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Human health toxicological assessment of contaminants in soil

Science Report – Final SC050021/SR2

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This report is the result of work undertaken by the Environment Agency's Science Programme.

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Author(s):
Mark Hosford

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Science Department

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The CLEA Guidance incorporates the following

1) *Science Report SC050021/SR2: Human health toxicological assessment of contaminants in soil.*

2) *Science Report SC050021/SR3: Updated technical background to the CLEA model.*

3) *Science Report SC050021/SR4: CLEA Software (Version 1.04) Handbook.*

4) *CLEA Software version 1.04 (2009)*

The CLEA Guidance can help suitably qualified assessors to estimate the risk that a child or adult may be exposed to a soil concentration on a given site over a long period of exposure that may be a cause for concern to human health. The CLEA Guidance does not cover other types of risk to humans, such as fire, suffocation or explosion, or short-term and acute exposures. Nor does it cover risks to the environment or the pollution of water.

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Steve Killeen

Head of Science

Executive summary

The assessment of sites with a legacy of chemical contamination from previous industrial use, for the purpose of determining whether it is contaminated land, is governed in England and Wales by Part 2A of the Environmental Protection Act and its supporting statutory guidance.

Contaminated land is determined by the potential risk posed by chemicals in on or under the land to humans, ecosystems, groundwater, and building structures.

This report describes the toxicological basis and approaches to deriving Health Criteria Values that serve as benchmarks for protecting human health. In conjunction with chemical exposure modelling methods, these Health Criteria Values enable the derivation of Soil Guideline Values and may be used in the overall assessment of risks to human health from land contamination.

Acknowledgements

The Environment Agency is very grateful to the Health Protection Agency, the Food Standards Agency, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment, and bibra toxicology advice and consulting, for reviewing this report. The Environment Agency would also like to thank those individuals and organisations that responded with feedback on the report published for comment in August 2008.

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1 Introduction

1.1 Update to R&D Publication CLR9

In December 2006, the Department for Environment, Food and Rural Affairs (Defra) issued a discussion paper entitled *Soil Guideline Values: The Way Forward*. The paper sought views from key organisations and groups on various ideas for how non-statutory technical guidance might be amended to make it more useful to assessors carrying out risk assessments, and to make clearer when land qualifies as contaminated land under Part 2A of the Environmental Protection Act 1990 in England and Wales. This exercise culminated in the publication by Defra of *Improvements to contaminated land guidance. Outcome of the "Way Forward" exercise* (Defra, 2008a).

The Environment Agency has updated its toxicological framework document that describes how the toxicity of chemical soil contaminants are assessed (previously published in 2002 as R&D Publication CLR9) to incorporate the changes proposed by Defra, and to provide more detailed guidance on chemical risk assessment. This report is the result and replaces Publication CLR9.

1.2 Background

The main purpose of this report is to provide technical guidance to regulators and their advisors in support of the statutory regimes addressing land contamination, particularly Part 2A of the Environmental Protection Act 1990 and development control under the Town and Country Planning Acts.

Part 2A defines the term *contaminated land* according to whether or not it poses a significant risk to human health and the environment. In relation to health only, it considers land to be *contaminated land* where *it appears to the local authority in whose area the land is situated to be in such a condition by reason of substances in, on or under the land that (a) significant harm [to human health] is being caused or there is a significant possibility of such harm being caused*. Statutory guidance explains that *significant harm* to a person would include such health effects as death, disease[1], serious injury, genetic mutation, birth defects or the impairment of reproductive function.

The definition of *significant harm* therefore encompasses a broad range of possible health outcomes from chemical exposure and these are considered in our framework. In addition, many toxicologists also review human and animal data to identify pre-cursor symptoms of diseases and other adverse health effects. It is good scientific practice to take this information into account.

Land contamination is a material consideration within the planning regime. A planning authority has to consider the potential implications of contamination both when it is developing structure or local plans (or unitary development plans) and when it is considering applications for planning permission. Planning Policy Statement 23 (England), in the granting of planning permission for new development including permission to carry out remediation, states that remediation must remove unacceptable

[1] For the purpose of the statutory guidance, disease is taken to mean an unhealthy condition of the body or a part of it and can include, for example, cancer, mental dysfunction, liver dysfunction or extensive skin ailments.

risk and make the site suitable for its intended use (ODPM, 2004a and 2004b). As a minimum, after development and commencement of its use, the land should not be capable of being determined as contaminated land under Part 2A.

This report has been prepared by the Environment Agency with the support of the Health Protection Agency (HPA) and the Food Standards Agency (FSA). It considers the scientific assessment of the risks to human health posed by exposure to chemicals in soils. It describes (in Section 3) a framework for the collation and review of toxicological data and its subsequent use in the derivation of soil contaminant intakes (Health Criteria Values, HCVs) that are considered to be protective of human health. These intakes are guidelines to a risk assessor on the level of long-term human exposure to individual chemicals in soil that are tolerable or pose a minimal risk. Combined with estimates of exposure, HCVs can be used by risk assessors and risk managers to consider whether land affected by contamination requires further investigation, assessment, and/or remediation. HCVs are established from a review of the evidence from occupational and environmental epidemiological studies, animal studies, and from scientific understanding of the mechanisms of absorption, transport, metabolism and toxicity of chemicals within the human body.

HCVs are an important part of the risk assessment process for contaminated soils and a critical component in the derivation of Soil Guideline Values (SGVs) and/or other generic or site-specific assessment criteria. The Contaminated Land Exposure Assessment (CLEA) model provides generic estimates of child and adult exposures to soil contaminants for those potentially living, working and/or playing on contaminated sites over long time periods. Further guidance on estimating human exposure to soil contamination and the derivation of SGVs using HCVs can be found in the CLEA Report (Environment Agency, 2009).

HCVs derived using the framework in Section 3 of this report set levels of minimal or tolerable risk for long-term human exposure to chemicals in soil. They represent a baseline and health protective position to minimise risks of *significant harm*; they do not themselves necessarily represent thresholds above which an intake would be *unacceptable*, representing a *significant possibility of significant harm* in the context of Part 2A, but they can be a useful starting point for such an assessment (Defra, 2008b). Science alone cannot answer the question of whether or not a given *possibility of significant harm* is *significant*, since what is either *significant* or *unacceptable* is a matter of socio-political judgement, and the law entrusts decisions on this to the enforcing authorities (Defra, 2008b).

In the context of Part 2A, an assessor using HCVs derived in accordance with the principles and framework in this report can conclude that (Defra, 2008b):

- human exposure below the HCV is unlikely to represent a *significant possibility of significant harm*;
- human exposure above the HCV might represent a *significant possibility of significant harm*, with the significance linked to the margin of exceedance, the duration and frequency of exposure, and other factors that the enforcing authority may wish to take into account.

1.3 Advice on using this report

The framework and explanatory material in this report has been written for the technical professional who is familiar with assessments of the risks posed to human health by land contamination. The report explains the basic toxicological principles used to derive HCVs and also directs readers to useful sources of more detailed information on the various concepts and approaches discussed.

The remainder of this report is separated into two sections:

- Section 2 provides an overview of the basic principles of toxicological risk assessment, describing the process and defining common terminology[2]. Further information on certain aspects is provided in grey-shaded text boxes.
- Section 3, the framework, explains the process used by the Environment Agency to prepare a risk assessment for a chemical contaminant of soil and derive HCVs for use in setting SGVs. This framework may be followed when assessing a contaminant for which HCVs have not been established at the national level. It is essential, however, that the review and evaluation of the toxicity of a contaminant and the derivation of HCVs is only undertaken by professionals suitably qualified and experienced in toxicology and chemical risk assessment.

[2] Terms printed in bold are defined in the Glossary. Abbreviations printed in bold are expanded in the List of Abbreviations.

2 Basic principles of chemical risk assessment

Toxicological risk assessment is the process by which the adverse (toxicological) effects of a chemical on humans are evaluated or estimated based on the available knowledge about the chemical. This knowledge may include anecdotal evidence of toxic effects from passive observation of human or animal exposure to the chemical, but in the main comes from more structured active investigation. Due to the ethical issues of human testing, a feature of toxicology and chemical risk assessment is the frequent need to rely on laboratory systems – predominantly experimental animals at the present time – as human surrogates, though for some chemicals human data from **epidemiology** (including occupational) studies may also be available.

This report is therefore written largely from the perspective of an assessment based (predominantly) on experimental data from studies using laboratory animals. If epidemiology or other human data are available for a contaminant, these will often take precedence over laboratory animal data and be preferentially used in the risk assessment, but this will depend on the extent and quality of the data available.

Many countries and regulatory agencies have undertaken work on the potential human health impacts from exposure to chemical contaminants. Each has developed new terminology or adopted an existing one with or without subtle variations. This section describes the key processes of chemical risk assessment, focussing on risk assessment of soil contaminants, and introduces principal terms used in this report. Some of the equivalent terms used by other organisations are also presented.

Chemical risk assessment is commonly described in four steps – hazard identification, hazard characterisation, exposure assessment, and risk characterisation – according to the paradigm proposed by the US National Academy of Sciences (NAS, 1983; IPCS, 1999). These processes are described in the following sections. A summary of the risk assessment process is provided in Figure 2.8.

2.1 Hazard identification

Hazard identification involves establishing the inherent toxicological properties of a substance, that is, the intrinsic ability of the chemical to cause an **adverse effect**. For example, a chemical may be a **hepatotoxicant**, a **mutagen**, a **carcinogen**, a **teratogen**, an **allergen** and so on. In itself, this classification step does not inform whether the substance *will* cause these effects in all circumstances; it merely identifies the principal hazards that will require further consideration in the assessment.

Identified effects may be confined to the site (body tissue) of contact/administration (**local toxicity**), such as lung cancer caused by inhaled asbestos fibres, or may be generalised in nature or occur in a tissue/organ distant from the site of initial contact (**systemic toxicity**).

2.1.1 Genotoxicity and genotoxic carcinogenesis

The classification of a chemical as **genotoxic** and a human **carcinogen** has important repercussions in terms of the approach followed later in the risk characterisation and the subsequent **risk management** policies and actions taken.

The identification of a chemical as a human carcinogen is most conclusively achieved with direct evidence in humans. The long latency of clinically diagnosable tumour development, however, adds to the limitations of epidemiological studies, which in the main suffer from **confounding**, **bias** and a lack of accurate exposure information, in addition to the often large costs involved in conducting such studies. For most chemicals, sound epidemiology data will not be available and data from carcinogenicity bioassays in laboratory animals are required to supplement the human evidence or are the only source of information on the carcinogenic potential of a chemical. The most common species used for carcinogenicity testing are the rat and mouse, though data from other species may be available, and as with all aspects of toxicology the data from the different species may not agree.

Carcinogenicity bioassays are, however, very expensive and time-consuming, and it is not feasible – economically or ethically – to subject all chemicals to such testing. For a significant number of chemicals, therefore, no carcinogenicity data are available either in humans or other species.

In such cases, judgements on potential genotoxic carcinogenicity in humans may be made based on data from mutagenicity/genotoxicity assays. A range of these assays, which are comparatively cheap and quick to perform, have been developed using both ***in vitro*** (including **prokaryotic** and **eukaryotic**) systems and ***in vivo*** systems. The assays and test systems cover a range of different techniques, which collectively can evaluate a variety of genotoxic/mutagenic mechanisms and endpoints[3].

Where there is evidence of carcinogenicity from human or animal data, the results of these mutagenicity/genotoxicity assays may be used to differentiate between carcinogens acting via genotoxic mechanisms, which may not have a threshold, and those acting via non-genotoxic mechanisms[4], which are expected to demonstrate a threshold (see Section 2.2.1 for discussion of threshold and non-threshold toxicity). However, since many chemical carcinogens operate through the induction of mutations in **somatic cells**[5], in the absence of carcinogenicity data, positive mutagenicity data will lead to the substance being assumed to be a (non-threshold) carcinogen.

For each area – epidemiology, animal carcinogenicity, and mutagenicity/genotoxicity – a weight of evidence approach (see, for example, IGHRC, 2002) is usually adopted, both within the discipline and when considering the totality of the evidence.

[3] See UKEMS (1990, 1993), McGregor *et al*. (1999), COM (2000), IPCS (2006) and Lambert *et al*. (2005) for a review of genotoxicity assays. The Guidelines for the Testing of Chemicals produced by the Organisation for Economic Co-operation and Development (OECD, 2007) also provide a useful source of information on the biological basis and methodology of each of the assays that has gained regulatory acceptance.

[4] Examples of non-genotoxic modes of carcinogenicity include sustained **cytotoxicity** and cell proliferation, **cytochrome P450** enzyme induction, and chronic perturbation of the **endocrine system** (IGHRC, 2002).

[5] Whereas a mutation in a **germ cell** can be transmitted to offspring, a mutation in a **somatic cell** can only be transferred to descendent daughter cells; however, this may lead to a clone of transformed cells and ultimately a malignant tumour (cancer) (IGHRC, 2002).

2.2 Hazard characterisation

Hazard characterisation involves refinement of the understanding of the hazard(s), in particular how the dose or extent of exposure to the chemical influences the probability, magnitude and/or severity of the effect[6]. It also includes gaining an understanding of the **kinetics** of the chemical and insights into the **mechanism/mode of action**, which will inform the ultimate assessment of risk to humans and may permit the derivation of **Health Criteria Values** (**HCVs**) applicable to the human population.

2.2.1 Dose-response characterisation

Hazard characterisation investigations typically enable the production of dose-response (or exposure-response) curves for the toxic effects. An example of dose-response data for a threshold effect is provided in Figure 2.1. A trendline is provided to show what the dose-response curve may be in this hypothetical example. However, with data for only three doses (a fairly common situation), in addition to the zero dose or 'control' group (marked 'A' in the figure), it is not possible to know with total confidence what the actual dose-response for the adverse effect is. It is, for example, possible that the true curve might be **sigmoidal** between the mid (C) and high (D) doses – especially if dose 'D' caused a high level of response.

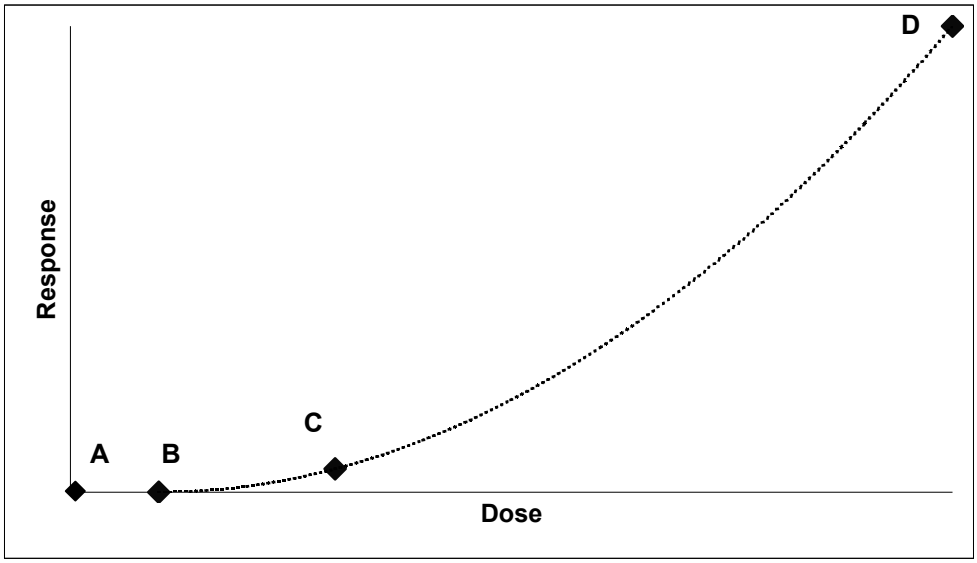

Figure 2.1 Typical dose-response data

The critical assumption that forms the basis of toxicological risk assessment, however, is that the response can only increase or stay the same with increasing dose, and vice versa (i.e. the dose-response curve is **monotonic**). In Figure 2.1, it is thus assumed that at any dose between zero (A) and the low-dose (B) the response would be zero.

[6] In practice, hazard identification and dose-response characterisation are usually approached as one process experimentally.

