure; involving a qualitative assessment of how likely it is that an agent is a human carcinogen, and a quantitative assessment of the cancer risk that is likely to occur at given levels and duration of exposure (WHO, 2000). In the early days of quantitative health risk assessment (early 1980s), the first of these steps was commonly referred to as "hazard identification" and the second as "dose-response assessment". More recently, the two steps together are commonly referred to as "toxicity assessment." The approach for risk assessment of carcinogens has evolved significantly over the past two decades due to scientific advances concerning the causes and mechanisms of cancer induction (US EPA, 2005; Boobis *et a*l, 2006). Indeed, the IARC now recognises that "some epidemiological and experimental studies indicate that different agents may act at different stages in the carcinogenic process, and several different mechanisms may be involved" (IARC, 2006). However, even to the present day, it is recognised that quantitative health risk assessment for carcinogenic soil contaminants presents difficult and possibly intractable methodological problems and challenges (Priestly, 2007).

The aim of this review is to discuss the advances in cancer risk assessment methodology theory, summarise current international cancer risk assessment practice and provide recommendations for the risk assessment of carcinogens in soil for application in Australia.

The review is for the purpose of supporting decisions on the framework for cancer risk assessment for soil contaminants as part of the revision of the National Environmental Protection (Assessment of Site Contamination) Measure, in particular Schedule B(4) *Guideline on Health Risk Assessment*. It is envisaged that the guidance supporting the methodologies recommended in this review will be given in Schedule B(4). The review takes into consideration the practical necessities of contaminated land risk assessment in that assessments will almost always be carried out with reference to established toxicity reference criteria (sourced from bodies such as the World Health Organization). It is therefore not the purpose of this review to provide guidance on how toxicity criteria should be derived.

Recommendations on methodology and level of acceptable risk will be made in consideration of current Australian risk assessment guidance such as enHealth (2004) *Guidelines for assessing human health risks from environmental hazards*, and the NHMRC (1999) *Toxicity assessment for carcinogenic soil contaminants*.

2 Carcinogens and Carcinogenesis

2.1 Introduction

The development of cancer (carcinogenesis) is a complex multi-stage process involving the sequential mutation of growth control genes and the clonal expansion and progression of the resulting precancerous and cancerous cells to a fully malignant tumour (or neoplasm) (NHMRC, 1999; Butterworth *et al*, 2007). Carcinogenic substances can cause neoplastic development through a number of mechanisms, including induction of genetic damage, or alteration of gene expression resulting in proliferation of transformed cells. A wide range of modifying factors, such as genetic make-up, lifestyle and other environmental factors, can influence the process of carcinogenesis (enHealth, 2004).

The global burden of cancer continues to increase; the annual number of new cases was estimated at 10.1 million in 2000 and is expected to reach 15 million by 2020 (Steward & Kleihues, 2004; IARC 2006).

IARC considers that a cancer 'hazard' is an agent that is capable of causing cancer under some circumstances, and a cancer 'risk' is a probability estimate of a carcinogenic effect occurring from a defined amount, frequency and duration of exposure to a carcinogenic agent (IARC, 2006).

2.2 Carcinogenic Mode of Action

Mode of Action (MOA) for carcinogenesis can be described as the sequence of key events by which the active form of a chemical or a product of its metabolism interacts with the organism, leading to a response (Clewel, 2005; Boobis *et al*, 2006). Mode of Action is contrasted with 'mechanism of action', which implies a more detailed understanding and description of events, often at the molecular level, than is meant by mode of action (US EPA, 2005; Lambert & Lipscomb, 2007).

It is recognised that there is flexibility in defining MOA, which can be described at almost any level of complexity, reflecting the extent of chemical-specific information available and the needs of the risk assessment (Clewell, 2005; Lambert & Lipscomb, 2007). It is now known that several modes of carcinogenic action exist, including mutagenicity, mitogenesis, inhibition of cell death, cytotoxicity with reparative cell proliferation, and immune suppression (US EPA, 2005; Butterworth *et al*, 2007). Typically however, carcinogenic substances are grouped into two different categories depending on their MOA, namely non-genotoxic and genotoxic. The recognition of this differentiation can be a useful strategy to focus on the rate limiting events that can be used as the basis for choosing appropriate cancer risk assessment models (Butterworth *et al*, 2007).

Non-genotoxic carcinogens are chemicals that induce tumours via a mechanism which does not involve direct damage to genetic material (IARC, 2006). For non-genotoxic carcinogens, it has been assumed that a threshold dose can be determined below which no toxic or carcinogenic effects are seen (i.e., a non-linear dose-response relationship can be established). A common approach for determining a safe dose for chemicals that a exhibit threshold or non-linear dose-response relationship is the selection of a 'no observable adverse effect level' (NOAEL) from relevant animal or human studies. A series of uncertainty and modifying factors are then applied to the NOAEL to calculate an acceptable daily intake (ADI).

Genotoxic carcinogens are defined as chemicals for which there is adequate evidence of the potential to interact with and/or modify the functions of genetic material and which has the ability to induce tumours via a mechanism involving direct damage to DNA (Butterworth, 1990; IARC, 2006). For genotoxic carcinogens, it is assumed that no level of exposure is entirely safe and even at extremely low levels some damage to the genetic material may increase the chance of developing cancer. This is known as a non-threshold (or linear) dose-response relationship and the application of a NOAEL is not considered appropriate.

As noted by enHealth (2004), this classification '… does not mean that a non-genotoxic carcinogen does not affect the genetic material of the cell under some circumstances, nor that a genotoxic effect is the only event required for the development of cancer by a genotoxic carcinogen'.

However, the use of the threshold model for non-genotoxic chemicals and the linear risk (or non-threshold) model for genotoxic chemicals has led to many difficulties because the way many chemicals cause cancer (i.e., either via genotoxic or non-genotoxic mechanisms) is not fully understood. The WHO considers that these approaches are not suitable to the development of generic guidance values in Environmental Health Criteria documents because they '…require socio-political judgments of acceptable health risks' (IPCS, 1994).

2.3 IARC Classification of Carcinogens

The International Agency for Research on Cancer (IARC) developed the first system to qualitatively categorise chemical carcinogens (IARC, 1978). Since this time, the classification of carcinogens has evolved with the IARC recognizing that 'in the absence of adequate data on humans, it is reasonable, for practical purposes, to regard chemicals for which there is sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk to humans (IARC, 1983; IARC, 1987). Furthermore, the IARC decided to incorporate information on the mechanism of carcinogenic action of chemicals in their evaluation process, which will become increasingly important as the understanding of the various mechanisms of action are elucidated (Vainio *et al*, 1992; enHealth 2004).

IARC categorises chemical substances into five groups (*Table 2.1*) on the basis of available information pertaining to carcinogenic potential in both laboratory animals and humans.

Table 2.1: IARC Classification of Carcinogens (IARC, 2006)

Group	Description
1	Agent is carcinogenic to humans
2A	Probable human carcinogen, an agent for which there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals
2B	Possible human carcinogen, an agent for which there is limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals
3	Not classifiable as to their carcinogenicity to humans
4	Probably not carcinogenic to humans

1. *IARC defines an agent as "specific chemical groups, groups of related chemicals, complex mixtures, occupational or environmental exposures, cultural or behavioural practices, biological organisms and physical agents." (IARC, 2006).*

Other systems for classification of carcinogens exist; the USEPA in particular has a well developed system which is also widely used internationally. Different systems will not always agree on the classification for a substance. For consistency in Australian contaminated land risk assessments, the revised NEPM Schedule B(4) recommends use of the IARC system as a primary source for determining whether a chemical should be treated as a carcinogen.