Threshold toxicity

The schematic dose-response curve in Figure 2.1 is an example of threshold toxicity. That is, there is some, non-zero, measurable amount of exposure (dose) that is required before a biological threshold is breached and an adverse effect is produced. When assessing an **endpoint** displaying a threshold, the highest dose at which no adverse effects were seen in the toxicity study is termed the **no-observed adverse effect level** (**NOAEL**). The next dose above the NOAEL, i.e. the lowest dose at which adverse effects were seen, is termed the **lowest-observed adverse effect level** (**LOAEL**). If the response being observed in Figure 2.1 was adverse, therefore, the low dose (B) would be the NOAEL and the mid-dose (C) would be the LOAEL.[7]

The NOAEL for the **critical adverse effect**, known as the **critical NOAEL** (or if a NOAEL has not been identified, the critical LOAEL), is the value (often termed the **point of departure**) commonly used in the derivation of HCVs (discussed in Section 2.2.5) and/or the risk characterisation (discussed in Section 2.4). The critical adverse effect will often be the most sensitive endpoint, i.e. that elicited at the lowest effect level, but another perhaps more relevant or serious effect may sometimes be judged to be the most important for human health.

Depending on the quantity and quality of toxicity data available for an adverse effect, in addition to the NOAEL and LOAEL – which are restricted to the doses used in the toxicity studies – it may also be possible to mathematically model the dose-response curve and estimate the so-called **benchmark dose** (**BMD**) that causes a predetermined change in response (usually 5 or 10%). It is commonly the statistical 95% lower confidence limit of the BMD, termed the **BMDL**, which is then used in the risk assessment (see Figure 2.2 and Box 2.1).

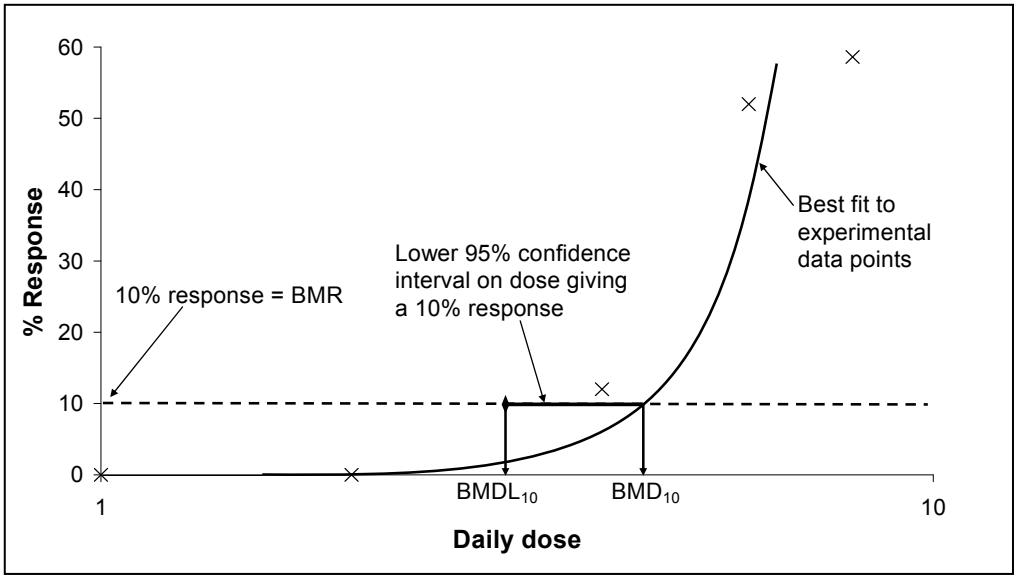

Figure 2.2 The benchmark dose (modified from EFSA, 2005a)

[7] The true no-adverse effect level (that is, the true threshold) will, in theory, lie somewhere between the experimental NOAEL and LOAEL (though it could be below the experimental NOAEL if the study was not sufficiently sensitive to detect the response). The greater the number of data points (dose groups) around the NOAEL/LOAEL region of the dose-response curve, the more the NOAEL and LOAEL will converge and the greater the confidence in the NOAEL as a measure of the actual threshold for the adverse effect in the test species.

The disadvantage of dose-response modelling is that it may not always be possible or appropriate based on the quality and quantity of data – the current design of regulatory toxicity studies is based on providing reliable estimates of the NOAEL rather than defining the shape of the dose-response curve. Mathematical modelling also requires familiarity with the software packages available and the variety of models they contain[8], and interpretation of the output from such models requires expert knowledge.

Box 2.1 The benchmark dose

The benchmark dose (BMD), first proposed by Crump (1984), is the dose that produces a predetermined change in response rate for an adverse effect (called the **benchmark response**; **BMR**) compared to background. Typically, the change in response (BMR) is 5% or 10%, but other response levels may be used – the endpoint and data being modelled will influence BMR selection. Commonly, it is the statistical 95% lower confidence limit of the BMD, termed the BMDL, that is used in the risk assessment (see Figure 2.2).

This approach therefore provides a point of departure based on the whole dose-response curve rather than a single data point, and also takes into account the statistical power and quality of the data as the confidence interval around the dose-response will be wider for smaller and/or poorly designed studies, leading in turn to a lower BMDL.

The BMD approach also helps in comparing results between studies of the same chemical and allows for comparison of potencies of different chemicals (IPCS, 1994). Appraisals of (mainly **developmental toxicity**) studies using narrow dosage intervals showed the BMDL (for a 5% BMR) to approximate the experimental NOAEL in the same study (see Allen *et al*., 1994; Auton, 1994; Kavlock *et al*., 1995).

BMD methods were originally used for modelling changes in response rates of the study population for dichotomous (quantal) data (i.e. how many of the study population are affected at a particular dose). The concept, however, may be, and more recently has been, extended to modelling changes in continuous endpoint variables (such as blood levels of a biomarker of toxicity) within a population (Crump, 1984, 1995, 2002). BMR, BMD and BMDL equivalents of Critical Effect Size (CES), Critical Effect Dose (CED), and lower confidence limit of the CED (CEDL) have been proposed for this purpose (Slob and Pieters, 1998; Slob, 2002). Due to the differing degree of natural variation in some continuous parameters, the CES will be specific to the endpoint being investigated (Slob and Pieters, 1998; Slob, 2002; Sand *et al.*, 2006; Dekkers *et al.*, 2006). Continuous data may also be modelled dichotomously – the so-called hybrid approach – by selecting a cut-off value representing an 'adverse' level of effect (Crump, 1995; Sand *et al.*, 2003; Falk Filipsson *et al.*, 2003).

BMD methods have mainly been applied to animal data, but may also be used with epidemiology findings (Budtz-Jorgensen *et al.*, 2001), and papers reporting such use are appearing in the literature (Budtz-Jorgensen *et al.*, 2000; Crump *et al.*, 2000; Murata *et al.*, 2002).

Non-threshold toxicity

Whilst the dose-responses of many of the adverse effects encountered in toxicology would be expected to exhibit a dose threshold, in some cases the toxicological mechanism responsible for producing the adverse effect is such that there is no basis to assume a threshold exists (see Figure 2.3). This is most notably the case for many **mutagens** and **genotoxic carcinogens**. The biological mechanisms by which these types of chemicals cause damage to **DNA** (**deoxyribonucleic acid**) and genetic

[8] A review of the BMD approach and the available models has been published by Falk Filipsson *et al*. (2003).

material, leading to the development of cancer, are becoming increasingly understood. Nevertheless, it is generally assumed by regulators that any exposure to these chemicals, no matter how small, will carry some level of risk. The theoretical basis for this is that one 'hit' on DNA can produce a mutation that may eventually lead to a tumour. In practice, this is unlikely to occur (e.g. because the compound or its reactive metabolite is detoxified before reaching DNA, or the DNA damage is repaired, or the mutation has no functional consequence), but it is not possible to identify the threshold with any confidence. Hence, the prudent assumption is made that such compounds do not have a threshold.

When a non-threshold mechanism of toxicity is suspected, such as for cancer caused by a direct-acting **genotoxin**, the absence of a measurable response in animal toxicity studies cannot be taken as proof of a threshold (Dorne and Renwick, 2005), and the dose should not be considered a no-effect level – the dose may have simply been too low to cause a measurable response in the small number of animals studied. Thus, if the dose-response data points in Figure 2.1 represented the number of tumour-bearing animals in each dose group at the end of a carcinogenicity bioassay in which laboratory animals had been administered a genotoxic chemical, the low dose (B) would not be considered a no-effect level even though there was no apparent response.[9]

Non-threshold toxicity therefore presents a clear departure from the threshold toxicity paradigm, and the consequent risk implications for human health necessitate a different approach to HCV derivation (see Section 2.2.5), risk characterisation (see Section 2.4) and risk management (including application of the **ALARP** principle; see Section 2.5).

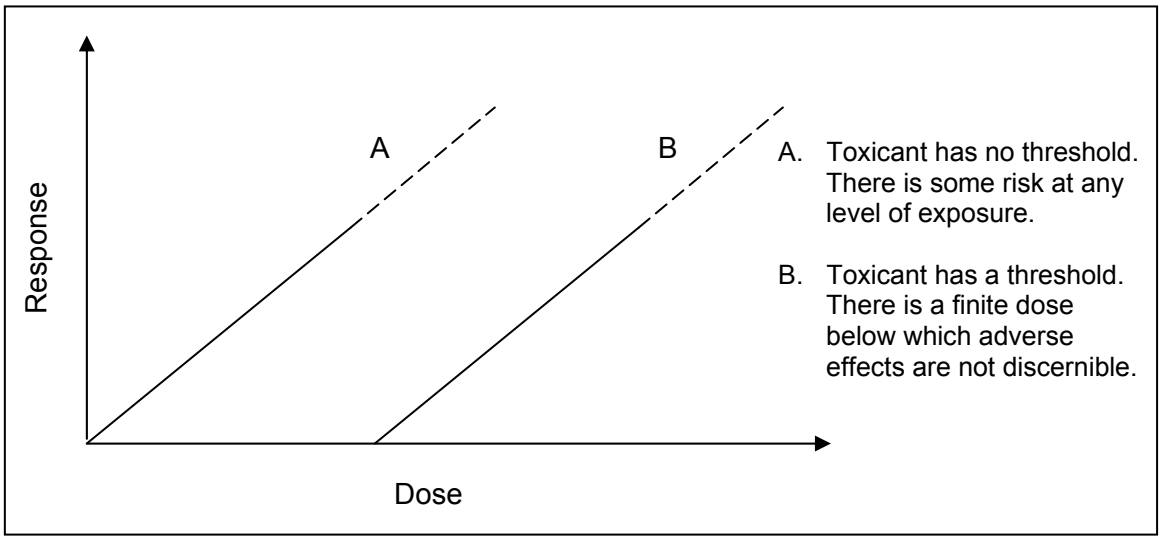

Figure 2.3 Diagrammatic representation of threshold and non-threshold toxicity

[9] Various authors would still refer to this as the NOAEL (or **NOEL**) – and this would be, literally, true since no adverse effects were observed at this dose in the study. However, in keeping with the definition of non-threshold, a response (adverse effect) would have been observed at this dose and any lower dose if sufficient animals were included in each dose group. Reserving 'no-effect level' terms for threshold effects is therefore preferred to avoid confusion with their use in the hazard characterisation and risk characterisation of threshold effects of chemicals.

2.2.2 The metric of exposure

When experimentally investigating a chemical's toxicity and when considering how the degree of exposure to a chemical affects the biological response produced, a suitable metric for quantifying the exposure must be used. The most common exposure metric employed in animal toxicity studies is the **intake dose** (usually abbreviated to "dose") expressed on a bodyweight basis, i.e. the amount of chemical administered to the animal per unit of its bodyweight, e.g. milligrams per kilogram bodyweight (mg kg^{-1} bw) or milligrams per kilogram bodyweight per day (mg kg^{-1} bw day^{-1}).

The predominant alternative to this used in experimental toxicology is the concentration of chemical in the medium used to deliver the chemical to the animal. For oral toxicity studies, this will typically be the diet or the drinking-water, in which case the exposure metric may be, for example, milligrams per kilogram of feed (mg kg^{-1}), milligrams per litre of drinking-water (mg L^{-1}), or parts of chemical per million/billion parts of feed or water (ppm/ppb). For inhalation studies, the concentration of the chemical in the ambient air breathed by the animal, for example milligrams per cubic metre of air (mg m^{-3}) or ppm[10], is frequently the preferred exposure metric, while for dermal studies it would typically be the concentration of the chemical in the solvent vehicle applied to the skin.

The amount of chemical is usually the mass, e.g. milligrams (mg) or micrograms (µg). This is because the mass is directly proportional – for a defined chemical – to the number of molecules, and it is the number of molecules able to interact with biochemical structures and pathways in the body that determines the extent of toxic effect of most chemicals.

Sometimes, though, mass may not be the most appropriate metric. Asbestos, for example, causes lung cancer and **mesothelioma** on inhalation, but it is the number of (appropriately sized) asbestos fibres that determines the risk. Since asbestos fibres vary in size and mass, the "amount" of asbestos is best measured as the number of fibres. Asbestos is also different from most chemicals in that it only causes notable toxicity if fibres become airborne and are inhaled. Usually, therefore, it is the concentration of fibres in air, for example fibres per cubic metre of air (f m^{-3}), that is used as the metric of exposure to asbestos.

Where exposures are given as concentrations in the delivery medium within a toxicity study, the actual intake of chemical by the animal (i.e. the dose) may be estimated using knowledge of feed consumption/drinking-water intake (usually measured per group rather than per individual) and/or estimates of inhalation rate, and bodyweight.

The intake dose and concentration of chemical in exposure medium represent practicable metrics for measuring exposure to toxicants. While it is the exposure of the **target** tissue/organ that is the actual determinant of toxicity and it is desirable for this exposure-response relationship to be known, for such information to be of practical use the relationship between intake and target tissue exposure would also need to be established.

[10] For chemicals in air, the relationship between the level in ppm and the level in mass per unit volume (e.g. mg m^{-3}) is specific to the chemical (at 25 ºC, the concentration in mg m^{-3} equals the concentration in ppm multiplied by the molecular weight/24.45). When using aerial concentration data in ppm, therefore, it is important that this relationship is known.

2.2.3 Mechanism/mode of action

The **mechanism of action** is the exact sequence of events and molecular interactions that occur in the organism, and ultimately result in the observed toxicity, following exposure to a chemical. Only rarely, if ever, however, is such an intricate level of detail learned for a chemical. Instead, knowledge of the key metabolic, biological and pathological events involved is generally aimed for. This is collectively termed the **mode of action**.

Characterising the dose-response in laboratory animals establishes the toxicity of the test chemical in those species across the range of doses used in the studies. However, in extrapolating this to humans, the potential hazards and risks arising from probably much lower exposures need to be evaluated. Knowledge of the mechanism/mode of action operating in the test species complements the dose-response data for an observed toxic effect by providing an indication of its relevance to low-level human exposure. In many cases, however, the mechanism/mode of action will not be known.

Appraisal of the mode of action and its likely relevance to humans (see, for example, ECETOC, 2006) will include considerations such as whether the target tissue exists in humans, and, if there is a target **receptor** for the toxicant, whether this is also present in humans. Even if this proves to be the case, the human receptor may not show the same sensitivity and level of response as its laboratory animal counterpart (see Box 2.2), or the consequential intracellular cascade (sequence of biochemical events) may differ between species.

Box 2.2 Mode of action: an example of species-specific activity

The **peroxisome** proliferator activated receptor alpha (PPARα) is expressed in both humans and rodents. Its activation by particular compounds (known as peroxisome proliferators) results in altered gene expression, an increase in intracellular peroxisomes and, at the whole animal level, a decrease in blood lipid (fat) levels. Some PPARα **agonists** have consequently been developed as pharmaceuticals for the treatment of high cholesterol. In rodents, however, PPARα activation can also lead to the development of liver cancer (non-genotoxic carcinogenesis), but this effect has not been seen in humans. PPARα is less abundant in human than in rodent liver and this may have a quantitative effect on the level of gene expression induced. This, as well as other, qualitative differences in gene expression may be responsible for the interspecies difference in carcinogenicity (Holden and Tugwood, 1999).

2.2.4 Toxicokinetics

In addition to the ability of a chemical to have an effect on a biological receptor or pathway (termed its **toxicodynamics**), the other determinant of a chemical's toxicity – and potential source of **interspecies** (and **intraspecies**) differences – is its **toxicokinetics**. Toxicokinetics covers the absorption, distribution, metabolism and excretion of the chemical (see also Section 2.3 and Figure 2.7), and each of these may show differences between species. Notably, when considering the mode of action and its relevance to humans, it is important to establish the identity of the chemical entity responsible for causing the observed biological response(s). Often this will be the chemical as administered (the **parent compound**), but in many cases a metabolite(s) may be the principal toxic moiety.

Knowledge of how a chemical is metabolised in experimental species and its likely or known metabolism in humans (either *in vivo* or from *in vitro* cell cultures) will indicate

whether the toxic moiety will, or is likely to, occur in humans and, if so, whether at greater or lower levels relative to the test species.