2.4 IPCS Harmonization Project – Mode of Action Framework

The International Programme on Chemical Safety (IPCS) has been leading an effort to harmonize approaches to cancer risk assessment as part of its larger project on the *Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals*. The aim of the Harmonization project is to strive for consistency among approaches and to enhance the understanding of various approaches to chemical risk worldwide (WHO, 2009).

In 2001, the IPCS published a framework for assessment of 'Mode of Action' (MOA) for carcinogenesis in laboratory animals, based on the Bradford Hill criteria for causality (Sonich-Mullin *et al*, 2001). Following on from this work, IPCS updated this framework in 2005, in conjunction with international partners such as the World Health Organization, and extended it to consider human relevance (the IPCS Human Relevance Framework) (Boobis *et al*, 2006). The MOA framework has been adopted by international organisations and regulatory agencies including Australia, the US Environmental Protection Agency (US EPA), Canada, United Kingdom and the European Union (Boobis *et al*, 2006).

3 Risk Assessment Approaches for Carcinogens

This section reviews the approaches that are used to derive cancer toxicity reference criteria (eg, slope factors, tolerable daily intakes, benchmark doses), which differ according to the mode of action of the chemical and the policy of the organisation undertaking the assessment. The focus is on the practices that underlie toxicity criteria that are available and that may be used in contaminated land risk assessment; it is not the intent to provide a view on how toxicity criteria "should" be derived.

3.1 Non Threshold Approach

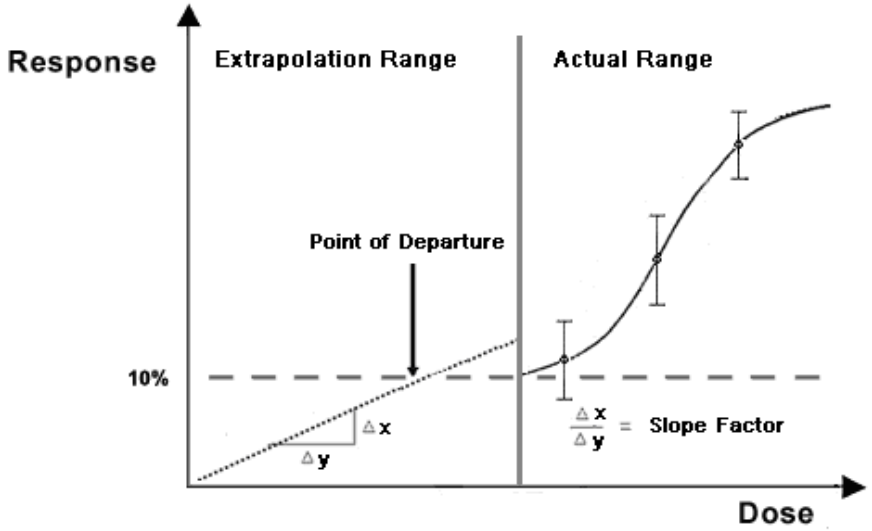
The 'non-threshold approach', described in Section 2.2 is used to assess genotoxic carcinogens. The toxicity criteria derived are known as cancer slope factors and unit risk factors.

A Cancer Slope Factor (CSF) is a plausible upper-bound estimate of the probability of a response per unit of intake of a chemical over a lifetime. The cancer slope factor is used in risk assessments to estimate an upper-bound lifetime probability of an individual developing cancer as a result of exposure to a particular level of a potential carcinogen (US EPA, 1989). This approach is also known as the 'linear' approach which implies a proportional (linear) relationship between risk and dose at low doses; although it is noted that the dose-response curve generally is not linear at higher doses (US EPA, 2005).

A Unit Risk Factor (URF) is an expression of carcinogenic potency in concentration terms, such as probability of cancer per 1.0 µg/L of drinking water or probability of cancer per 1.0 µg/m^3 or ppm in air. Generally, the drinking water URF is derived by converting a CSF from units of mg/kg-day to units of µg/L, and an inhalation URF is developed directly from a dose-response analysis using equivalent human concentration already expressed in units of µg/m^3 (US EPA, 2005). Derivation of URFs often assume a standard intake rate (e.g., inhalation of 20 m^3 of air per day or ingestion of 2 L of water per day) and body weight (e.g., 70 kg). When a theoretical upper-bound cancer risk estimate is calculated using a URF instead of a CSF, it is often termed the unit risk.

The discussion below refers throughout to development of cancer slope factors, however it applies equally to unit risk factors, since they are essentially different ways of expressing the same thing.

Figure 3.1: Diagrammatical representation of a cancer slope factor



Adapted from US EPA (2009) *Toxicological Parameters for Cancer Effects*, Water Quality Standards Academy, http://www.epa.gov/waterscience/standards/academy/supp/health/index.htm, accessed December 2009. The X axis represents the doses of the carcinogen that were studied in the critical cancer study. The Y axis is the response observed in the experimental animals (usually percent of animals with tumors). Usually 10% tumors response is selected as the Point of Departure for the determination of the slope factor if that is justified by the data.

The development of a cancer slope factor (sometimes called a 'cancer potency factor) generally involves extrapolation of the available data set from the relatively high doses administered to experimental animals to the lower exposure levels expected for human contact in the environment (US EPA, 1989). This high-to-low dose extrapolation approach is necessary because of the lack of sufficient data on low dose exposures in humans. However, depending on the dose-response model employed, large difference in the projected risk at low doses can occur.

There are a number of models that can be used for performing high-to-low dose extrapolations. Results from these various models can lead to a wide variation in risk estimates. US EPA recommends the relatively conservative linearized multistage (LMS) model be used for extrapolation in the absence of adequate information permitting non-linear extrapolation (US EPA, 2005).

Empirical evidence supporting low-dose linearity is virtually impossible to obtain because of the inability to demonstrate or detect carcinogenic effects at the low dosage levels typifying human exposures, which are outside the directly observable response range. Another limitation results from the extrapolation of dose-response data from a relatively small population of test animals (e.g., typically less than 100 laboratory animals per dosage group) to the human population comprised of millions of members.

Once the dose-response data are fit to an appropriate model, the upper 95th percent confidence limit of the slope of the resulting dose-response curve (in the relevant low dose region) is calculated. This value is defined as the cancer slope factor (CSF) and is expressed as the probability (or risk) of cancer incidence per 1.0 mg of chemical per kg of body weight per day (mg/kg-day). CSFs can also be calculated based on human dose-response data which represents the 'best' estimate rather than the upper 95th percent confidence limit.

US EPA states that CSFs should always be accompanied by a weight-of-evidence classification to indicate the strength of the evidence that the agent can cause cancer in humans (US EPA, 1989). Furthermore, the US EPA (2005) specifies that linear extrapolation to derive CSFs should be used in two distinct circumstances:

1) when there are data to indicate that the dose-response curve has a linear component below the point of departure (i.e., the estimated dose near the lower end of the observed range, without significant extrapolation to lower doses); or

2) as a default for a tumour site where the mode of action is not established.

The relative advantages and disadvantages of applying the linear low-dose extrapolation approach for cancer risk assessment is presented in *Table 3.1.*

Table 3.1: Advantages and Disadvantages of the linear low-dose extrapolation approach for cancer risk assessment.

Advantages	Disadvantages
Provides numerical estimates of risk at all doses (US EPA, 2005).	Can sometimes over estimate theoretical upper-bound cancer risks.
Allows computation of comparative risks below the sub-experimental range.	Non-threshold models are inflexible and generally do not take account of the complexities of the events between exposure to an agent and the induction of neoplasm (enHealth, 2004).
Allows potency comparisons between chemicals at a particular risk level.	Risks estimated at doses below the range of experimental data can vary considerably depending on the model used, even though the various mathematical models used generally fit the experimental data equally well (Crump, 1985; Paustenbach, 1995).
Allows estimates of the increased risk if a particular dose is exceeded.	The numerical expression of the estimated risk (i.e. mg/kg-day^{-1}) falsely gives the impression that it represents an exact measure of actual risk and does not allow for comparison with values for non-cancer health effects (enHealth, 2004).
There is a greater quantity of slope factor data available in comparison to benchmark dose-response data.	It is impossible to experimentally test the shape of the dose-response curve at extremely low doses, and hence impossible to support the low dose linearity assumption (Purchase and Auton, 1995).

3.2 Threshold Approach

The threshold approach has traditionally involved the use of a NOAEL (no observed adverse effect level) to specify a dose below which no adverse effect is predicted to occur. It has been used for both cancer and non-cancer end points. Uncertainty factors are applied to the experimentally derived value to account for differences between the conditions of the experiment and the application of the toxicity criterion that is being derived.

Examples of these would be factors for interspecies variation, intraspecies variation, and inter-individual variation. The method has the advantage of simplicity, but the disadvantage of extreme reliance on the study that produced the NOAEL. In practice, adverse effects have been found to occur at doses below the NOAEL, and the health protective effect of the toxicity criterion is largely due to the applied uncertainty factors (Health Council of the Netherlands, 2003).

For substances that are considered to have a threshold, Benchmark Doses (BMD) are increasingly calculated. The benchmark dose approach has the advantage of providing a method that takes account of uncertainty more rigorously, and permits derivation of toxicity criteria with lower uncertainties than the NOAEL method. Although the BMD has mainly been used for risk assessment of non-cancer end-points, the BMD approach can also be applied for cancer end-points.

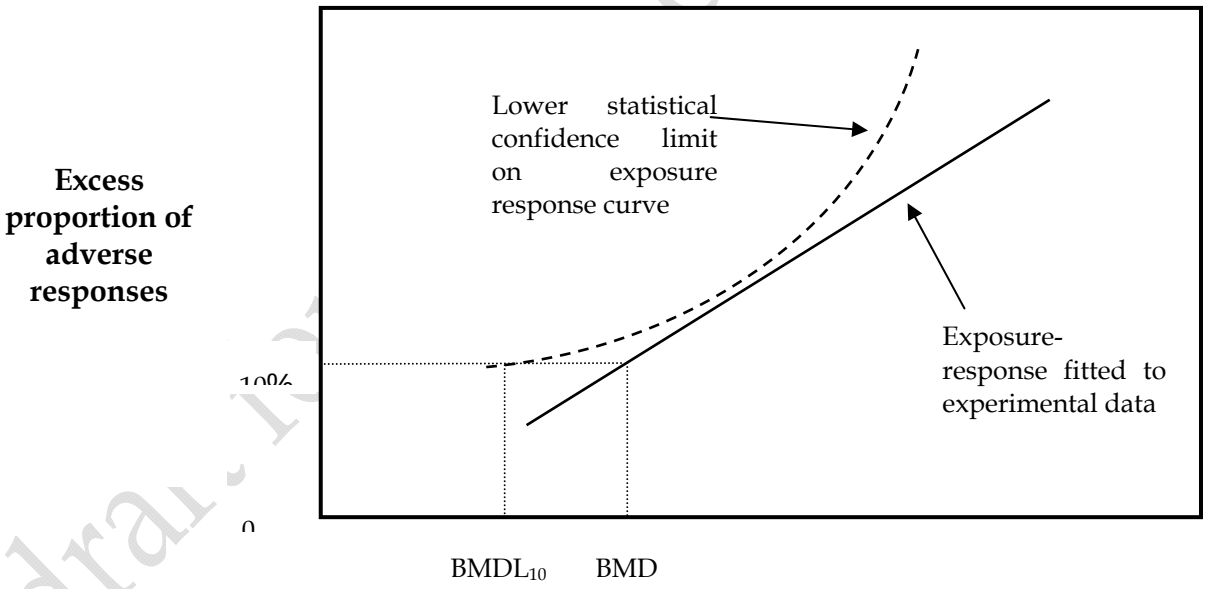
The BMD in health risk assessment of chemicals was first mentioned by Crump (1984). A BMD is defined as the dose that corresponds to a specified change in adverse response compared to the response in untreated animals (Crump, 1995). The dose is associated with a given incidence (e.g., 1%, 5% or 10% incidence) of effect, the Benchmark Risk, based on the best fitting dose-response curve in the region of the dose-response relationship where biologically observable data are available (Filipsson et al. 2003; enHealth, 2004). The resulting BMD is termed BMD_{10} for a 10% incidence; BMD_5 for a 5% incidence.

The selection of the specified change level varies between standards setting bodies; USEPA uses 10% for setting chronic reference concentrations for air quality and California Environmental Protection Agency Office of Environmental Health Hazard Assessment uses 5% for both chronic and acute reference concentrations (NEPC 2009). In an Australian context BMD_{10} is likely to be preferred, however this review could not locate a policy position to this effect in any published document.

Traditionally, the BMD is selected from a position on the 95% lower confidence limit on the dose-response curve (Barnes *et al*, 1995; US EPA 1995;1996). This point is termed the BMDL. The preference for choosing the 95% lower statistical limit as the starting point in the risk assessment is thought to account for the uncertainty and variability in the experimental data; and is therefore considered a conservative approach protective of public health (NHMRC, 1999). It can be argued that the lower confidence limit tends to be too conservative and thus may lead to substantial over-estimates of the actual risk (NHMRC, 1999). In Australia, an alternative approach to the calculation of the BMD (e.g. the *modified*-BMD recommended by NHMRC (1999)) has been proposed for use with carcinogenic soil contaminants.

It is generally considered that use of the BMD is preferable to the use of CSFs in cancer risk assessment because the BMD makes no assumptions regarding the shape of the dose-response curve substantially outside the experimental range (i.e. the low dose range). Furthermore, it does not require a judgment on the existence of thresholds for different types of carcinogens and can accommodate both cancer and non-cancer endpoints.

Figure 3.2: Derivation of a benchmark dose (adapted from NEPC 2009)



The $BMCL_{10}$ above illustrates the lower 95% confidence interval of the BMC_{10}, which is the concentration at which there is a 10% increase in adverse responses.

However, it is argued that the theoretical advantages of the BMD approach are often outweighed by the practical disadvantages posed in a regulatory context, and that "…the BMD will never entirely replace the NOAEL" (Travis et al, 2005). Travis et al (2005) stated that "Attempts to seek consensus for the routine use of BMD methodology tend to involve diluting its potential advantages as much as they address the disadvantages, resulting in a relatively complex interpolation tool that delivers little more than the NOAEL".