Toxicity may arise only when metabolic detoxification systems become overloaded and the body becomes exposed to excess parent compound or a metabolite(s) produced only when the normal metabolic pathways are saturated. Toxicity via such mechanisms may therefore not be relevant if human exposure is not expected to saturate primary metabolic capacity.

If a chemical accumulates in tissues, its critical toxicity may be a consequence of long-term accumulation. In such instance, the rate of **elimination** (metabolism and/or excretion), which may be different in humans than in laboratory animal species, and overall **body burden** will influence toxicity. The much greater lifespan of humans compared to typical laboratory animals may also affect the potential for a chronic toxic effect to be realised.

2.2.5 Health Criteria Value derivation

Knowledge of the dose-response profile of a chemical in test populations (often laboratory animal species only) as well as its kinetics and, ideally, mode of action enables the dose-response profile to be conservatively extrapolated to derive HCVs for the human population as a whole.

The basic toxicological approaches to deriving HCVs for environmental chemicals are similar throughout the international scientific community. However, with so many different organisations conducting assessments, and regulatory bodies each working to the unique wording of their governing legislation, inevitably differences exist in the precise methods followed and terminology used. It is not practical to cover all these in this report, but the following sections provide a brief description of the principal approaches, terminology and definitions used by some of the most authoritative organisations worldwide.

Threshold toxicity

A variety of HCVs are derived by organisations worldwide for chemicals displaying threshold critical toxicity. The most well established of these, and most universally adopted in chemical risk assessment programmes, including those of the UK, is the **tolerable daily intake** (**TDI**). The TDI is defined as an estimate of the amount of a contaminant, expressed on a bodyweight basis [e.g. mg kg^{-1} bw day^{-1}], that can be ingested daily over a lifetime without appreciable health risk (see Box 2.3).

The TDI concept has been extended from its origins in food safety to address exposure via other, non-oral, routes, such as inhalation and skin contact. In addition, for inhalation, an HCV similar to a TDI but expressed as an atmospheric concentration of the chemical (e.g. mg m^{-3}) rather than a bodyweight dose is preferred by some agencies (such as RIVM in the Netherlands, Baars *et al.* 2001) and is commonly termed the tolerable concentration in air (**TCA**).

Box 2.3 The tolerable daily intake (TDI)

An extension of the acceptable daily intake (**ADI**) originally developed for setting standards for dietary safety of food additives, the tolerable daily intake (TDI) was proposed in the 1970s by the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA) for contaminants within foodstuffs. Whereas additives have some desirable technological purpose, contaminants have no intended function. JECFA therefore adopted the term "tolerable" for contaminants, with the intention of implying something rather less than "acceptable"; that is, "tolerable" should be taken to mean "permissible" rather than "satisfactory" (IPCS, 1987).

Some authoritative bodies use longer reference times when setting tolerable intakes for cumulative contaminants. JECFA, for example, uses the term provisional tolerable weekly intake (**PTWI**). The PTWI is the same as the TDI, but reflects the fact that it is exposure averaged over longer than a single day that is important. JECFA uses the term "provisional" for contaminants, whether referring to daily or weekly intake, in recognition of the fact that the toxicological database is commonly less complete than for substances that are subject to regulatory approval (Herrman and Younes, 1999). For dioxin-like compounds, JECFA uses an even longer reference period – a provisional tolerable monthly intake (**PTMI**).

The United States Environmental Protection Agency (USEPA) uses largely the same methodology as JECFA/WHO (see below) but has adopted the term **reference dose** (**RfD**) instead of ADI or TDI, though using a very similar definition. USEPA defines the RfD as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive groups) that is likely to be without an appreciable risk of deleterious effects during a lifetime (USEPA, 2007). The **reference concentration** (**RfC**), also of USEPA, is equivalent to the RfD, but is based on inhalation and is defined as a concentration in air (similar to the TCA). Critically though, the RfD and RfC are based on non-cancer effects only (USEPA assesses cancer effects separately), and so may be derived by USEPA for non-threshold genotoxic carcinogens for which a TDI would not be derived.

The US Agency for Toxic Substances and Disease Registry (**ATSDR**), which is responsible for preparing toxicological profiles for priority hazardous substances commonly found at contaminated sites in the Unites States, derives oral and inhalation **minimal risk levels** (**MRLs**) equivalent to the RfD and RfC, respectively, but for each of chronic, intermediate (up to one year), and acute exposure (ATSDR, 2007).

For simplicity, the 'TDI' is referred to in the remainder of this section, but the principles and processes discussed are equally applicable – subject to their particular definitions – to other types of threshold HCV such as PTWI, TCA, RfD, RfC, and MRL.

Occasionally, for contaminants of notoriety arising from a long history of human exposure and known impacts on health, there will be sufficient qualitative and quantitative knowledge of the chemical's toxicity to humans from good quality **epidemiology** studies that a TDI may be proposed with a high degree of confidence. This is, however, a rare situation. Reliable data from human populations exposed to known levels of chemicals are not common, except for the case of human pharmaceuticals. For the majority of chemical contaminants, therefore, the characterisation of the risks to human health and derivation of the TDI must rely mainly on data from toxicity studies conducted in laboratory animals and model systems.

TDIs are derived by the application of **uncertainty factors** to a reference point identified from the toxicity data (see Figure 2.4). Typically, this point of departure will be the highest NOAEL (or BMDL if the data have been modelled) for the critical adverse effect (often the most sensitive effect – the effect with the lowest NOAEL) in the most

sensitive species (or another species if there is evidence it is more relevant to humans). If no NOAEL or BMDL can be identified from the most important/pivotal studies, the LOAEL may be used. Selection of the most appropriate point of departure, however, may be influenced by a variety of factors, not least the quality of the data available, and requires expert judgement.

$$TDI = \frac{POD}{UF}$$

Where: POD = point of departure (e.g. NOAEL, LOAEL, BMDL)
UF = uncertainty factor

Figure 2.4 Derivation of the tolerable daily intake

The purpose of applying uncertainty factors (to the NOAEL, for example) is to estimate an intake for humans that is adequately protective of public health. The selection of uncertainty factors will therefore depend on a number of considerations. These include the quality and types of study available (e.g. kinetic, chronic toxicity, reproductive toxicity, developmental toxicity, genotoxicity, carcinogenicity, epidemiology), the species for which data are available (e.g. rodent, dog, human), and the critical adverse effects observed. Collectively, uncertainty factors must account for the total uncertainty in the assessment (see Box 2.4). This may most notably include potential differences in human response compared to that of another animal species – with the expectation that humans may be more sensitive per unit dose – and the variability in response in the human population due to factors such as genetic profile, age, and health status[11]. Examples of uncertainty factors used in chemical risk assessment are provided in Table 2.1.

Box 2.4 Uncertainty factors

Uncertainty factor is the generic term used in the UK for the numerical factors applied to toxicity data (points of departure) to take into account the uncertainty in extrapolating the data to derive HCVs for humans. Various terms are used by different organisations to denote such factors, including **safety factor**, **variability factor**, **assessment factor** and others. These terms are generally interchangeable. In some cases, however, it may not be uncertainty that dictates the application of the factor, but rather evidence that humans or a human subpopulation are more sensitive than the subjects (either animal or human) of the critical study. Similarly, there may be evidence of decreased sensitivity of the target population relative to the test population, in which case a smaller than usual factor may be applied. Where the difference in sensitivity of the test and target populations to a particular chemical is known and can be quantified or estimated, a **chemical-specific adjustment factor** is applied (see IPCS, 2005).

[11] A review of uncertainty in UK chemical risk assessments has been published by the Interdepartmental Group on Health Risks from Chemicals (IGHRC, 2003). The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) has also published a review of variability and uncertainty in toxicology and risk assessment (COT, 2007).

Table 2.1 Examples of uncertainty factors used in chemical risk assessment (Renwick, 1993, 1995; IPCS, 1994; IGHRC, 2003; COT, 2007)

Consideration	Typical uncertainty factor applied
Interspecies variability	A 10-fold factor is normally used to account for variability in species susceptibility between humans and animal species.
Intraspecies variability	A 10-fold factor is normally used to account for variability of responses in human populations.
LOAEL to NOAEL	A 10-fold factor may be used when a LOAEL instead of a NOAEL is used in the derivation. For a minimal LOAEL, an intermediate factor of three may be used.[a]
Data gaps	A factor, usually three- to 10-fold, may be used for "incomplete" databases (with missing studies, such as no chronic bioassays or no reproductive toxicity data). It accounts for the inability of any study to consider all toxic endpoints.
Steep dose-response curve	Where the dose-response curve is steep and a small error in the extrapolation would have dramatic consequences, an additional factor may be applied.[b]

[a] It is inappropriate to use a LOAEL to set an HCV if the undetermined NOAEL is judged to be (likely) more than ten times less than the LOAEL.

[b] A steep dose-response curve does, however, provide greater confidence in the NOAEL (Renwick and Walker, 1993).

Where a NOAEL is available for the critical endpoint identified from a good laboratory animal data set, the uncertainty factor applied will usually be 100. This factor, which has been used in chemical risk assessment for over 50 years (Lehman and Fitzhugh, 1954), is considered to comprise two component factors of ten. The first accounts for interspecies variability: the potential increased susceptibility of humans compared to the laboratory animal species in which the chemical has been tested. The second factor of ten is to allow for intraspecies (interindividual) variation: the genetic diversity and variable health status of the human population (e.g. see Dybing and Søderlund, 1999) which are not present in the inbred strains of animals used for toxicity testing.[12]

While originally based on very limited evidence (Lehman and Fitzhugh, 1954), the setting of these factors at ten has been supported by scientific analyses suggesting they provide a default position that matches the degree of reassurance sought (Renwick and Lazarus, 1998; IGHRC, 2003). Although they are precautionary in their general nature, there may be instances where a factor of ten is insufficient for its intended purpose (RATSC, 1999a; RATSC, 1999b; COT, 2007).

The uncertainties in extrapolating animal data, which must be accounted for in public health risk assessments, by and large remain today. In recent years, however, attention has been given to these standard factors of ten for interspecies and intraspecies variability. Renwick (1993) analysed data for some, mainly pharmaceutical, compounds (for which there were good data) in order to subdivide

[12] When the total uncertainty factor of 100 was originally proposed by Lehman and Fitzhugh (1954), they cited possible cocktail effects of exposure to multiple chemicals as well as interspecies and interindividual variation in their justifications. Scientific opinion on the cocktail effect has moved on since this time, and is addressed separately (see Section 3.5.3).

each factor by separating out the two basic variabilities for which it is responsible, i.e. potential differences in toxicokinetics and in toxicodynamics. Subsequently taken forward with minor modification under the auspices of the International Programme on Chemical Safety (IPCS, 1994), factors of 2.5 and 4.0 for interspecies toxicodynamics and toxicokinetics, and 3.2 and 3.2 for interindividual toxicodynamics and toxicokinetics, respectively (see Figure 2.5), offer refinements of the composite default factor where suitable data exist. Due to the more extensive data requirements, application of such chemical-specific adjustment factors in the risk assessment of environmental contaminants has so far been limited. If chemical-specific adjustment factors are used, the adequacy of the remaining default factors should be explicitly considered (COT, 2007).

As with all elements of toxicological risk assessment, it is important that the assessor employs expert professional judgement to determine the appropriateness – in both selection and magnitude – of each factor.

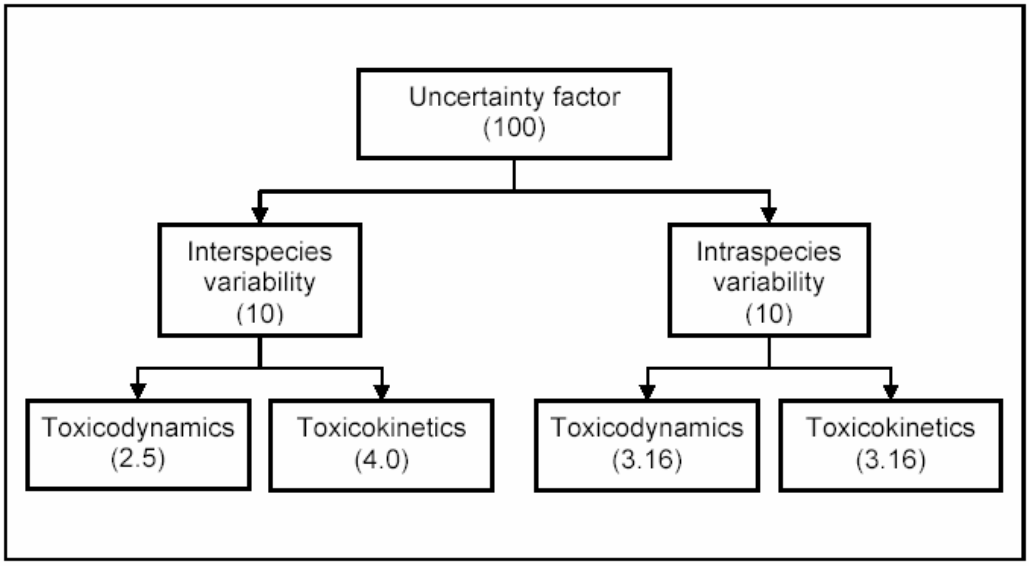

Figure 2.5 Subdivision of interspecies and intraspecies uncertainty factor of 100 typically used in the derivation of health criteria values

Non-threshold toxicity

As discussed in Section 2.2.1, the nature of non-threshold toxicity (predominantly, non-threshold carcinogenicity) is such that no matter how low a guideline is set (unless set at zero), it will, theoretically, never provide an exposure associated with no risk (and therefore the ALARP principle applies – see Section 2.5). Characterising the dose-response for such chemicals is therefore problematic, since it is the dose-response profile at very low exposures and responses that is normally of interest, and only very rarely are sufficient human data available for this to be established.

Two approaches exist to derive HCVs for non-threshold carcinogens: quantitative dose-response modelling and non-quantitative extrapolation.

Quantitative dose-response modelling

Quantitative dose-response modelling, or quantitative risk assessment (QRA) as it is more commonly known, is a procedure used by some authorities to derive numerical estimates of risk (e.g. 1 in 100,000) for exposure to non-threshold carcinogens.[13]

Epidemiological studies with large numbers of subjects may provide sufficient information to establish the low-dose-response profile with reasonable confidence – as is the case for cancer caused by ionising radiation (Cooper *et al.*, 2007). Often, though, no human data are available and estimates are based on data from carcinogenicity bioassays in laboratory animals. The relatively small numbers of animals used in these studies necessitate large doses to be administered to have confidence that any carcinogenic potential of the chemical will be detected, i.e. to avoid getting a **false negative** result. The results of such studies, therefore, provide dose-response data for cancer, but only at doses far greater than the low exposures experienced by the human population.

A variety of mathematical models are available to extrapolate animal carcinogenicity data to low levels of exposure and risk, but the models are generally not based on biological mechanisms (Maynard *et al.* 1995; COC, 2004) and there are significant uncertainties in the extrapolations. Different models may produce cancer risk estimates for the same chemical that differ by orders of magnitude at the same dose, or doses spanning orders of magnitude associated with a specific risk estimate (see Figure 2.6). Most published risk estimates are also presented as the 95% upper confidence limit on the risk[14] rather than the maximum likelihood estimate (statistical 'best guess'). Hence, while such models provide quantitative cancer risk estimates, their purpose is more to be protective of than predictive of cancer risk (Felter and Dourson, 1998; SOT, 2006).

While QRA is used by some public health organisations and non-UK regulatory bodies (e.g. the WHO drinking-water guidelines working group and USEPA), QRA based on animal data has generally not been used in the UK. This is because the UK Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (**COC**) does not recommend its use for routine risk assessment. COC considers that the models do not simulate the carcinogenic processes adequately and is critical of the precision of cancer risk erroneously implied (COC, 1991, 2004).

Even amongst organisations that use and publish quantitative cancer risk estimates, there has been a tendency in recent years to move away from low-dose extrapolation models (such as those in Figure 2.6) to simple linear extrapolation (unless there is evidence of non-linearity). In linear extrapolation, a line is effectively drawn on the dose-response curve from the point of departure to the origin. In practice, linear extrapolation is most simply achieved by calculating the BMD_{10} (the BMD producing a 10% response, or one in 10 response) or $BMDL_{10}$ (the lower 95% confidence limit of the BMD_{10}) and then dividing this by orders of magnitude to achieve the desired risk level, e.g. dividing by 10,000 to give a 1 in 100,000 risk.