The relative advantages and disadvantages of applying BMDs for carcinogenic risk assessment are summarised in *Table 3.2*.

Table 3.2: Advantages and Disadvantages of the BMD approach for cancer risk assessment.

Advantages	Disadvantages
Takes into account information from the entire dose response curve rather than focusing on a single test dose (enHealth, 2004).	It may not be possible to define the shape of the dose response curve because of limited dose groups or the number of animals per group.
Is applicable to all carcinogens; genotoxic and non-genotoxic. Does not require judgment on the existence of thresholds for different carcinogens.	There are no agreed standards for calculation of BMDs (although this is not unique to the BMD approach)
Avoids extrapolation methods, which is an essential part of low dose risk assessment methods for calculating slope factors.	
Uses responses within or near the experimental range versus relying on extrapolations to doses considerably below the experimental range.	Availability of BMDs are limited in comparison to the availability of slope factors.
Has a consistent benchmark response level that cross a range of studies and endpoints.	
The approach is relatively model-independent when compared with models which extrapolate to extremely low doses (enHealth, 2004).	
Ability to be rigorously described.	
Takes into account variability in the data.	

4 Review of International Practices on acceptable risk

The following section reviews some international practice in determining what level of risk is acceptable when adopting a non-threshold model.

4.1 World Health Organization

The World Health Organization makes use of threshold and non-threshold methodologies in deriving its health guidelines. The limitations of linear extrapolation models to derive cancer slope factors and unit risk factors are recognised, but used in many instances. Where a non-threshold approach is taken, WHO prefers not to specify 'acceptable risk levels' but to provide guidelines representing risk levels of excess cancer risk of 1 in 10,000, 1 in 100,000 and 1 in 1,000,000. National authorities are then able to determine for themselves what level of acceptable risk they favour.

Drinking Water Guidelines (WHO, 2008)

When deriving the drinking water guidelines, WHO considered that "there is a theoretic risk at any level of exposure (i.e., no threshold). On the other hand, there are carcinogens that are capable of producing tumours in animals or humans without exerting a genotoxic activity, but acting through an indirect mechanism. It is generally believed that a demonstrable threshold dose exists for non-genotoxic carcinogens." Therefore, when deriving the drinking water guidelines for carcinogens, WHO gave consideration to the potential mechanism(s) by which the substance may cause cancer in order to decide whether a threshold (non-genotoxic) or non-threshold (genotoxic) approach should be assumed.

For genotoxic carcinogens, the linearized multistage (LMS) model is generally adopted, but other models are considered more appropriate in a few cases (e.g., a one-stage Weibull time-to-tumour model for bromate). The guideline values presented represent the concentrations in drinking-water associated with an estimated upper-bound excess lifetime cancer risk of 10^{-5}. WHO (2008) considers that the '…mathematical models used for deriving guidelines values for non-threshold chemicals cannot be verified experimentally, and they do not usually take into account a number of biologically important considerations such as pharmacokinetics, DNA repair or protection of the immune system. They also assume the validity of a linear extrapolation of very high dose exposures in test animals to very low doses in humans. As a consequence, the models used are conservative."

Air Quality Guidelines (WHO, 2000)

When deriving the air quality guidelines, WHO applies the low-dose risk extrapolation approach for compounds classed as Group 1 and 2A by the IARC.

WHO considers that the choice of the extrapolation model depends on the current understanding of the mechanisms of carcinogenesis, and no single model can be regarded as appropriate for low-dose extrapolation. The carcinogenic potency is expressed as the incremental unit risk estimate, which is defined as "the additional lifetime cancer risk occurring in a hypothetical population in which all individuals are exposed continuously from birth throughout their lifetimes to a concentration of 1 $\mu g/m^3$ of the agent in the air they breathe" (WHO, 2000). Therefore, by using unit risk estimates, any reference to the 'acceptability' of risk is avoided.

For compounds in Groups 2B, 3 and 4, the WHO air quality guidelines values are derived using the threshold approach. For compounds in Group 2B, a separate factor for the possibility of carcinogenic effect in humans is incorporated.

However, WHO (2000) states that in the case of sufficient scientific evidence deviation from the above mentioned approach may be justified. For example, a compound classified in Group 1 or 2A may be assessed via the threshold approach provided that there is strong evidence that it is not genotoxic.

Furthermore, a compound in Group 2B may be assessed via the non-threshold low-dose extrapolation approach when the mechanism of carcinogenesis in animals is likely to be a non-threshold phenomenon as indicated, for example, by the genotoxic activity of the compound in different short-term test systems (e.g., in vitro or in vivo mutagenicity assays).

4.2 United States Environmental Protection Agency (US EPA)

For carcinogenic risk assessment, US EPA has traditionally assumed that there is no level of exposure to carcinogenic chemicals that does not pose a finite probability, however small, of generating a carcinogenic response (i.e., a non-threshold dose-response relationship is assumed). Therefore, no dose is thought to be risk-free and the presumption of a threshold is inappropriate. The derivation of CSFs via the LMS model using upper bound estimates has been foundational in US regulatory risk assessment of carcinogens for several decades. The LMS model describes both linear and non-linear dose-response patterns and produces an upper confidence bound on the linear low-dose slope of the dose-response curve. These upper bounds on the dose-response curve become the slope factors or unit risks employed for the estimation of theoretical upper-bound cancer incidence rates. This approach has been described as 'one of the most conservative models used in [quantitative risk assessment]' because the slope factor or unit risk for carcinogenic substances intentionally overestimates true cancer incidence associated with low-dose exposure to environmental pollutants (Kelly, 1991; IEH, 1999).

In 2005, the US EPA revised the Federal Cancer Assessment Guidelines for cancer risk assessment and, whilst relying almost exclusively on the non-threshold, low dose extrapolation for cancer risk assessment in the past, now appears to be accepting an approach which considers mode of action and multiple dose-response relationships (enHealth 2004).

The revised US EPA guidelines for cancer risk assessment state that:

"A linear extrapolation approach is used when the mode of action information is supportive of linearity or mode of action is not understood".

"When adequate data on mode of action provide sufficient evidence to support a nonlinear mode of action for the general population and/or any subpopulations of concern, a different approach – a reference dose/reference concentration that assumed nonlinearity – is used".

"When the mode of action information indicates that the dose-response function may be adequately described by both linear and nonlinear approach, then the results of both the linear and nonlinear analyses are presented".

"Absent data to the contrary, the default assumption is that the cumulative dose received over a lifetime, expressed as a lifetime average daily dose or lifetime average daily exposure, is an appropriate measure of dose or exposure" (US EPA, 2005).

In recognition that variation exists among people in their susceptibility to carcinogens, the US EPA identifies that specific considerations should be made when assessing the potential cancer risks to children (US EPA, 2005a).

4.3 United Kingdom

The UK uses a concept called Index Dose to express acceptable doses for carcinogenic chemicals in soil. The Index Dose is expressed in terms of mass per kg body weight per day, and is therefore applicable over the whole range of body weights, including infants, children and adults.

The UK does not support risk modelling from animal data to derive quantitative risk estimates, and only uses a linear extrapolation approach on human data that it considers adequate (Environment Agency 2009). The UK prefers an approach in which the Index Dose is set by an expert committee, and is based on $BMDL_{10}$, TD50 or T25 judged qualitatively to represent 'no discernible carcinogenic effect' (Environment Agency 2009). The TD50 is a measure of tumour probability represented by the dose required to halve the probability of remaining tumourless at the end of a standard lifetime (COC 2004). The T25 is the dose producing a 25% in the incidence of a specific tumour above the spontaneous background rate (COC 2004).