[13] Where human data are available, it may be possible to model both risk of cancer (e.g. excess lifetime risk of cancer) and risk of death from cancer. These are sometimes used as though they are synonymous, which they are not; their inter-relation depends on the survival/fatality rate for the malignancy. For example, fatality rates for non-melanoma skin cancer are quite low in Western countries (a few per cent), while for lung cancer they are high (around 95%).

[14] The output of a mathematical model of cancer risk is usually given as an upper confidence limit of the cancer incidence. This limit describes the degree of confidence in the estimated risk against what the model might predict if more data were available. The limit also indicates how well the model fits the data within the dose range for which data are available. It does not, however, describe how well the model reflects the true risks at low doses.

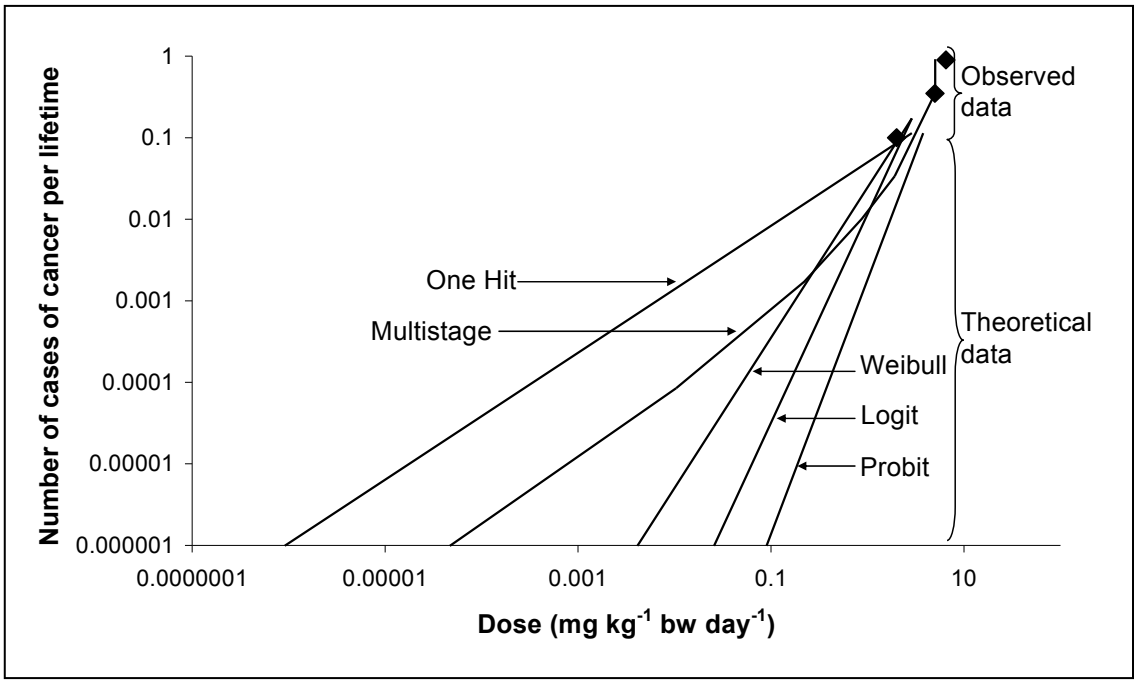

Figure 2.6 Example of variance of quantitative cancer risk models when modelling the same data set (modified from COC, 2004)

Non-quantitative extrapolation

The predominant alternative (non-quantitative) approach to setting HCVs for non-threshold carcinogens involves assessment of all available carcinogenicity dose-response data to identify an appropriate dose without discernible carcinogenic effect, or the lowest dose tested if effects are apparent at all doses, and the use of expert judgement to derive a suitable margin (COC, 2004).

HCVs derived using this approach have previously been called **minimal risk levels**[15] by COC. COC (2004) defined a minimal risk level as "an estimate of daily human exposure to a chemical identified by expert judgement that is likely to be associated with a negligible risk of carcinogenic effect over a specified duration of exposure (usually a lifetime)". Minimal risk levels have been favoured over quantitative cancer risk estimates by COC, since they are considered to carry only a minimal cancer risk and thus fulfil their health protection goal without attempting to quantify the risk and imply a precision which may not be valid.

In practice, the minimal risk level approach is similar to that for threshold chemicals, applying numerical (uncertainty) factors to a point of departure identified from the dose-response data. Where the assessment is based on animal data, it is usually not possible to identify a dose without discernible carcinogenic effect; effect level data are therefore used. Several indices of tumour production that may be used as the point of departure are commonly reported in the experimental carcinogenicity literature. The most common are the BMDL (as for threshold toxicity), the **TD_{50}**, and the **T25**. The TD_{50} is defined as the chronic dose rate that would induce tumours in a given target site(s) in 50% of the test animals at the end of a standard lifespan for the species, provided there were no tumours in control animals. However, since tumours unrelated to the test chemical often occur in control animals, the TD_{50} is better defined as the daily dose

[15] Note these are not the same as the minimal risk levels derived by the US ATSDR.

rate required to halve the probability of remaining tumourless at the end of a standard lifespan (Peto *et al.*, 1994; COC, 2004). The T25 is defined as the dose producing a 25% increase in the incidence of a specific tumour above the spontaneous background rate (COC, 2004).

The uncertainty factor applied must account not only for the potential interspecies and interindividual variation, but also the seriousness of the endpoint (cancer) and the assumption that there is no threshold. Application of a factor of 10,000 to a $BMDL_{10}$ has been proposed, while it has been suggested that this may be inadequate for T25 data (EFSA, 2005a), though these proposals have yet to be universally accepted.

More recently, COC has been developing a margin of exposure approach (see Section 2.4.2) for assessing genotoxic carcinogens when only animal data are available, which is based on the $BMDL_{10}$.

For substances for which there is limited evidence of carcinogenicity and genotoxicity, derivation of a TDI may be appropriate with the uncertainty of potential carcinogenicity incorporated into the uncertainty factors used. For example, an additional uncertainty factor of 10 was used by WHO in setting its TDI for hexachlorobutadiene to allow for limited evidence of carcinogenicity and genotoxicity of some metabolites (WHO, 2004).

2.3 Exposure assessment

No matter the hazards posed by a chemical, if there is no exposure then there is no **risk**; risk is inextricably linked to exposure. Therefore, evaluating and quantifying exposure is as important as characterising the hazards when considering the risk.

Humans may be exposed to chemicals via a number of routes, and the various physicochemical and biological obstacles that may affect absorption mean that different chemicals will gain entry to the body to different extents. In the light of these factors, an extensive terminology has been developed to describe the various facets of chemical exposure. Some of the principal concepts and terminology are discussed here.

Human exposure to chemicals in the environment occurs via three main routes: oral (ingestion), inhalation, and **topical**. In most cases, topical exposure is almost exclusively across the skin and is therefore usually termed **dermal** exposure. The absorption of a chemical through the skin is called dermal absorption or **cutaneous** (or **transcutaneous**) absorption. Absorption of a chemical through the lungs following inhalation is called **pulmonary** absorption.

Following oral exposure, unless the chemical is readily absorbed through the lining of the mouth (like glucose, for example) it will be swallowed and move through the gastrointestinal tract where it may be absorbed into the body and transported to the liver. Once in the liver, some chemicals will be largely returned to the gastrointestinal tract via the bile, while others will mostly enter the **systemic circulation**. Some chemicals undergo significant **first-pass metabolism** in the liver before entering the circulation and being distributed around the body.

In addition, some or all of an ingested chemical may not be absorbed, but may remain in the gut and be excreted. In such cases, unless the chemical has a toxic action directly on the gut lining or on the **gut microflora** it will be unable to cause an adverse response.

The proportion of an ingested dose (intake dose)[16] of a chemical that is absorbed from the gut into the body and reaches the systemic circulation unchanged (i.e. without

[16] See Section 2.2.2 for information on exposure metrics and units.

undergoing first-pass metabolism) is referred to as the bioavailable fraction. The amount of chemical this fraction represents is known as the **systemic dose** (see Figure 2.7). Hence, the bioavailability of a chemical will be between zero (if no amount of chemical reaches the systemic circulation intact) and one (if all of the chemical ingested reaches the systemic circulation intact), although it is often described as a percentage. The term **uptake dose** is sometimes used to refer to the total amount of chemical that enters the body, including for example for oral exposure that which acts on the liver or is metabolised by the liver before entering the systemic circulation.

Even where absorption is limited and the bioavailability is low, the potential for local toxicity (to the gastrointestinal tract or lung, for example) should not be ignored.

2.3.1 Bioaccessibility

When considering oral exposure, unless kinetic data are available to the contrary, it is usually assumed that the bioavailability of a chemical in humans will be at least the same as in experimental animals. In oral toxicity studies, however, chemicals may be administered via a number of ways (e.g. in drinking-water, in feed, in capsules or by **gavage**), and either with or without solvent vehicles. In the case of humans ingesting chemicals in contaminated soil, however, the chemical may be tightly bound to soil particles or contained within the mineral matrix. In order to become potentially bioavailable, therefore, the chemical must first dissociate from the soil. The proportion of a chemical released from soil following ingestion and digestion, and entering into solution, is referred to as the bioaccessible fraction (see Figure 2.7).

As for bioavailability, the **bioaccessibility** of a chemical will be between zero (all of the chemical remains bound to soil) and one (all of the chemical is released into solution in the gut), although, again, it is often described as a percentage.

When considering oral exposure to chemical contaminants in soil, therefore, there will be an initial ingested dose, of which there will be a bioaccessible fraction, of which there will in turn be a bioavailable fraction[17], which is the systemic dose.

While for some chemicals (as present within soil in their particular chemical form), bioaccessibility will be essentially complete, for other chemicals bioaccessibility may have a measurable impact on bioavailability (and hence risk). An overestimation of the risk of a chemical to humans would only result, however, if the bioaccessibility of the chemical was notably higher in the available epidemiological and/or animal toxicity studies.

While not affecting the hazard characterisation or HCV derivation for a chemical, bioaccessibility considerations may be incorporated into the ultimate risk assessment and, for soil contaminants, could be incorporated into the setting of **Soil Guideline Values** (**SGVs**). This relatively new area of risk assessment is being explored by agencies and academics in several countries. In the UK, attention is primarily focussed on evaluating a range of *in vitro* tests for their ability to accurately and reproducibly predict the bioaccessibility of arsenic from different soil types. Further information on *in vitro* models of bioaccessibility and the use of bioaccessibility data in the risk assessment of chemicals in soil is available via the Environment Agency website.

[17] The bioavailable fraction refers to the fraction of the intake dose that is absorbed, not the fraction of the bioaccessible dose that is absorbed.

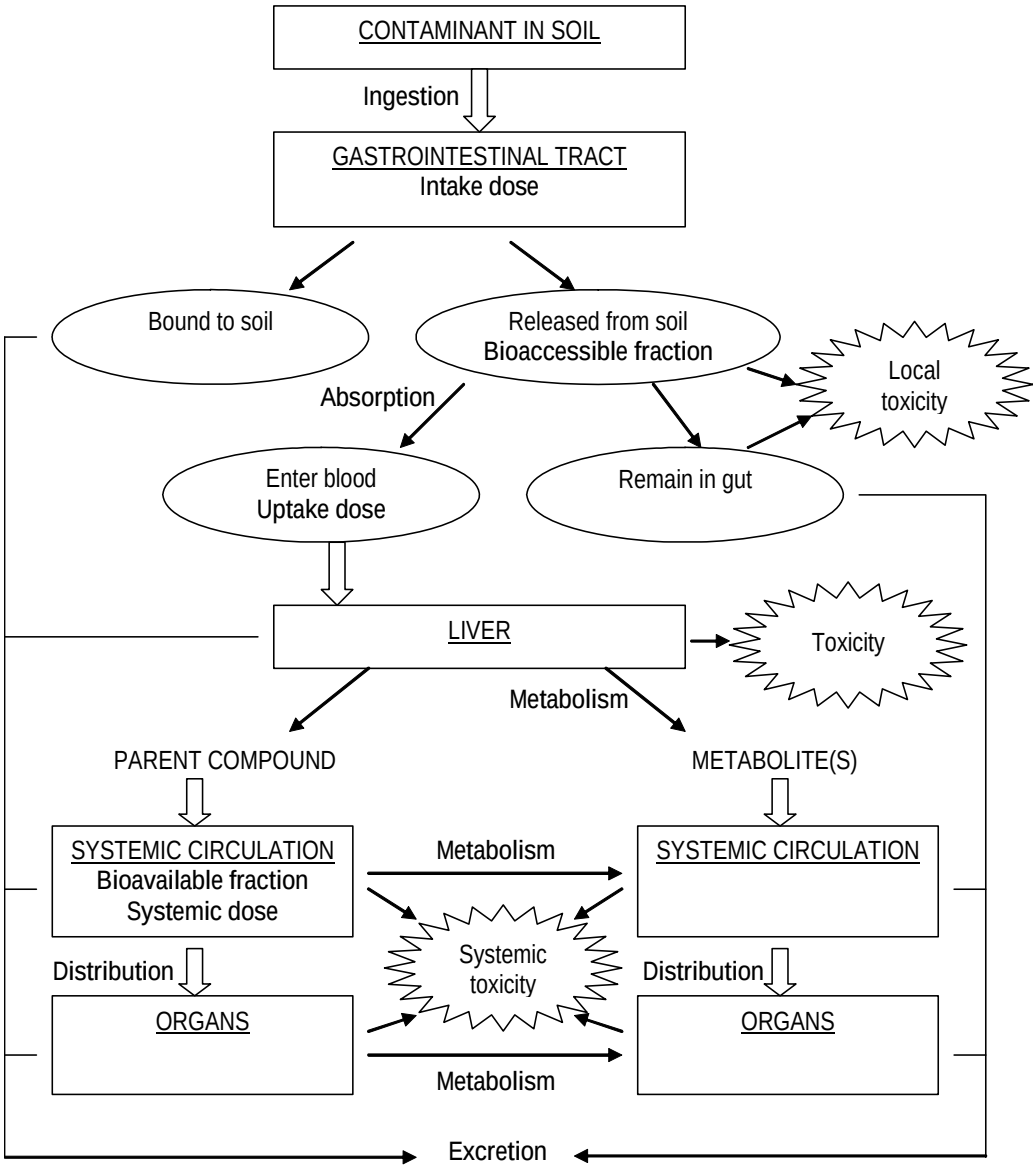

Figure 2.7 Simplified kinetic pathway for oral exposure

2.4 Risk characterisation

Risk characterisation involves consideration of all the physical-chemical, toxicity, kinetic, mode of action and exposure data in order to evaluate the risk posed by the chemical to humans (or a human subpopulation). The approach followed depends on whether HCVs exist for the chemical being assessed. If HCVs are available, the risk is characterised (at least in the first instance) by comparing the estimated human exposure with the HCV. If HCVs are not available, the estimated human exposure is compared directly against data from the available toxicity studies. This second approach is called the **margin of exposure** (**MoE**) approach.

2.4.1 Comparison with a Health Criteria Value

When an HCV is available for a chemical, the first step in the risk characterisation is to compare the estimated human exposure with the HCV (ensuring both values are in the

same units). If human exposure is estimated to be less than the HCV, the risk to humans is not considered of concern; however, if it exceeds the HCV, the implications are dependent on whether the HCV is based on threshold or non-threshold effects.

Threshold HCVs

Lifetime exposures at or below the TDI are considered to be without appreciable health risk, and above the TDI are undesirable but may not inevitably lead to increased health risk. The TDI is not itself a threshold for effect; hence, above the TDI there is a region – specific to each chemical – of uncertainty about the risk.

Often in chemical risk assessment, though less so in the case of contaminated land, it is the consequences of short-duration excursions above the TDI that are of interest. It has been stated that since TDIs are in most cases based on chronic exposures and effects, relate to lifetime exposure and incorporate a margin of safety, short-term exceedances are not of particular concern so long as the average intake over longer periods does not exceed it (IPCS, 1987). Whilst in the main true, this often-heard generalised statement must be interpreted with caution.

The likelihood of adverse health impacts resulting from exposures greater than the TDI can only be considered on a case-by-case basis, but some general principles can guide such an evaluation. These include: the magnitude and duration of the exceedance; whether the TDI is based on an acute or chronic toxic effect; if a chronic toxic effect, whether it is the result of chronic stress or long-term bioaccumulation breaching a threshold **steady-state** body burden; the steepness of the dose-response curve; the difference in NOAEL(s) from short-term toxicity studies from the NOAEL on which the TDI was based; and whether the critical subchronic toxicity is reversible (WHO, 1989; Renwick and Walker, 1993; Larsen and Richold, 1999; Renwick, 1999b; Speijers, 1999; Walker, 1999). The production of a toxic response will depend on the intake causing the body burden to exceed the threshold for toxicity. In this regard, the effect on the body burden of a short period of intake above the TDI will be inversely proportional to the elimination half-life of the chemical (Renwick, 1999a). The consequences of longer-term intakes exceeding the TDI cannot in general be predicted from knowledge of short-term exceedances.

Irrespective of whether a TDI exceedance is short or long-term, it is vital the other toxic effects produced at doses above those causing the 'critical' toxicity used in the HCV derivation be considered. It may be the case, for example, that a serious acute effect (such as death or teratogenicity) occurs at exposures not markedly greater than those producing a less serious chronic effect on which the HCV may have been based. The acute effects may therefore become the critical toxicity when evaluating an exceedance of the TDI (WHO, 1989; Walker, 1999). Consideration of acute toxicity – indeed the entire spectrum of a contaminant's toxicity – must therefore inform not only the derivation of HCVs, but also the assessment of risk in cases where HCVs are exceeded.

For HCVs based on extensive, good quality epidemiology data, where there is less uncertainty and the uncertainty factors are smaller (such as for selenium), much better confidence may be placed in estimates of risk arising from (long-term, especially) exceedance.

Non-threshold HCVs

Because there is no known threshold for the adverse effects of some chemicals, it must be assumed that exposure to these chemicals at or below the HCV will be associated

with some, possibly unquantifiable, low level of risk. Accordingly, it is assumed that any exceedance of the HCV will be associated with an increased risk to health.

2.4.2 Margin of Exposure

The MoE approach, as in HCV derivation, first involves the evaluation of all the available toxicity data and selection of the critical point of departure. When using animal toxicity data, the point of departure is usually a NOAEL, LOAEL or BMDL for threshold chemical toxicity, or a BMDL, T25 or TD_{50} for non-threshold carcinogenic effects. In the MoE approach, however, the point of departure is directly compared against the estimated exposure of the human population; that is, the point of departure (in mg kg^{-1} bw day^{-1} or mg m^{-3}, for example) is divided by the human exposure to the chemical (in the same units). The resulting ratio is the MoE. Attention is then focussed on whether the MoE is considered adequate for safeguarding public health.

Acceptability of the size of the MoE will depend on a variety of factors including the quantity and quality of toxicity data available, the species for which data are available, the critical adverse effect (including whether it is expected to have a threshold or not), and the expected duration of human exposure. The MoE is therefore analogous to the total uncertainty factor used in the derivation of an HCV – though they may differ with respect to duration of exposure considerations. When evaluating the MoE, the size of the uncertainty factors used in the derivation of HCVs (see Section 2.2.5) serves as a useful, though by no means complete, guide.

The MoE may be the preferred approach for an assessment when an established HCV is not available. In these instances, even when toxicity data are limited, a preliminary judgement about the potential risk posed by a chemical may be made by calculating the MoE. This can be used to inform the risk manager and decision-making process in the absence of a detailed risk assessment. The MoE approach has recently, for example, been used by the European Food Safety Authority (EFSA) to assess the potential risks posed by the presence of non-dioxin-like polychlorinated biphenyls in food (EFSA, 2005b).

2.5 Risk management

A fifth step, which is not part of risk assessment, but which is required where an assessment concludes there is an unacceptable risk, is risk management. Risk management involves taking practical steps to mitigate the identified risks such that they are eliminated or at least reduced to an acceptable level.

In the workplace, this might include the wearing of respirators or protective clothing, improving the ventilation, or limiting the amount of time employees may spend in a particular area. In the case of contaminated land, the main risk management options are removing or remediating the soil, putting in place physical barriers to block exposure pathways, or restricting the use of the land.

In the case of chemicals believed to act via non-threshold mechanisms (such as most genotoxic carcinogens), the ALARP principle will automatically apply in the UK. The ALARP principle ensures that, irrespective of whether a health-based guideline is being breached or not, exposures are kept ‘as low as reasonably practicable’.

2.6 Review of key points

Chemical risk assessment is commonly described in four steps: hazard identification, hazard characterisation, exposure assessment, and risk characterisation. For the majority of chemicals, most data used to identify and characterise the hazards of a chemical will come from toxicity studies in laboratory animals. Although toxicity studies have been refined in recent decades, the basic objective of regulatory toxicity studies has largely remained unchanged: to identify the hazards and, for those effects expected to have a threshold, to identify the NOAEL.

NOAEL values (or LOAEL values where effects were seen at all doses) will ideally be identified for each of the (threshold) adverse effects identified in each of the available toxicity studies. Expert judgement must be used to select which of these values is the most appropriate from which to derive a TDI for humans.

In addition to basing the TDI on one of the discrete dose levels from the toxicity studies (i.e. the NOAEL or LOAEL), it is sometimes possible to model the dose-response data to calculate the BMDL, which may be used in place of the NOAEL. Because toxicity studies have not traditionally been designed to determine the shape of the dose-response curve, however, BMD modelling is not always possible or apposite.

The TDI is derived by applying uncertainty factors to the point of departure identified from the dose-response data (NOAEL/LOAEL/BMDL). The uncertainty factors must together account for the total uncertainty in the derivation, including the potential increased susceptibility of humans compared to laboratory animals (default factor of 10) and the diversity of response that may be seen within the human population (default factor of 10) as well as other factors such as limitations in the toxicity database and/or use of a LOAEL instead of a NOAEL.

Where a TDI exists for a chemical, risk characterisation is achieved by comparing the estimated human exposure against the TDI. Where a TDI does not exist, the risk may be characterised using the MoE approach, by dividing the experimental point of departure (NOAEL, LOAEL or BMDL) by the estimated human exposure, and judging the level of concern based on the magnitude of MoE considered against the uncertainty in the assessment (analogous to the consideration of uncertainty in deriving a TDI).

While most adverse effects caused by chemicals are expected to demonstrate a threshold, for some effects the underlying mode of action is such that there is no basis to assume such a threshold. Genotoxicity and mutagenicity are the most commonly encountered examples of such effects. In the absence of data to the contrary, it is assumed that chemicals that have shown evidence of genotoxicity or mutagenicity may cause cancer in humans via mechanisms that do not show a threshold; hence, any exposure has the theoretical potential to cause an effect. TDIs cannot be derived for such chemicals and a different approach to HCV derivation is required.

If suitable carcinogenicity data are available in humans, these may be used to derive quantitative estimates of cancer risk. Animal studies may provide an indication of how potent a carcinogen the chemical is; however, to ensure that any carcinogenic potential is detected in the relatively small number of animals used in such studies, the doses used are quite high, usually much higher than any predicted human exposure. Such studies therefore do not permit characterisation of the hazard at the much lower levels of exposure experienced by humans. Despite this, models do exist which provide cancer risk estimates from animal data, but use of such models in routine risk assessment is not recommended by the relevant expert committee (COC) in the UK. Where an assessment is based on animal data, non-quantitative approaches such as the MoE between human exposure and the most appropriate $BMDL_{10}$ for **tumourigenicity** provide an indication of the level of concern for public health.

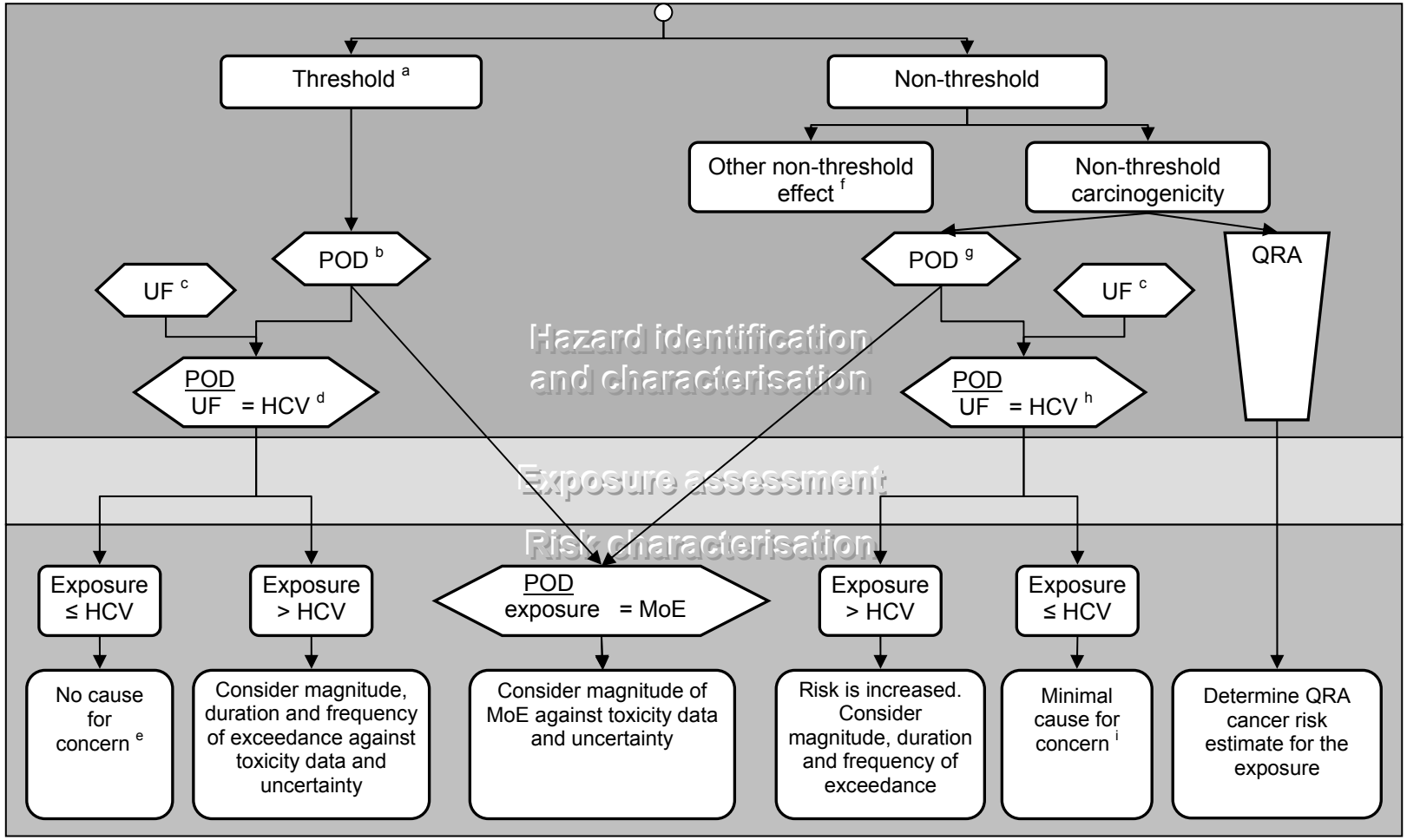

Figure 2.8 Summary of the risk assessment process

[a] Including threshold carcinogenicity.

[b] Point of departure for deriving an HCV based on threshold effects is normally a NOAEL, LOAEL or BMDL. For calculating an MoE based on threshold effects, other data points may also be used if NOAEL/LOAEL/BMDL values are not available.

[c] Uncertainty factor.

[d] For example, TDI.

[e] Dependent on the basis of the derived HCV and the purpose of the assessment.

[f] Non-carcinogenic non-threshold effects may be addressed in different ways, including approaches similar to those for threshold chemicals or non-threshold carcinogens, or using an alternative, possibly chemical-specific, approach.

[g] Point of departure for calculating an MoE for a non-threshold carcinogen, e.g. BMDL or T25.

[h] This type of HCV has been given various names by different groups. Within the remainder of this report, however, an HCV derived for a non-threshold carcinogen soil contaminant in accordance with the methods presented in Section 3, whether quantitative or non-quantitative, is termed an Index Dose.

[i] Dependent on the basis of the derived HCV and the purpose of the assessment; however, ALARP nevertheless applies.

3 Framework for toxicological risk assessment of chemical contaminants in soil

This section outlines a framework for conducting a toxicological risk assessment and for deriving HCVs that may be used in the setting of SGVs. It addresses the collection and evaluation of data, as well as the risk assessment and HCV-derivation processes. Information is provided in the final sections on the assessment of mixtures of chemicals and consideration of exposure via multiple routes (that is, oral, inhalation and dermal).

3.1 Collection of data

A fundamental element of risk assessment is the comprehensiveness of the literature search on which it is based. A wealth of toxicological data sources are available and a host of databases and electronic search engines for conducting searches. Information and data may be found in books, peer-reviewed journals, reviews and reports by industry, government and non-governmental organisations, and in electronic articles on the worldwide web, to name a few.

The literature search should be sufficiently broad in both number of sources and search terms to encapsulate the latest and most salient information. A record should be kept of the strategy used to identify information, including a list of all sources searched and the search terms or method used. The record should be sufficiently detailed for a third party to be able to complete a duplicate search and produce the same results.

A list of some useful sources of information is provided in Appendix A. This list is by no means exhaustive and would be expected to constitute the minimum requirements of a literature search used for the risk assessment of chemical soil contaminants in the UK.

3.2 Evaluation of data

The wealth of accessible sources of chemical and toxicological information appearing in recent years – not least, those created as a result of the worldwide web – means that it has never been easier to locate information. However, much of this information is found in secondary sources, which often do not provide reference citations or a bibliography, or any satisfactory identification of the sources used to create the article. Such articles are also often undated.

Where the quality or authenticity of information in secondary sources is questionable, every attempt should be made to identify the original source documents for evaluation and corroboration. Caution and professional judgement should be exercised when considering the value of information identified during a search. This remains true even for peer-reviewed publications, which cannot simply be assumed to be of good quality.

Various standard protocols for toxicology studies have been produced, which may be used to evaluate a study. The guidelines for the testing of chemicals of the Organisation for Economic Co-operation and Development (OECD), for example, set out internationally harmonised methods for most routine and regulatory toxicology studies. However, the science of toxicology and consequently such protocols have changed over recent decades, and will continue to do so. It is therefore essential that

the risk assessor has sufficient expert knowledge of the subject to recognise studies of good quality and also the limitations of older studies or those not conducted to modern standards.

Often, much information may be available in reviews by well-respected chemical risk assessment bodies (including those listed in Appendix A). The preparation of such expert group reviews should have been sufficiently robust and authoritative to have confidence in the use of their interpretations and conclusions. However, the risk assessor should be capable of challenging an expert group pronouncement if there is due cause; for example, if the science has moved on since its publication.

Often, several expert group reviews will be available for a chemical and may not all concur. This may be a consequence of the timing of the reviews and the data available at the time, or may be due to differences of opinion in the interpretation of a study. In such instances, the risk assessor must choose which, if any, of the interpretations should prevail, being supported by the risk assessor as most justified from the data.

3.3 Collation of data

Just as the collection of data should follow a transparent, documented approach, the collation of data within the risk assessment report should be similarly logical and structured.

The TOX reports for chemical soil contaminants published by the Environment Agency strive to follow a consistent format, to enable quick and easy location of information within the document. While risk assessments prepared by others are not required to follow this format, it is recommended that a similar logical structure be followed, with the information discussed in the following sections presented as a minimum. In all cases, presented text and data should be fully referenced.

Whenever possible, data should be presented using the SI international system of units (see Environment Agency, 2008, for further information). Where source documents have used other units, it is recommended that data be presented in these units with calculated SI equivalents presented afterwards in parentheses.

3.3.1 Physical-chemical characteristics

Detailed physical-chemical data are crucial to SGV derivation, when exposure pathways are quantitatively modelled; however, some knowledge of the physical-chemical characteristics of a substance is also useful when considering its toxicology.

The potential of a chemical to gain entry to the body, the predominant **route of exposure**, and the kinetics of the chemical following absorption are all influenced by the chemical's physical-chemical characteristics. Where available, parameters such as those listed in Table 3.1 should be included in the toxicity risk assessment.

Table 3.1 Examples of physical-chemical data useful for toxicological risk assessment [a]

Parameter	Units
Molecular weight	g mol^{-1}
Physical state at environmental temperatures/pressures	Dimensionless
Solubility in water	mg L^{-1}
Octanol-water partition coefficient (K_{OW} or log K_{OW})	Dimensionless
Soil organic carbon partition coefficient (K_{OC} or log K_{OC})	L kg^{-1}
Acid dissociation constant (pKa)	Dimensionless
Henry's Law constant	Pa m^3 mol^{-1}
Vapour pressure	Pa

a Further information on the collation of information for these parameters can be found in Environment Agency (2008)

3.3.2 Toxicokinetics

Where available, data should be presented on the kinetics of the contaminant in humans (and any subcategories of the human population) and all laboratory animal species, particularly those for which toxicity data are available. This information is required to evaluate the appropriateness of any animal models used in the toxicity assessment and identify potentially sensitive groups within the human population. In some cases, where good quality data are available, they may be used to refine the uncertainty factors used to account for interspecies and interindividual variability in the derivation of HCVs (see Section 2.2.5).