Where a linear low dose extrapolation model is used, an acceptable risk level of 1 in 100,000 is adopted (Environment Agency 2009).

For threshold carcinogens the Index Dose is derived using $BMDL_{10}$ or the NOAEL approach.

4.4 Netherlands

When deriving the Target and Intervention Values, the Dutch recognised the distinction between genotoxic (non-threshold contaminants) and non-genotoxic carcinogens (threshold contaminants); hence, they adopted different risk assessment approaches accordingly.

For genotoxic carcinogens, the approach adopted assumes a linear relationship (also at very low doses) between dose and cancer incidence, which implies that the cancer incidence due to exposure to a particular genotoxic chemical is zero only if the dose is also zero (Lijzen JPA *et al*, 2001; deBruijn *et al*, 1991). For genotoxic carcinogens, "the Maximum Permissible Risk is defined as the dose of a contaminant (based on body weight for oral intake or air volume for inhalator intake) which forms a risk of one additional case of lethal tumour in 10,000 lifelong exposed individuals; this definition is based on a political decision" (Swartjes, 1999).

When deriving the maximum permissible risk (MPR) for non-genotoxic carcinogens, a NOAEL is identified following examination of existing toxicology reviews, which include information such as the dose-effect relationship as well as information regarding the mechanism(s) of the toxic effect(s) observed. A number of uncertainty factors are then applied to extrapolate from the NOAEL to the MPR (Lijzen JPA *et al*, 2001).

4.5 Canada

When assessing risks posed by exposure to carcinogenic substances, Health Canada has adopted an approach consistent with the US EPA in that any level of exposure (other than zero) is associated with some hypothetical cancer risk (Health Canada, 2004).

When extrapolating the dose-response curve in the low-dose region, Health Canada applies two types of methods:1) the LMS model consistent with US EPA (Crump, 1996) methodology; and 2) a model-free approach (Krewski et al, 1991), which assumes low-dose linearity and zero intercept but makes no *a priori* judgments regarding the shape of the dose-response curve in the low-dose range (Health Canada, 2004). The model-free approach can also provide a upper-bound estimate on the slope of the dose-response curve in the low-dose range.

Table 4.1: Adopted international acceptable cancer risk levels

Organisation	Acceptable risk level	Context	Comments
WHO	1:100,000	WHO Guidelines for Drinking Water Quality (2008).	Concentrations representing excess lifetime cancer risks of 10^{-4}, 10^{-5} and 10^{-6} risk are presented, and the recommended guideline value is associated with 10^{-5} cancer risk. WHO (2008) accepts that this is a conservative recommendation, which 'almost certainly overestimates the true risk'. WHO (2008) considers that "there is some (theoretical) risk at any level of exposure" to carcinogens.
WHO	Unit risk estimate (i.e. risk per 1µg/m^3) presented	WHO Air Quality Guidelines (2000)	WHO consider that the decision on the acceptability of a risk should be made by national authorities within the frame work of risk management. Similar to the WHO Drinking Water Guidelines (2008), concentrations in air associated with an excess cancer risk of 10^{-4}, 10^{-5} and 10^{-6} are given.
US EPA	1:1,000,000	US EPA (1996a) Soil Screening Levels	EPA (1996a) believes that "….setting a 10^{-6} risk level for individual chemicals and pathways will generally lead to cumulative risks within the risk range (10^{-4} to 10^{-6}) for the combinations of chemicals typically found at Superfund sites."
Netherlands	1:10,000	Technical evaluation of the Intervention Values for Soil/sediment and Groundwater (RIVM report, 2001).	For genotoxic carcinogens the acceptable excess lifetime cancer risk was set at 1 per 10,000 individuals; for non-genotoxic carcinogens the MPR does not result in any adverse health effects during lifetime exposure (70 years) (Lijzen JPA *et al*, 2001).
United Kingdom	1:100,000	Environment Agency 2009	UK generally prefers not to use quantitative expressions of acceptable risk, and does not base policy specifically on them. 1 in 100,000 is the risk level used when the UK judges that a linear low dose extrapolation is the most appropriate basis for its Index Dose.
Canada	1:100,000	Health Canada (2004)	This value was recommended given the conservative margin associated with slope factors and the negligible impact of a 1:100,000 incremental risk level for contaminated site exposures.

5 Acceptable Level of Cancer Risk

The concept of 'acceptable' risk is very subjective and variable; consequently there is no global consensus position on a level of theoretical cancer risk that is considered "acceptable" (Hrudy & Krewski, 1995). An acceptable level of theoretical cancer risk is uniformly viewed globally as a policy-based decision, not a science-based decision. WHO notes that:

> *"crude expression of risk in terms of excess incidence or numbers of cancer per unit of the population at doses or concentrations much less than those on which the estimates are based may be inappropriate, owing to the uncertainties of quantitative extrapolation over several orders of magnitude. Estimated risks are believed to represent only the plausible upper bounds and vary depending upon the assumptions on which they are based" (WHO, 1994)".*

Everyday all individuals make decisions that includes determining an acceptable level of risk. An involuntary risk (a risk that is outside the individual's decision making power) is generally viewed as less acceptable than a voluntary risk (a risk that is within the individual's decision making power). An acceptable level of risk can also vary depending on:

- particular circumstances;
- the size and type of the exposed population;
- available technology and the cost of remediation;
- the political climate;
- land use;
- geographical location;
- the level of uncertainty in the calculated risk(s); and
- the potential benefits of remediation (NHMRC, 1999).

As noted by enHealth (2004), 'the problems of nominating an acceptable level of risk are compounded by the inability of current methods to accurately quantitate risk at low levels of exposure and hence to provide an accurate value that can be compared to 'an acceptable level of risk'. Nevertheless, defining an acceptable level of cancer risk is a necessary aspect of performing cancer risk assessments particularly since numerical descriptors of risk are used as outcomes of quantitative risk assessment for genotoxic carcinogens.

6 Australian Cancer Risk Assessment Methodology

6.1 NHMRC Technical Working Party on Cancer Risk Assessment

In 1995, the NHMRC established the Technical Working Party on Cancer Risk Assessment (TWP), which proposed a method for assessment of cancer risk that is appropriate for contaminated sites in Australia. The recommended method is described in "*NHMRC (1999) Toxicity assessment for carcinogenic soil contaminants, Commonwealth of Australia*". Recognizing the limitations inherent in existing cancer risk assessment methods (e.g., genotoxic and non-genotoxic methods), the Technical Working Party proposed that all carcinogenic chemicals be assessed using a consistent approach: the *modified*-Benchmark Dose (BMD) approach. It is noted that the NHMRC (1999) document has been rescinded as guidance, however it remains important as background to Australian thinking on the approach to carcinogens, and is included for this reason.

The *modified*-BMD approach combines toxicological dose-response data and a conventional mathematical model to generate a dose-response curve for the chemical in question, even in the sub-experimental region, and does not assume a linear relationship in this region.