Information should be presented on absorption, distribution, metabolism and excretion. Examples of data concerned with absorption include the rate of absorption, the extent of absorption and bioavailability. For distribution, the mechanism by which the substance is distributed around the body (e.g. bound to protein in the blood) and the organs accessed by the substance and in which it preferentially resides[18] are the key factors. Whether the substance is able to cross the **blood-brain barrier** and the placenta is of particular note. Regarding metabolism, information should be included on the rate (e.g. **elimination half-life**) and extent of metabolism, with details of the metabolites produced (note: metabolism does not always result in removal or reduction of the toxic hazard – metabolite(s) may be the principal toxic entities responsible for the adverse effects observed). Information on **first-pass metabolism** is also important when considering **route-to-route extrapolation** (see Section 3.4.4). Excretion data are useful in evaluating absorption as well as residence time of the chemical in the body. In combination with knowledge of its metabolism, excretion data may provide information on whether a chemical undergoes **enterohepatic recirculation**, thus resulting in prolonged exposure.

The route of exposure (oral, inhalation or dermal) can affect not only absorption, but also distribution, metabolism (including first-pass metabolism) and excretion. Complete

[18] The tissues/organs most affected by a chemical are often not the site of the chemical's highest concentration, but rather the site or tissue with the greatest susceptibility to damage by that chemical or its metabolites (Covello and Merkhofer, 1993).

kinetic information should therefore be sought for each route of exposure, though there may be considerable data gaps in this area (which are taken into account in setting uncertainty factors).

In all aspects of toxicokinetics, both qualitative and quantitative information may be useful.

3.3.3 Toxicity

Toxicity data for chemical soil contaminants may be extensive, covering different types of study investigating different endpoints, of varying study duration, with different treatment strategies and routes of exposure, and possibly in several species. The data should therefore be presented in a logical and structured manner to enable readers to locate data readily and ensure transparency in the assessment and HCV derivation.

The typical structure of toxicity reviews by risk assessors, especially when reviewing primary data, is shown in Table 3.2 for reference. There is no requirement for chemical risk assessments for soil contaminants to follow this structure – and the final structure adopted will often be dictated by the extent and profile of the data available – but efforts towards harmonisation should aid any quality assurance checking or auditing.

Table 3.2 Suggested structure for presentation of toxicity data

Subheading level 1: Type of study	**Subheading level 2: Route of exposure/ administration**	**Subheading level 3: Species**
Acute toxicity	Oral	Human Mouse Rat Dog Other species
	Inhalation	[c]
	Dermal	[c]
	Other routes [a]	[c]
Short-term repeat dose toxicity studies (subacute studies)	[b]	[c]
Longer-term toxicity studies (subchronic studies)	[b]	[c]
Chronic toxicity studies	[b]	[c]
Reproductive toxicity studies	[b]	[c]
Developmental toxicity studies	[b]	[c]
Genotoxicity studies	*In vitro* prokaryotic assays *In vitro* eukaryotic assays *In vivo* assays	
Carcinogenicity studies	[b]	[c]
Other studies	[b]	[c]

[a] For example, intravenous, intramuscular, intraperitoneal, subcutaneous, intraocular.
[b] Level 2 subheadings should follow those presented under Acute toxicity.
[c] Level 3 subheadings should follow those presented under Acute toxicity, Oral.

3.3.4 Background intake

Knowledge of the toxicity of a chemical and the exposure of human receptors arising from its presence in soil does not alone provide a true picture of the toxicological risks to humans; it only points to the risks originating from the soil. Concurrent exposures from other, non-soil, sources must also be considered in order to evaluate the overall risks to public health.

In the case of contaminated land, the main other sources of exposure contributing to the so-called 'background intake' will be from food, drinking-water, and ambient air. Thus, information on such intakes by the UK population should be included.

In some cases, other, possibly significant, exposures may exist as a result of individual human behaviours (such as smoking or extreme dietary habits) or occupations. While it may not be appropriate to incorporate such exposures into the risk assessment (see Section 3.4.1), information should nevertheless be presented where available.

3.4 Derivation of Health Criteria Values

In any risk assessment, the derivation of HCVs should be transparent, with explanatory text accompanying the numerical derivations and proper justification for the decisions taken in the derivation process.

This section describes the principal processes for deriving HCVs for individual soil contaminants, as used by the Environment Agency. The method followed for deriving an HCV is dependent on whether the critical adverse effect is produced via a threshold or non-threshold mechanism of toxicity. These methods are discussed separately in Sections 3.4.1 and 3.4.2 below.[19]

The approaches described should be used to derive HCVs for both oral and inhalation exposure[20]. Where data are insufficient for direct HCV derivation, it may be possible to use route-to-route extrapolation to indirectly derive an HCV for one route of exposure based on data for a different route. This concept is described in Section 3.4.4.

[19] Note: A chemical may produce both threshold and non-threshold effects and the critical effect via one route of exposure may be a threshold effect while for another route of exposure may be non-threshold.

[20] Exposure to chemical contaminants in soil will usually also be via dermal exposure. However, only rarely are sufficient dermal toxicity data available from which HCVs may be derived. Thus, the CLEA model does not require a dermal HCV in deriving SGVs. Instead, it compares both oral and dermal exposure against the oral HCV – with the default assumption of 10% dermal absorption, which may be refined if dermal absorption data are available for the contaminant (see Environment Agency, 2009). In keeping with this approach, our guidance does not specifically refer to the derivation of dermal HCVs. If, when reviewing the toxicity of a contaminant, the data show that toxicity via the dermal route is significantly different to that from the oral route – and would not be appropriately accounted for using this approach – this should be addressed specifically.

3.4.1 Threshold toxicity

As mentioned in Section 3.3.4, exposure to chemicals in soil should be considered against other exposures from non-soil sources (Defra, 2006). This section describes how the HCV for contaminants displaying threshold toxicity, the TDI, is derived, as well as how background exposure should be accounted for.

Derivation of the tolerable daily intake

TDIs should be derived according to standard international practice, using the process described in Section 2.2.5, with the application of uncertainty factors to a point of departure (NOAEL, LOAEL or BMDL) identified for the critical endpoint of concern from the pivotal toxicity study. Where possible, TDIs should be derived for each route of exposure (i.e. $\mathbf{TDI_{oral}}$ and $\mathbf{TDI_{inh}}$), preferably directly from toxicity data for that route; otherwise, if appropriate, by using route-to-route extrapolation (see Section 3.4.4).

For the chemical contaminants most commonly found in soil from historical industrial use, there will often be risk assessments available which have already derived HCVs. These may have been prepared by a UK, EU, foreign national, or international body to assess the contaminant in the environment, in food or in drinking-water, for example, or to register a chemical product such as a pesticide.

Often, existing risk assessments offer a good foundation for a new evaluation, and may sometimes provide a thorough review of salient data and studies for a chemical. In such cases, it may be appropriate to adopt HCVs already proposed by these bodies.

Existing HCVs should not, however, be adopted naively. The risk assessor must be sufficiently familiar with the practices of domestic and foreign agencies to give due consideration to the appropriateness of adopting these HCVs. Such a decision will include the reputation of the organisation, the date and purpose of the assessment, and the basis and precise definition of the health criteria derivation. As discussed in Section 2.2.5, for example, the derivation of RfDs and RfCs by USEPA largely follows the same principles as those used in the UK to derive TDIs; however, RfDs and RfCs are based on non-cancer effects only. Thus, it will normally be inappropriate to adopt an RfD or RfC for a contaminant if it is a non-threshold carcinogen. The World Health Organization (WHO), on the other hand, may derive a TDI for a drinking-water contaminant, but then take other considerations such as technological and economic feasibility into account when establishing its guideline for drinking-water quality (WHO, 2004). Extrapolation from the drinking-water guideline may therefore not be appropriate and the underlying TDI must be sought.

The risk assessor must also be sufficiently experienced to be able to question an expert group evaluation of a chemical and be capable of deriving an HCV *de novo* if appropriate. Indeed, if HCVs have been derived for a contaminant by several different organisations, only rarely will they all concur. A UK pronouncement should normally be given preference; however, the use of expert judgement is essential in evaluating the relative merits of each assessment, and proposing which, if any, should be adopted.

Even where recent, high quality reviews are available, other literature should not be disregarded. Expert group pronouncements can sometimes take years to be published, and it is especially important that studies published after such deliberations are not overlooked.

Background exposure and estimation of the mean daily intake

Persons exposed to chemical contaminants in soil may be subject to exposure from other sources – principally ambient levels of contaminants in food, drinking-water, and air. The risk assessment therefore needs to make allowance for these other exposures.

At the individual level, additional factors such as occupation or lifestyle (such as smoking) may contribute to total exposure. Such exposures may vary widely between individuals and may not be readily quantifiable. Where exposure to chemicals from such sources is known, it should be acknowledged and any data presented. However, it is generally not appropriate to include these types of exposure in the assessment.

A balanced consideration of background exposure should be achieved by estimating the **mean daily intake** (**MDI**)[21] for the UK population for oral exposure ($\mathbf{MDI_{oral}}$) and inhalation exposure ($\mathbf{MDI_{inh}}$). The MDI should be reported in units of mass per day (e.g. μg day^{-1}).

In the absence of direct data on daily intakes, the MDI for a contaminant can be estimated from published information on the concentration of the chemical in the media of concern, together with information on the exposure frequency and duration. In general, the media of concern will be food, drinking-water and air (ambient and indoor).

Daily intakes from food consumption may be derived from data published by the Food Standards Agency (FSA)[22], although other published sources may be used for those contaminants not included in recent FSA surveys. Concentrations of contaminants in drinking-water and ambient air can be obtained from the literature (see Appendix A for some examples). Where available, UK data should be used; otherwise, international data or data for another country may be used. If non-UK data are used, consideration should be given to the likely extent to which they reflect the current UK situation.

To calculate human intakes from contaminant concentration data for water and air, default values for various physiological parameters (bodyweight, inhalation rate, and drinking-water consumption) must be used. The default values for adults are provided in Table 3.3 (more extensive data for various age groups are provided in Environment Agency, 2009).

Table 3.3 Default values for adult physiological parameters

Parameter	Default value	Units	
Bodyweight	70	kilograms	(kg)
Inhalation rate	20 [a]	cubic metres of air per day	(m^3 day^{-1})
Drinking-water consumption	2 [b]	litres per day	(L day^{-1})

[a] WHO (2000)
[b] WHO (2004)

MDI_{oral} and MDI_{inh} values estimated using the above approaches are appropriate for the average UK adult. In order to apply an adult MDI to children, it is necessary to take into account factors such as children's dietary intakes and respiration rates compared to a

[21] Use of the MDI as the measure of pre-existing background exposure in the risk assessment accepts that a proportion of the population may receive total intakes that exceed the TDI.

[22] Formerly published by the Ministry of Agriculture, Fisheries and Food, until April 2000.

typical adult. Although lower in absolute terms, children's dietary intakes and respiration rates are greater than those of adults per unit of bodyweight. Table 3.4 summarises the correction factors that are applied by the CLEA model (see Environment Agency, 2009) to adult MDI data for different infant and juvenile age groups. The correction factors are applied directly to the adult MDI in units of mass per day. For example, an adult oral MDI of 10 mg day^{-1} (equivalent to 0.14 mg kg^{-1} bw day^{-1} for a 70 kg adult) corresponds to an MDI of 7.4 mg day^{-1} for a five- to six-year old child (equivalent to 0.37 mg kg^{-1} bw day^{-1} assuming a bodyweight of 20 kg).

If no data or information on background exposure are available, background exposure should be assumed to be negligible and the MDI set to zero for all age groups. If only qualitative information is available, judgement will be required as to how it should be quantitatively accounted for.

Use of TDI and MDI data in setting Soil Guideline Values

The basic starting principle for establishing SGVs is that they are set such that the estimated Average Daily Exposure (ADE; see Environment Agency, 2009) to a chemical arising from its presence in soil at its SGV, when added to its background exposure (MDI)[23], equals its TDI (i.e. ADE + MDI = TDI). For some contaminants, however, the MDI may already occupy a high proportion of the TDI or may even exceed it. It would therefore be impracticable to propose SGVs on this basis without reserving a minimum proportion of the TDI for exposure from land. Defra (2008b) proposed the pragmatic default that land should be allowed to contribute at least half the TDI; thus, the following conceptual 'rules' are used in setting SGVs:[24]

- If MDI < ½ TDI, ADE = TDI – MDI
- If MDI ≥ ½ TDI, ADE = ½ TDI

In the CLEA Report (Environment Agency, 2009) the portion of the TDI that remains once background exposure has been accounted for is termed the **tolerable daily soil intake** (**TDSI**); thus, ADE = TDSI at the SGV.

[23] The MDI must be converted to units of mass kg^{-1} bw day^{-1} prior to comparison with the TDI.

[24] Details of the processes used to derive SGVs can be found in Environment Agency (2009).

Table 3.4 Correction factors used to adjust adult MDI to younger age groups[25]

Age (years)	Typical bodyweight (kg) [a]	Correction factor for oral MDI	Typical inhalation rate (m^3 day^{-1}) [a]	Correction factor for inhalation MDI
0–1	6.3	0.53	8.7	0.51
1–2	10.2	0.66	13.4	0.80
2–3	13.0	0.65	13.0	0.77
3–4	15.5	0.65	12.5	0.74
4–5	17.3	0.74	12.5	0.74
5–6	19.7	0.74	12.5	0.74
6–7	22.5	0.74	12.9	0.76
7–8	25.4	0.80	12.9	0.76
8–9	27.8	0.80	12.9	0.76
9–10	32.3	0.80	12.9	0.76
10–11	35.7	0.80	12.9	0.76
11–12	40.8	0.81	14.4	0.85
12–13	45.5	0.81	14.4	0.85
13–14	50.5	0.81	14.4	0.85
14–15	57.8	0.81	14.4	0.85
15–16	60.1	0.88	14.4	0.85
16–59	76.6	1.00	17.1	1.00
60–70	76.8	1.00	14.2	1.00

[a] Default bodyweight and inhalation rate values (e.g. 70 kg and 20 m^3 day^{-1} for an adult) are usually used in converting toxicity data – which may come from another country or apply internationally – rather than using more specific values as presented here.

3.4.2 Non-threshold carcinogenicity

This section describes the methods used to derive an Index Dose (ID) – the term used herein to describe an HCV, expressed as a daily dose, derived for a non-threshold carcinogen, which is expected to be associated with a minimal excess risk of cancer. The section also explains how IDs are used in the setting of SGVs.

Deriving an Index Dose

The extent and quality of data available determines which method should be followed in deriving an ID. Data from animal carcinogenicity bioassays may be used to derive an ID by BMD modelling (see Sections 2.2.1 and 2.2.5) of the tumour data and application

[25] Oral correction factors based on dietary surveys. Food consumption rates set by Byrom *et al.* (1995) have been widely used in regulatory risk assessments. However, these data apply only to a limited number of age classes. To correct for all age classes, the approach was applied to a wider analysis of the National Diet and Nutrition Survey (NDNS) data from 1995-2002 (Gregory *et al*., 1995, 2000; Henderson *et al*., 2002). NDNS data were corrected from consumer data to population data by multiplying by the fraction of consumers in each survey category. The Byrom *et al*. (1995) data for children less than one year old were used for age class one.

Inhalation correction factors are the ratio of the average male and female inhalation rates for each age class to the adult rate at age class 17 (age 16–59 years) and are based on the rates used by the CLEA model for residential land use to derive SGVs (Environment Agency, 2009; Lordo *et al*., 2006).

of a large default uncertainty factor of 10,000 to the critical $BMDL_{10}$ (Defra, 2008b). Often more than one type of treatment-related tumour will have been produced in a carcinogenicity study, and sometimes more than one study will be available. Furthermore, BMD software packages contain several models that may each derive a statistically "acceptable" BMD_{10} and $BMDL_{10}$. Consequently, a number of $BMDL_{10}$ values may be produced for a contaminant, and expert judgement must be employed in selecting which should form the basis of the ID derivation. If it is not possible to derive a $BMDL_{10}$, the T25 (see Section 2.2.5) may be used instead, but a much larger uncertainty factor would be required.

This approach is less well developed for use with human data; therefore when sufficient human data are available, alternative approaches may be used, including quantitative dose-response modelling of suitable human cancer data (while acknowledging the imprecision of quantitative estimates of cancer risk; see Section 2.2.5). In such case, the ID should be based on estimates of the dose corresponding to an excess lifetime cancer risk of 1 in 100,000 (10^{-5}) (Defra, 2008b). Where human data are available, but have not undergone or are not suitable for quantitative modelling, it may be possible to propose an ID based on evaluation of the available data and identification of the dose associated with no discernible increase in cancer, and the use of expert judgement to extrapolate this to the wider population (see Section 2.2.5).