This approach avoids the conservatism of other BMD models by relying on best-fit modelling rather than 95% lower confidence limits on dose (Fitzgerald et al, 2004). The *modified*-BMD is standardized to one level of extra risk (i.e., 5%), allowing comparison of potency between carcinogens in the observed dose range in the animal bioassay or other modelled data.

NHMRC previously recommended that the *modified*-BMD method be applied in the same way to all carcinogens considered to pose a carcinogenic hazard to humans; both genotoxic and non-genotoxic carcinogens.

A Guideline Dose is then calculated from the *modified*-BMD by applying a number of safety factors to account for inter- and intra-species variability, quality of the information and the seriousness of the carcinogenic response. The Guideline Dose is the average daily intake of a chemical which, over an average life time, is unlikely to result in cancer, based on all the available information at the time of the assessment. The Guideline Dose is considered to be protective of public health and is analogous to the ADI and the US Reference Dose (RfD). The focus is therefore placed on regulation of the control of exposure to environmental contaminants rather than calculation or discussions of risk.

Following recommendations set out by NHMRC's TWP, Fitzgerald *et al* (2004) published a benzo[a]pyrene soil guideline value of 5 mg/kg (assuming the soil ingestion pathway) based on the *modified*-BMD approach.

The TWP recognised that BMD data are currently limited and therefore proposed that the *modified*-BMD method set "*the stage for future incorporation of the important information into the assessment of environmental carcinogens*". However, with the exception of Fitzgerald *et al* (2004), it has become apparent that advancement in the publication of Australian Guideline Doses has not been made and consequently the concept of modified-BMD approach has failed to be fully implemented in Australian contaminated land risk assessment practice. This has led to confusion regarding the 'preferred' Australian approach for performing quantitative cancer risk assessments, and consequently alternate international approaches have been adopted; mostly the US EPA's CSFs published on the Integrated Risk Information System (IRIS) online database.

6.2 Availability of Toxicity Criteria for Carcinogens

As a practical matter for contaminated land risk assessment practitioners, the availability of toxicity criteria for carcinogenic substances is often the limiting factor in deciding which assessment approach to adopt for risk assessments. This was particularly relevant for the *modified*-BMD approach. Since 1995, only one *modified*-BMD has been published for benzo[a]pyrene (Fitzgerald *et al*, (2004) essentially forcing practitioners to adopt alternative approaches.

Previously, NEPM (1999) guidance stipulated that risk assessment practitioners were to derive their own *modified*-BMDs (and subsequently Guideline Doses) if this data was not readily available or published. Development of *modified*-BMDs and Guideline Doses is a complex process that should be undertaken by skilled toxicologists, preferably as part of a public health standards setting exercise. It is rarely practical to derive toxicity criteria on a project-specific basis, and therefore *modified*-BMDs have not been extensively used. It has become generally agreed that the development of *modified*-BMDs is too expensive for the purpose of contaminated land risk assessment.

Since it is now unlikely that Australia will develop a set of Australian criteria for cancer risk assessment, internationally available data will be used. As has been the case historically, the availability of data is likely to drive the risk assessment approach. The most common toxicity criteria adopted in Australian risk assessment of carcinogenic substances have been CSFs and URFs published either by WHO (WHO, 2000; 2008), the Australian Drinking Water Guidelines (NHMRC, 2004), or the US EPA (IRIS online database).

To provide a more pragmatic approach for contaminated land risk practitioners, the decision making process for choosing appropriate toxicity criteria has been revised from the NEPM (1999) suggested methodology. This process is outlined in the section below.

6.3 Decision making process for choosing appropriate toxicity criteria

The decision-making process presented here was adopted when revising the HILs for carcinogenic substances in soil. Consequently, this process should also be applied when performing site-specific risk assessments (i.e., a Tier 2 risk assessment) where HILs are exceeded, or where HILs have not been developed for a particular contaminant.

A basis for determining which data source to use is set out in Schedule B(4) in *Table 5.1*; it provides guidance on which data sources are preferred but does not specify in absolute terms the means to select an approach to cancer risk assessment. In general it is recommended that the hierarchy should be followed as a first step in researching the available toxicity criteria, however it should not be applied rigidly at the expense of use of the most appropriate criterion. As organisations such as WHO and USEPA review their toxicity assessments, the availability of published criteria will change. It is therefore envisaged that Australian practitioners will need to select toxicity criteria with reference to the risk assessment approach inherent in the value, as well as by the policy position established by the Schedule B(4) hierarchy.

A step-wise process for deciding on the dose-response data to adopt for the risk assessment of carcinogens in soil is presented in *Figure 6.1*. This decision-making process focuses on applying toxicity criteria based on BMD where available. As a practical approach however, where appropriate BMD data are not available, alternative toxicity criteria should be sourced which may include the use of CSFs and URFs (for genotoxic carcinogens) and ADI/TDI (for non-genotoxic carcinogens). Note that the procedure in *Figure 6.1* assumes inherently that the assessor checks that the toxicity criteria reviewed are sufficiently relevant to the form of the contaminant which is present in soil.

In the 1970s, the US Food and Drug Agency (FDA) adopted a risk level of 1 in 1,000,000 (10^{-6}) as the incremental cancer risk for carcinogenic residues in foods that was considered to be 'essentially zero' (Kelly, 1991). It is understood that the origin of this 'essentially zero' risk level was purely arbitrary and was applied to decision making about animal drug residues and not contaminated sites regulation. However, since then the 10^{-6} risk level has become commonplace in the regulation and management of environmental contaminants in soil with apparently no sound scientific, social, economic or other basis for its selection (Kelley, 1991). The concept of 'zero risk' is based on the assumption that only the absence of the chemical (zero exposure) poses no risk and depends on the ability to detect a chemical which becomes increasingly impracticable for ubiquitous environmental chemicals.

Although a 1 in 1,000,000 (10^{-6}) cancer risk is the most frequently used target risk level for risk management decision making of environmental (including soil) contamination situations, many agencies identify a range of increased cancer incidence risks; ranging from 1 in 10,000 (10^{-4}) to 1 in 1,000,000 (10^{-6}) (e.g. WHO, 2000; WHO, 2008). As discussed above, the acceptable risk range depends on the situation and circumstances of exposure. In the U.S., the 10^{-6} cancer risk level is applied as a "point of departure"; final risk-based decision making considers other factors such as technical feasibility, economics, etc. Therefore, final risk-based objectives may equate to a theoretical upper-bound cancer risk of significantly less than 10^{-6}.