As for threshold contaminants, existing evaluations by authoritative groups will often provide a good foundation for a risk assessment of a non-threshold carcinogenic contaminant, and sometimes it may be appropriate to adopt HCVs already proposed by these bodies. Again, HCVs should not be adopted naively, and due consideration should be given to the suitability of the values (for example, use of an HCV based on quantitative cancer risk modelling of animal data would not normally be supported).[26]

Consideration of threshold effects

Whilst a serious adverse heath effect, cancer may not necessarily be the critical toxic effect of a non-threshold genotoxic carcinogen on which the HCV should be based. Such chemicals may also cause other, threshold, adverse effects; hence, for low potency carcinogens the threshold effects may drive the risk assessment.

It is essential, therefore, that risk assessments of genotoxic carcinogens, as for any other contaminant, methodically investigate all toxic endpoints before selecting the critical effect for deriving the HCV.

If a TDI, based on threshold critical toxicity, is proposed for a contaminant that also produces non-threshold effects (either for the same or for a different route of exposure), the ALARP principle (see Section 2.5) will nonetheless apply.

[26] If a guideline for a non-threshold carcinogen has been produced under a different regulatory regime with UK jurisdiction that is less stringent than the derived ID, it may be considered disproportionate to enforce a stricter limit for contaminated land, and therefore inappropriate to set the SGV on the derived ID. In such instances, the ID and SGV may be set based on equivalence to the existing guideline. The guideline should be applicable to the UK population as a whole, and should relate to lifetime exposure. The UK Water Supply (Water Quality) Regulations 2000, for example, specify a limit of 10 $\mu g\ L^{-1}$ for arsenic in drinking-water (HMSO, 2000). In setting this standard, which is equivalent to an estimated excess lifetime cancer risk of about one in 1,000 (10^{-3}) derived from good epidemiology data, technical achievability and economic considerations (the ALARP principle) were taken into account in addition to health protection.

It would not, by contrast, be appropriate to set HCVs and SGVs based on equivalence to UK occupational standards for chemicals (Workplace Exposure Limits), since these relate only to persons of working age, and are based on working hours not continuous lifetime exposure.

This principle applies to all types of contaminants, but is expected to only have notable consequence for non-threshold carcinogens.

Use of IDs in setting Soil Guideline Values

IDs are established for non-threshold carcinogenic soil contaminants at a low level of cancer risk, but often this will not be quantified and even if a quantitative risk estimate is available from good epidemiology data it will be subject to uncertainty. It is therefore accepted that any exposure to these contaminants from other, non-soil, sources will increase the overall risk of cancer of an individual, but this is not accounted for in the setting of the SGV; the SGV is based on the ID without consideration of the MDI. This is in line with current standard practice; for example, WHO does not consider other sources of exposure when setting a drinking-water guideline for a non-threshold carcinogen.

3.4.3 Other non-threshold effects

In addition to carcinogenicity via some genotoxic mechanisms, other adverse endpoints may also display no threshold of effect. The approach that should be adopted to derive HCVs for such contaminants will be dependent on the chemical and its critical adverse effects. It may be appropriate to follow, either in full or in part, one of the approaches described above for threshold contaminants or non-threshold carcinogens, or a chemical-specific approach may be appropriate.

The critical toxicity of lead, for example, is its ability to impair cognitive development, especially of children, and there appears to be no discernible threshold for this detrimental effect (although this could be due to the background exposure being above the threshold). Unlike cancer, which is a discrete binary endpoint, the effect of lead on neurological development is a continuous variable. In setting the HCV for lead, therefore, it is not possible to use disease risk estimates such as 1 in 100,000 (10^{-5}). Instead, the HCV is selected from all available toxicological and clinical (human) data.

3.4.4 Route-to-route extrapolation

The approaches described above should be used to derive HCVs for both of the primary routes of exposure – oral and inhalation[27] – based on toxicity data for that exposure route. Where data are insufficient to derive a HCV for one route of exposure, it may be possible to use route-to-route extrapolation to indirectly derive the HCV based on data for a different route of exposure.

Route-to-route extrapolation is used in instances of limited data for a specific route of exposure. By definition, therefore, it involves an additional level of uncertainty and must follow methods that aim to avoid underestimation of toxicity.

In order to use this technique, there must be adequate data for at least one route of exposure to enable an initial hazard characterisation for that route. The toxicity data for that route must also show that the predominant adverse effects, including the critical toxic effect, are systemic effects, not local effects at the site of contact. In addition, knowledge of route-specific metabolism (such as digestive breakdown in the gut and/or first-pass metabolism following ingestion) and whether the parent compound or a metabolite(s) is primarily responsible for the toxicity observed will also indicate whether route-to-route extrapolation may or may not be appropriate.

[27] As previously discussed, HCVs would not normally be derived for dermal exposure. The CLEA model considers oral and dermal exposure together, comparing the combined oral-dermal exposure with the oral HCV; it cannot consider dermal exposure separately.

If the contaminant is particulate, knowledge of the particle size will also inform the likelihood of pulmonary absorption. Particles with an aerodynamic diameter less than 10 μm may be expected to reach the **alveoli** in the deep lung. For these so-called **respirable particles** the default is to assume 100% pulmonary absorption. Particles with an aerodynamic diameter of 10–100 μm, however, are less likely to reach the deep lung, but will be deposited in the upper respiratory tract. Following deposition, the body will attempt to remove these **inhalable particles** via **mucociliary clearance**, ultimately ending up in swallowing into the stomach. For these particles, therefore, toxicity following inhalation may be expected to be similar to that following direct ingestion (IGHRC, 2006).

The practice of route-to-route extrapolation has recently been reviewed by the Interdepartmental Group on Health Risks from Chemicals (IGHRC). The principles put forward in its report (IGHRC, 2006) should be followed in using route-to-route extrapolation to propose HCVs, and the IGHRC report should be consulted for further guidance.

In general, chemical toxicity data are more abundant for the oral route than the inhalation route (and good dermal data are not often encountered). In proposing HCVs for soil contaminants, therefore, oral to inhalation will be the extrapolation most commonly employed. IGHRC (2006) provides a decision tree and conversion factors for, respectively, considering and applying this extrapolation. It is important to recognise, however, that these generic considerations were proposed to guide the process of route-to-route extrapolation; they do not replace the need to consider chemicals on a case-by-case basis with expert judgement (IGHRC, 2006).

For some volatile chemicals, toxicity data may principally be available for the inhalation route, but consideration must also be given to oral exposure from soil. In such an instance, the use of inhalation to oral extrapolation may be appropriate. Whilst pulmonary absorption is likely to be at least as great as oral absorption, extrapolation of inhalation toxicity data may underestimate oral toxicity if metabolism following ingestion (for example by digestive enzymes, gut microflora and/or first-pass metabolism by the liver) produces chemical entities that are more toxic than the parent compound. In the absence of data on the extent of pulmonary or oral absorption, 50% pulmonary absorption and 100% oral absorption should be assumed for inhalation to oral extrapolation (IGHRC, 2006).

In all uses of route-to-route extrapolation, the potential effects of all metabolic and kinetic inter-route differences must be considered and incorporated, and a precautionary approach should always be adopted in areas of uncertainty or where data are lacking.

3.5 Risk characterisation

This section briefly describes the basic approaches to risk characterisation, which are dependent on whether the contaminant displays threshold or non-threshold critical toxicity, and whether HCVs are available.

Risk assessment has thus far in this report primarily been described in the most basic context – that is, exposure to a single contaminant via a single route of exposure. In reality, exposure will be to multiple contaminants, normally via more than one route of exposure. The overall risk assessment must therefore consider both the totality of the hazards – the numerous chemical contaminants that may be present at a site – and the exposures – simultaneous exposure to a contaminant via ingestion and/or inhalation and/or skin contact. These aspects of risk characterisation are also addressed here.

3.5.1 Risk characterisation of contaminants with a TDI

As discussed in Section 2.4.1, exposures equal to or less than the TDI are considered to be without appreciable health risk. Where an SGV is available for a threshold contaminant, soil contaminant concentrations equal to or less than the SGV would normally be considered similarly tolerable.[28]

Where a TDI is expected to be exceeded, this is undesirable but does not necessarily mean that adverse health effects will result. The likelihood and severity of health impacts from TDI exceedances need to be considered on a case-by-case basis and require expert judgement. Section 2.4.1 provides examples of some of the considerations that should form part of such an evaluation.

3.5.2 Risk characterisation of contaminants with an ID

IDs are derived for contaminants for which a threshold for adverse effects cannot be presumed. Exposure at the ID is therefore considered to carry some, albeit minimal and often unquantifiable, level of risk. Where exposures are predicted to be below the ID, the consequential risks are expected to be minimal, but the overriding risk management (see Section 2.5) requirement for exposures to be kept as low as reasonably practicable (ALARP) still applies.

Where an ID is exceeded, there will be an increased risk to health. The significance of this increased health risk requires expert judgement, but often will not be quantifiable.

3.5.3 Hazard and risk characterisation of mixtures of chemicals

Knowledge about the toxicology of a chemical comes mainly from studies in which relatively large doses of the substance are administered to experimental animals. In contrast, the human population is exposed to vast numbers of chemicals every day, including many priority soil contaminants. The possibility exists, therefore, that the cocktail of chemicals to which humans are exposed will have a greater cumulative effect on health than that predicted by risk assessments of individual chemicals.

The possible effects on toxicity resulting from the presence of other toxicants will not only depend on the number and identity of the chemicals, but also on their absolute concentrations and relative proportions. In addition, the toxicokinetics of different chemicals will determine whether non-concurrent external exposure will result in combined systemic exposure. Lasting effects of a chemical may also affect those of another even when the exposures do not overlap. With almost infinite permutations that could be envisaged, routine toxicity testing of chemical mixtures is clearly impossible. The pressures on the use of experimental animals – primarily ethical and financial – means that even rudimentary testing of a limited number of the chemicals in existence, to the extent that the findings would be sufficiently informative, is not viable.

Even epidemiology studies, while based on human subjects exposed to multiple chemicals, are of limited value in informing about chemical mixture toxicity, because the chemical exposures involved are usually ill-defined and there is often only sufficient

[28] It is possible for a high MDI to result in total exposure exceeding the TDI even when the SGV is not exceeded. However, in such an instance the exposure from the land would alone be considered tolerable (it would, in fact, be at most half the TDI, in theory) and the soil contamination would be contributing less than 50% to the total exposure (and therefore risk).

power in the study to investigate the potential effects of one substance or defined group of substances to which the exposure of the test population is unusually high.

It is generally therefore only possible to derive HCVs for individual substances. When assessing the potential risks from chemical contaminants in soil, however, adherence to each HCV does not necessarily eliminate the potential for the chemicals to collectively pose a risk.

In the absence of direct, conclusive data, evaluation of the potential for combination effects of chemicals must in practice rely on assumptions based on knowledge of the modes of toxicity. Four main types of combined action are possible: **dose additivity**, **response additivity**, **supra-additivity**, and **sub-additivity** (COT, 2002; IGHRC, in preparation).

Chemicals with **simple similar action** cause the same biological (adverse) effect via the same mode of action, possibly differing only in their potency. Thus, when administered in combination, the effect will be that which would be seen if either chemical had been given at the total combined dose (after adjustment for differences in potency). This type of action is therefore also known as dose additivity.

Response additivity assumes the modes of action differ between the chemicals, which exert their individual effects and do not modulate the effects of the other chemicals. Thus, when two such chemicals are administered in combination, the effect will be that which would be predicted by adding the response produced by the first chemical to that produced by the second chemical. This is also known as **independent action** or **simple dissimilar action**.

The other two types of combined action are termed **interactions** (COT, 2002). The effect of the interaction may be that the combined effect is greater than that which would be predicted based on additivity, which is variously described as supra-additivity, **potentiation** or **synergy**, or less than would be predicted based on additivity, termed sub-additivity, **inhibition**, **masking**, **antagonism** or **negative synergy**[29] (COT, 2002; IGHRC, in preparation).

Interactive effects may arise due to effects on either toxicokinetics or toxicodynamics and may change at different absolute and relative dose levels of each chemical in the mixture. Prediction of such effects may not be possible based on limited toxicity and mechanistic data. Where there is evidence for chemical interaction, this should be taken into account; when such evidence is not available, each chemical should be assumed to be acting independently. Furthermore, interactions, whether synergistic or antagonistic, often occur only once a metabolic or cellular threshold is breached. Such effects are therefore unlikely at exposures below the HCV (COT, 2002).

Threshold toxicity

For chemicals exhibiting threshold critical toxicity with different modes of action, the potential for additivity is different depending on whether the individual chemicals are present at levels above or below their respective thresholds. If each exposure is below its toxic threshold, and thus the substances are not individually producing effects, it may be assumed that the combination will also not cause an effect; however, if the thresholds are exceeded, there will be potential for response addition. This principle may be extended to the assessment of contaminated land by assuming that exposure

[29] Refer to the Glossary for definitions of these interactions. For more detailed discussion of the types of interactions that can occur, refer to COT (2002) and IGHRC (in preparation).

to threshold soil contaminants with different modes of action at levels below their respective TDIs will not give rise to response addition.

If multiple chemicals are present that act via the same mode of action, dose addition may give rise to an adverse effect even when the exposure to each individual chemical is below its respective threshold (and therefore, in theory, TDI).

In deriving TDIs, consideration should be given to whether contaminants belong to groups with a shared mode of action (such as inhibition of acetylcholinesterase by organophosphate pesticides) and whether it is more appropriate to propose a TDI for the total group rather than for individual members.

For chemical **congeners** that share a common mode of toxic action, but show notable inter-congener differences in potency, the group TDI may need to be defined in units that account for potency as well as dose. Such an approach is used for so-called dioxin-like compounds, which each produce their principal toxic effects via the activation of the aryl hydrocarbon (Ah) receptor, but whose potencies differ over orders of magnitude. Knowledge, albeit crude, of the potencies enabled the assignment of a Toxic Equivalency Factor (TEF) to each compound (see Ahlborg *et al.*, 1994; van den Berg *et al.*, 2006; COT, 2006). The TEF is the potency of the compound relative to a reference compound – in this case, the most potent of the dioxin-like compounds, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. The index of toxicity of a dioxin-like compound is its Toxic Equivalent (TEQ), which is its concentration multiplied by its TEF. The TEQ of a mixture of dioxin-like compounds is the sum of the TEQs for the individual compounds present. The TDI for dioxin-like compounds is therefore also expressed in TEQ – the TDI set by the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (**COT**), for example, is 2 pg TEQ kg^{-1} bw day^{-1} (COT, 2001).

Group TDIs (and hence SGVs) will not always be proposed for groups of chemicals with a common mode of action. This can be due to a lack of adequate data, but will often be because the chemicals are likely to be encountered individually, perhaps much more so than as mixtures.

Where two or more chemicals thought to share a common toxic action are identified in a piece of land, site-specific assessment may make provision for potential dose addition. This is achieved by calculating the Hazard Quotient (HQ) for each chemical by dividing the estimated ADE (see Environment Agency, 2009) by its TDI after consideration of MDI background exposure (i.e. TDSI), and then summing the HQs to give the Hazard Index (HI) (see Figure 3.1). If the HI exceeds unity (i.e. is above one), this equates to exceeding a TD(S)I from potential dose addition. It is therefore treated in the same way as an exceedance of a TDI by a single contaminant.

$$HI = \sum_{i=1}^{n} HQ_i$$

$$HQ_i = \frac{ADE_i \ (mg\,kg^{-1}\ bw\ day^{-1})}{TDSI_i \ (mg\,kg^{-1}\ \ bw\ day^{-1})}$$

where:
HI = Hazard Index
HQ = Hazard Quotient
ADE = Average Daily Exposure from soil
TDSI = Tolerable Daily Soil Intake
n = Number of chemicals present sharing a common mode of toxicity

Figure 3.1 Calculation of the Hazard Quotient and Hazard Index

In practice, where SGVs exist for each of the contaminants, an approximate indication of the potential for dose addition (i.e. the HQs and HI) can be achieved by dividing the soil concentration of each contaminant by its SGV and summing the results.

If two or more contaminants are present for which there is evidence of an interactive effect, be it supra-additive or sub-additive, the likelihood of the interaction occurring at the levels of exposure predicted should be considered before any allowance for interaction is made in the risk assessment. If it is judged that this will not occur at intakes at or below the TDI, then it may be considered irrelevant to the risk assessment if exposures are kept within the limits of the TDIs.