Perhaps a sensible approach would be to adopt a position that states:

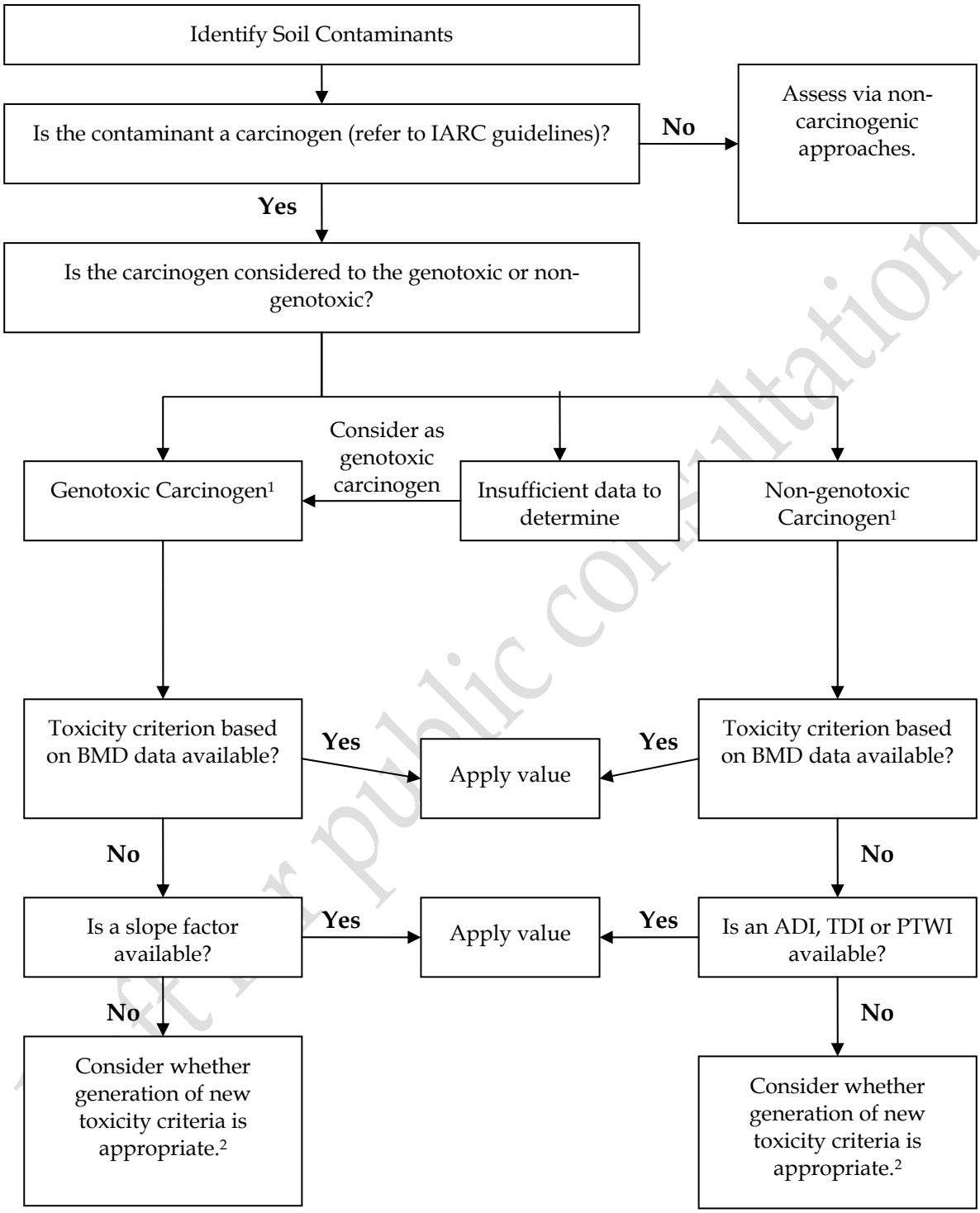
> *Incremental risks that are less than one in a million (10^{-6}) theoretical upper-bound cancer risk are considered to be negligible. Incremental risks greater than one in 10,000 (10^{-4}) are considered to be unacceptable. Risks between these two limits are judged on a case-by-case basis taking into consideration various factors that can vary an acceptable level of risk.*

The Canadian Council of Ministers of the Environment (CCME) (1996) identified that the 1:1,000,000 (10^{-6}) level of risk is essentially negligible, and acknowledged that the designation of negligible cancer risk is an issue of policy rather than of science. This acknowledgement allows different agencies to establish a policy consistent with their respective environmental regulatory agendas.

Health Canada recommends a target cancer risk level of 1 in 100,000 (10^{-5}) for the purpose of assessing and managing federal sites contaminated with carcinogenic substances (Health Canada, 2004). This recommendation was made "given the conservative (safety) margin associated with the derivation of cancer slope factors and unit risks, and the negligible impact of a 1-in-100,000 incremental risk level for contaminated site exposures…" (Health Canada, 2004).

A summary of the adopted acceptable cancer risk levels from a number of international regulatory bodies and agencies is presented in *Table 4.1*.

Figure 6.1: Decision making process for choosing toxicity criteria in risk assessment of carcinogenic substances



Notes:
1. If a chemical has both genotoxic and non-genotoxic modes of action, results from both analyses should be presented.
2. If generating toxicity criteria is not possible, consider whether it is acceptable to assume data from a comparable substance.

7 References

Barnes DG, Daston GP, Evans JS, Jarabek AM, Kavlock RJ, Kimmel CA, Park C and Spitzer HL (1995). Benchmark dose workshop: criteria for use of a benchmark dose to estimate a reference dose. *Regulatory Toxicology and Pharmacology* 21: 296-306.

Boobis AR, Cohen SM, Dellarco V, McGregor D, Meek ME, Vickers C, Willcocks D, Farland W (2006). IPCS Framework for analyzing the relevance of a cancer mode of action for humans. *Critical Reviews in Toxicology* 36:781-792.

Butterworth BE (1990). Consideration of both genotoxic and non-genotoxic mechanisms in predicting carcinogenic potential. *Mutation Research* 239: 117-132.

Butterworth BE (2007). A mechanism-based cancer risk assessment for 1,4-dichlorobenzene. *Regulatory Toxicology and Pharmacology* 49:138-148.

Canadian Council of Ministers of the Environment (CCME) (1996). *A protocol for the derivation of environmental and human health soil quality guidelines.* Report CCME EPC-101E, CCME. March 1996.

Clewell H (2005). Use of mode of action in risk assessment: Past, present, and future. *Regulatory Toxicology and Pharmacology* 42:3014.

CLR9 (2002) *Contaminants in Soil: Collation of Toxicological Data in Intake value for Humans*. Department for Environment, Food and Rural Affairs and The Environment Agency.

COC (2004) *Guidance on a strategy for the risk assessment of chemical carcinogens.* Committee on the Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. September 2004

Crump K (1984). A new method for determining allowable daily intakes. *Fundamental and Applied Toxicology* 4: 854-891.

Crump K (1985). Mechanisms leading to dose-response models. In: Ricci P (ed). *Principles of Health Risk Assessment*, Prentice Hall, Englewood Cliffs, New Jersey.

Crump K (1995). Calculation of the benchmark doses from continuous data. *Risk Analysis* 15:79-89.

Crump KS (1996). The linearized multistage model and the future of quantitative risk assessment. *Hum. Exp. Toxicol.* 15(10):787-798.

de Bruijn JHM, Jager DT, Kalf DF, Mensink BJWG, Montforts MHMM, Sijm DTHM, Smit CS, van Vlaardingen PLA, Verbruggen EMJ, van Wezel AP (2001). *Guidance on deriving Environmental Risk Limits*. RIVM report 601501 012. National Institute of Public Health and the Environment (RIVM), Bilthoven.

Department of Health (1991) *Guidelines for the Evaluation of Chemicals for Carcinogenicity*, Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment, Report RHSS 42, HMSO, London.

enHealth (2004). *Environmental Health Risk Assessment. Guidelines for assessing human health risks from environmental hazards*. Department of Health and Aging and enHealth Council, Canberra.

Environment Agency (2009) Human Health Toxicological Assessment of Contaminants in Soil. SC050021 SR2 Environment Agency, Bristol

Environmental Protection Department (2007a). *Guidance Manual for Use of Risk-Based Remediation Goals for Contaminated Land Management*. The Government of Hong Kong, Special Administrative Region.

Environmental Protection Department (2007b). *Background Document on Development of Risk-Based Remediation Goals for Contaminated Land Management*. The Government of Hong Kong, Special Administrative Region.

Filipsson AF, Sand S, Nilsson J, Victorin K (2003) The benchmark dose method – review of available models, and recommendation for application in health risk assessment. *Critical Reviews in Toxicology* 33(5):505-542.

Fitzgerald DJ, Robinson NI, Pester BA (2004). Application of benzo(a)pyrene and coal tar tumor Dose-Response data to a Modified Benchmark Dose Method of Guideline Development. *Environmental Health Perspectives* 12(14):1341-1346.

Health Canada (2004) *Federal Contaminated Site Risk Assessment in Canada. Part I: Guidance on Human Health Preliminary Quantitative Risk Assessment (PQRA).* Environmental Health Assessment Services, Safe Environments Programme.

Health Council of the Netherlands (2003) *Benchmark dose method: derivation of health-based recommended exposure limits in new perspective*, Health Council of the Netherlands, The Hague, Netherlands

Hrudey SE, Krewski D (1995). Is there a safe level of exposure to a carcinogen? *Environmental Science and Technology* 29(8):370A-375A.

Institute for Environment and Health (IEH) (1999). *Risk Assessment Approaches used by UK Government for Evaluating Human Health Effects of Chemicals*. Institute for Environment Health. Leicester.

IARC (1983). *Approaches to Classifying Chemical Carcinogens According to Mechanism of Action* (IARC intern. tech. Rep. No. 83/001).

IARC (1987). *Overall Evaluation of Carcinogenicity: an updating of IARC Monographs Volumes 1 to 42 – Suppl. 7.* IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. IARC, Lyon.

IARC (2006) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Preamble*. World Health Organization, International Agency for Research on Cancer. Lyon, France.

IPCS (1994). *Assessing human health risks of chemicals: derivation of guidance values for health based exposure limits*. Environmental Health Criteria 170. International Programme on Chemical Safety, Geneva.

Kelly KE (1991). *The Myth of 10^{-6} as a Definition of "Acceptable Risk"*. Presented at the 84th Annual Meeting and Exhibition of the Air and Waste Management Association, Vancouver, BC, June 16-21.

Krewski D, Gaylor D, Szyszkowicz M (1991). A model-free approach to low-dose extrapolation. *Environmental Health Perspectives* 90:279-285.

Lambert JC, Lipscomb JC (2007). Mode of action as a determining factor in additivity models for chemical mixture risk assessment. *Regulatory Toxicology and Pharmacology* 49:183-194.

Lijzen JPA, Baars AJ, Otte PF, Rikken MGJ, Swartjes FA, Verbruggen EMJ, van Wezel AP (2001). *Technical Evaluation of the Intervention Values for Soil/Sediment and Groundwater.* RIVM report 711701 023. National Institute of Public Health and the Environment (RIVM), Bilthoven.

Maynard RL, Cameron KM, Fielder R, McDonald A, Wadge A (1995). Setting air quality standards for carcinogens: an alternative to mathematical quantitative risk assessment – a discussion paper. *Human Exposure and Toxicology* 14:175-186.

National Environmental Protection Council (NEPC) 2009 (unpub) An Australian Approach to Setting Air Quality Standards, Technical Support Document: Confidential Draft as edited by the Standards Setting Working Group

National Health and Medical Research Council (1999) *Toxicity Assessment for Carcinogenic Soil Contaminants.* Commonwealth of Australia. Canberra.

National Health and Medical Research Council (2004) *Australian Drinking Water Guidelines*. National Water Quality Management Strategy. Australian Government, Canberra.

Paustenbachh DJ (1995). The practice of health risk assessment in the United States (1975-1995): How the US and other countries can benefit from that experience. *Human and Ecological Risk Assessment* 1:29-79.

Priestly, BG (2007) *Carcinogen risk assessment, methodological issues relating to the review of health investigation levels (HILs) for the contaminated site NEPM* – Scoping Paper. Australian Centre for Human Health Risk Assessment (ACHHRA), Monash University, Victoria.

Purchase IFH, Auton TR (1995). Thresholds in chemical carcinogenesis. *Regulatory Toxicology and Pharmacology* 22:199-205.

Steward BW, Kleihues P (eds) (2003) *World Cancer Report*, Lyon, IARC.

Sonich-Mullin C, Fielder R, Wiltse J, Baetcke K, Dempsey J, Fenner-Crisp P, Grant D, Hartley M, Knaap A, Kroese D, Mangelsdorf I, Meek E, Rice J, Younes M (2001). IPCS Conceptual framework for evaluating a mode of action for chemical carcinogenesis. *Regul. Toxicol. Pharmacol*. 34:146-152.

Swartjes FA (1999). Risk-based assessment of soil and groundwater quality in the Netherlands: Standards and remediation urgency. *Risk Analysis* 19:1235-1249.

Travis KZ, Pate I, Welsh ZK (2005). The role of the benchmark dose in a regulatory context. *Regulatory Toxicology and Pharmacology* 43:280-291.

US EPA (1989). *Risk Assessment Guidance for Superfund Volume I, Human Health Evaluation Manual (Part A).* Interim Final. Office of Emergency and Remedial Response. U.S. Environmental Protection Agency, Washington D.C.

US EPA (1995). *The use of the benchmark dose approach in health risk assessment*. Risk Assessment Forum, EPA/630/R-94-007, United States Environmental Protection Agency, Washington D.C.

US EPA (1996). *Draft Revision to the guidelines for carcinogen risk assessment*. Office of Health and Environment Assessment, Office of Research and Development, United States Environmental Protection Agency, Washington D.C.

US EPA (1996a). *Soil Screening Guidance: Technical Background Document*. United States Environmental Protection Agency. Office of Solid Waste and Emergency Response, Washington, DC 20460. EPA 540.

US EPA (2005) *Guidelines for Carcinogen Risk Assessment*. Risk Assessment Forum, U.S. Environmental Protection Agency, Washington D.C. EPA/630/P-03/001B

US EPA (2005a) *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens*. Risk Assessment Forum, U.S. Environmental Protection Agency, Washington D.C. EPA/630/R-03/003F, March 2005.

US EPA (2009) *Toxicological Parameters for Cancer Effects*, Water Quality Standards Academy, http://www.epa.gov/waterscience/standards/academy/supp/health/index.htm, accessed December 2009

Vainio H, Heseltine E, McGregor D, Tomatis L, Wilbourn J (1992). Working group on mechanisms of carcinogenesis and the evaluation of carcinogenic risks. *Cancer Research* 52:2357-2361.

WHO (1994). *Assessing human health risks of chemicals: derivation of guidance values for health based exposure limits*. Environmental Health Criteria 170. IPCS/WHO. Geneva.

WHO (2000). *Air Quality Guidelines for Europe, 2nd Edition*. WHO Regional Publications, European Series No 91. World Health Organization, Copenhagen.

WHO (2009) *Principles for modeling dose-response for the risk assessment of chemicals*. Environmental Health Criteria 239. International Programme on Chemical Safety, World Health Organization, Geneva.

WHO (2008) *Guidelines for drinking-water quality*. Third Edition incorporating first and second addenda. Volume 1 Recommendations. World Heath Organization, Geneva.