In the absence of evidence for an interactive effect, or for a common mode of action that may give rise to dose additivity, the default should be to assume simple dissimilar action (response additivity).

Non-threshold toxicity

There is a theoretical risk of cancer at any level of exposure to a non-threshold genotoxic carcinogen. When considering exposures to multiple non-threshold genotoxicants, therefore, there may be the potential for combination effects irrespective of the modes of action and whether the chemicals share the same target tissues. Unless there is evidence for a common mode of action, this potential increase in cancer risk does not influence the derivation of IDs (though it may be considered during site assessment using a similar approach to that shown in Figure 3.1 for dose addition of threshold chemicals).

For chemicals with a known or suspected common mode of non-threshold genotoxic action, consideration of dose additivity may be given at the stage of ID derivation by proposing a group total ID. As in the case of threshold toxicity, if data show that members of a chemical group vary notably in their carcinogenic potency, this may be factored into the ID derivation via a potency ranking scale (see earlier discussion of TEFs for dioxin-like compounds).

3.5.4 Consideration of exposure via multiple routes

The procedures described in this report thus far enable the production of HCVs and the characterisation of risk for each route of exposure – or, more rightly, for oral and inhalation exposure, with a consideration of dermal. Where possible, the HCV for each route will be based on studies of toxicity via that route; otherwise, route-to-route extrapolation of data is required (see Section 3.4.4). A TDI_{oral}, for example, will usually be based on studies in which the (usually, laboratory animal) test population has been orally exposed to relatively high levels of the test material, with negligible inhalation or dermal exposure. Human receptors exposed to chemical soil contaminants, by contrast, may be concomitantly exposed to the same contaminant via all three routes of exposure. If the contaminant produces systemic critical toxicity, therefore, each route of exposure may contribute to an aggregate systemic effect even when exposure via each separate route is below its corresponding HCV.

Even if a contaminant has an HCV_{oral} and HCV_{inh}, each derived based on local toxic effects, it is still possible that exposures within these limits could contribute to a total systemic load that results in adverse effects, if systemic effects are seen at intakes not much exceeding those causing local effects (and the HCVs are close to the true thresholds).

Unless the toxicity data indicate otherwise, this should be taken into consideration when proposing SGVs or conducting a site-specific assessment. This is achieved using the mathematical principle set out in Figure 3.2. Using this equation, the sum of the soil exposure/HCV[30] ratios exceeding unity (i.e. greater than one) is considered equivalent to exceedance of an HCV by a single contaminant via a single route of exposure.

This principle and its application in the SGV derivation process are expanded upon in the CLEA report (Environment Agency, 2009).

a) General principle

$$\frac{ADE_{oral}}{HCV_{oral}} + \frac{ADE_{inh}}{HCV_{inh}} + \frac{ADE_{dermal}}{HCV_{dermal}} > 1$$

b) Approach as used in practice by the CLEA model

$$\frac{ADE_{oral} + ADE_{dermal}}{HCV_{oral}} + \frac{ADE_{inh}}{HCV_{inh}} > 1$$

where: ADE_R = Average Daily Exposure from soil (mg kg^{-1} bw day^{-1})
HCV_R = Health Criteria Value (mg kg^{-1} bw day^{-1}) [30]
R = Route of exposure (oral, inhalation and dermal)

Figure 3.2 Consideration of total systemic load from multiple routes of exposure

[30] If the HCV is a TDI, background exposure will need to be taken into account (i.e. the TDSI is calculated and used).

If, at a site, multiple contaminants are present that are expected to share a common target organ and mode of toxicity (i.e. they can be considered a dose additive mixture and should be evaluated as described in Section 3.5.3), and the adverse effect is systemic and exposure is via multiple routes (the conditions for consideration of total systemic load), then the ADE/HCV ratios in the equation presented in Figure 3.2 may be replaced by the HI for each route of exposure.

3.5.5 Risk characterisation of contaminants in the absence of an HCV

For some contaminants there may be no existing health criteria derived by expert groups that are suitable for use as TDIs or IDs, and the available toxicity data may be inadequate for deriving HCVs *de novo* either directly or through route-to-route extrapolation (see Section 3.4.4). Consequently, it will also not be possible to establish SGVs.

Assessment of the potential risk posed by the presence of such a contaminant in land will therefore require site-specific assessment. Predictions of receptor exposures (oral, inhalation, and dermal) to the contaminant should be modelled (see Environment Agency, 2009) and compared with the available toxicity data using the MoE approach described in Section 2.4.2.

Expert professional judgement will be required in appraising the margins of exposure and deciding whether they reasonably preclude an unacceptable risk to health. The extent of knowledge of the contaminant's toxicity – the quality and quantity of data, as well as notable gaps in the knowledge – the nature (seriousness) of the critical toxic endpoint and the profile of receptors will all feed into this decision (see Section 2.4.2).

3.6 Review of key points

A risk assessment is only as good as the data it is based on. Every effort should therefore be made to: capture all salient information and data when conducting the literature search; evaluate the data identified; and present the data in a logical format within the risk assessment report.

For chemicals that produce only threshold toxicity via a particular route of exposure, the TDI (see Table 3.5) and MDI should be calculated, and both figures should be considered in the risk assessment (as a pragmatic approach, Defra (2008b) has suggested that a minimum of 50% of the TDI is reserved for exposure from land).

For contaminants that are expected to cause cancer via mechanisms that may not demonstrate a threshold, the ID (see Table 3.5) is derived. The ID may be derived by the application of a large uncertainty factor to animal tumour data; for example a factor of 10,000 to the critical $BMDL_{10}$ (Defra, 2008b). This approach is less well developed for use with human data; therefore when sufficient human cancer data are available, it may be appropriate to use alternative methods, including QRA (while acknowledging the imprecision of quantitative estimates of cancer risk). When using QRA of suitable human data, the ID is based on estimates of the daily dose corresponding to an excess lifetime cancer risk of 1 in 100,000 (Defra, 2008b). Alternatively, if quantitative assessment is not possible but the dose causing no discernible increase in cancer in humans is identifiable, expert judgement may be used to extrapolate this to the population as a whole with the use of an appropriate uncertainty factor. Contaminants causing non-threshold toxicity may also cause threshold effects, and these should not be overlooked. SGVs for non-threshold carcinogens are set based on the ID and represent a minimal risk from this particular source of exposure (soil); no allowance is made for the MDI.

For other types of non-threshold effect, a chemical-specific assessment may be appropriate, and expert judgement must be employed in selecting the methodology and proposing the HCV.

HCVs should be derived for both oral and inhalation routes of exposure. Derivations should preferably be based on toxicity data for that route of exposure. Where there are insufficient data available for a particular route, it may be possible to use route-to-route extrapolation to propose an HCV.

Where an HCV (or SGV) is exceeded, this indicates that the exposure to the chemical arising from its presence in the land may be of concern. For non-threshold contaminants, which may theoretically pose a risk at any level of exposure, exposures should be kept as low as reasonably practicable (ALARP).

If multiple contaminants are present at a site that share a common adverse effect and mode of toxicity, this should be accounted for. Also, if humans may be exposed to a contaminant(s) via more than one route of exposure, and the critical toxicity of the contaminant is a systemic effect, or an adverse systemic effect may be caused at exposures only a few-fold higher than those causing the critical toxic effect, the total systemic exposure should similarly be considered.

Where toxicity data for a contaminant are sparse and insufficient for deriving HCVs, a site-specific assessment using the MoE approach may be possible.

Table 3.5 Comparison of the tolerable daily intake (TDI) and the Index Dose (ID)

	TDI	ID
Definition	Estimate of the daily intake of a chemical that can be experienced over a lifetime without appreciable health risk.	Estimate of the daily intake of a chemical that can be experienced over a lifetime with minimal cancer risk. [a]
Applicability	Derived for chemicals exhibiting threshold critical toxicity.	Derived for chemicals exhibiting non-threshold carcinogenicity. [a]
Units	Mass per kilogram bodyweight per day (e.g. mg kg^{-1} bw day^{-1}).	Mass per kilogram bodyweight per day (e.g. mg kg^{-1} bw day^{-1}).
Derivation	Application of uncertainty factors to a point of departure (e.g. NOAEL, LOAEL, or BMDL) for the critical adverse effect in the pivotal toxicity study.	Application of a large uncertainty factor to a point of departure (e.g. BMDL) for tumourigenicity from an animal carcinogenicity bioassay. Quantitative dose-response modelling of human cancer data. Application of uncertainty factors to the dose causing no discernible increase in cancer in a human study.
Exceedance	Exceedance is undesirable but does not necessarily carry a health risk. The likelihood of adverse health impacts will be affected by several factors (see Section 2.4.1), and be subject to uncertainty, and can only be judged on a case-by-case basis.	An ID is already considered to be associated with a degree of risk. Therefore any exceedance will be associated with an increased risk to health. The significance of an exceedance can only be judged on a case-by-case basis. [a]
Examples	Most non-carcinogens (e.g. toluene) and non-genotoxic carcinogens (e.g. carbon tetrachloride).	Most genotoxic carcinogens (e.g. benzene).

[a] Where an ID is derived for a contaminant, the ALARP principle will apply since, by definition, it will relate to non-threshold toxicity.

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List of abbreviations

ADI	Acceptable daily intake
ALARP	As low as reasonably practicable
ATSDR	Agency for Toxic Substances and Disease Registry of the US Department of Health and Human Services
BMD	Benchmark dose
BMDL	Lower confidence limit of the benchmark dose
BMR	Benchmark response
COC	Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment
COM	Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment
COMEAP	Committee on the Medical Effects of Air Pollutants
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
Defra	Department for Environment, Food and Rural Affairs
DH	Department of Health
DNA	Deoxyribonucleic acid
EPAQS	Expert Panel on Air Quality Standards
FAO	Food and Agricultural Organization of the United Nations
FSA	Food Standards Agency
HCV	Health Criteria Value
HPA	Health Protection Agency
HSE	Health and Safety Executive
ID	Index Dose
ID_{inh}	Index Dose derived for inhalation exposure
ID_{oral}	Index Dose derived for oral exposure
IRIS	Integrated Risk Information System of USEPA
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LOAEL	Lowest-observed adverse effect level
MAFF	Ministry of Agriculture, Fisheries and Food
MDI	Mean daily intake
MDI_{inh}	Mean daily intake via inhalation exposure

MDI_{oral}	Mean daily intake via oral exposure
MoE	Margin of Exposure
MRL	Minimal risk level
NOAEL	No-observed adverse effect level
NOEL	No-observed effect level
PTMI	Provisional tolerable monthly intake
PTWI	Provisional tolerable weekly intake
QRA	Quantitative risk assessment
RfC	Reference concentration
RfD	Reference dose
TCA	Tolerable concentration in air
TDI	Tolerable daily intake
TDI_{oral}	Tolerable daily intake derived for oral exposure
TDI_{inh}	Tolerable daily intake derived for inhalation exposure
TDSI	Tolerable Daily Soil Intake
TEF	Toxic Equivalency Factor
TEQ	Toxic Equivalent
UNEP	United Nations Environment Programme
USEPA	United States Environmental Protection Agency
WHO	World Health Organization

Glossary [31]

Additivity	See **dose additivity** and **response additivity**.
Adverse effect	A change in morphology, physiology, growth, development, reproduction, or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects of other environmental influences. Decisions on whether or not any effect is adverse require expert judgement.
Aerodynamic diameter	The diameter of a sphere with unit density that has aerodynamic behaviour identical to that of the particle in question; an expression of aerodynamic behaviour of an irregularly shaped particle in terms of an idealised particle. Particles having the same aerodynamic diameter may have different dimensions and shapes.
Agonist	A substance that binds to a specific **receptor** and triggers a response.
Allergen	A substance capable of inducing an allergic reaction.
Alveoli	The tiny capillary-rich air sacs in the lung where the exchange of oxygen and carbon dioxide takes place (singular: alveolus).
Antagonism	An **interaction** in which two or more chemicals affect the toxicity of each other and the toxicity of both chemicals is reduced (cf. **inhibition**). The overall effect is therefore less than would be expected based on knowledge of the chemicals' individual effects.
Assessment factor	See **uncertainty factor**.
Benchmark concentration	A concentration of a chemical that produces a predetermined change in response rate of an adverse effect (called the **benchmark response**, BMR) compared to background.
Benchmark dose	A dose of a chemical that produces a predetermined change in response rate of an adverse effect (called the **benchmark response**, BMR) compared to background.
Benchmark response	An adverse effect used to define a **benchmark dose** or **benchmark concentration**. The change in response rate over background is often 5 or 10%.
Bias	The general term used in epidemiology to denote a systematic tendency to underestimate or overestimate a parameter of interest (e.g. a relative risk) because of a deficiency in the design or execution of a study. For example, the results of a study may have been artificially influenced by the way in which people were selected for inclusion in the study (selection bias) or, in a case-control study, a person suffering with the disease being investigated may tend to remember being associated with the risk factor of interest more than a control subject and the memory may be distorted or (unknowingly) exaggerated (recall bias).

[31] Including definitions taken or adapted from various texts including ATSDR (2007), COC (2004), COM (2000), COT (2007), IGHRC (2002), IPCS (1994), IPCS (2004), IUPAC (2007), USEPA (2007).

Biliary excretion	The excretion of a chemical by the liver into the gastrointestinal tract via the bile.
Bioaccessibility	The degree to which a chemical is released from soil into solution (and thereby becomes available for absorption) when that soil is ingested and undergoes digestion.
Bioavailability	The degree to which a substance is absorbed and becomes available to the target tissue (without first being metabolised).
Blood-brain barrier	A membrane that controls the passage of substances from the blood into the central nervous system.
Body burden	The total amount of a substance present in an organism at a given time.
Carcinogen	An agent capable of inducing tumours and causing cancer (see **genotoxic carcinogen** and **non-genotoxic carcinogen**).
Chemical-specific adjustment factor	A numerical factor applied, when supporting data are available, in place of a default **uncertainty factor** in the derivation of a **Health Criteria Value**.
Confounding	A term used in epidemiology to describe the situation in which a risk factor of interest is associated with another (confounding) factor that independently determines the risk of the health outcome under study.
Congener	One of two or more chemicals of the same chemical class, sharing a common chemical structure.
Critical adverse effect	The adverse effect judged to be the most important for setting a **Health Criteria Value**. This is usually the most sensitive adverse effect (that is, the lowest effect level) or sometimes a more serious effect, not necessarily having the lowest effect level.
Critical NOAEL	The **NOAEL** for the **critical adverse effect**.
Cutaneous	Of or pertaining to the skin (same as **dermal**).
Cytochrome P450	A large superfamily of enzymes involved in the metabolism of **xenobiotics**.
Cytotoxicity	Toxicity to cells.
Dermal	Of or pertaining to the skin.
Dermal absorption	Absorption of a chemical through the skin.
Deoxyribonucleic acid	The biological substance containing the genetic code.
Developmental toxicity	Adverse effects on the developing organism that may result from chemical exposure prior to conception (either parent), during gestation (pregnancy), or after birth until the point of sexual maturation.
Dose	The amount of a substance administered to, taken up by, or absorbed by an organism. See also **intake**, **uptake**, and **exposure**.
Dose additivity	The effect seen on exposure to two or more chemicals with **simple similar action**. The effect is that which would be expected if either chemical had been administered at the total dose (after adjustment for potency differences) (cf. **response additivity**).

Elimination	The removal of a chemical by the body, either by metabolism to a different moiety or by excretion.
Elimination half-life	The time taken for half of an absorbed dose of a chemical to be eliminated (see **elimination**).
Endocrine system	The system of organs responsible for the production and release of hormones.
Endpoint	An undesirable health event or **adverse effect** such as the occurrence of disease or death. In general, an endpoint is the undesirable health consequence of some exposure.
Enterohepatic recirculation	The cyclical process involving intestinal re-absorption of a substance that has been excreted through the bile, followed by transfer back to the liver, making it available for **biliary excretion** again.
Epidemiology	The study of the incidence, prevalence and distribution of diseases (or injuries) in human populations.
Eukaryote	A single-celled or multi-cellular organism whose cells contain a distinct membrane-bound nucleus.
Eukaryotic	Pertaining to a eukaryote.
Exposure	Contact between a chemical and the external surfaces of the human body. Quantitatively, it is the amount of a chemical that is available for intake by a target receptor/population. Exposure may be quantified as the **dose** or the concentration of the chemical in the medium (for example, air, water, food) integrated over the duration of exposure, expressed in terms of mass of substance per kg of soil, unit volume of air or litre of water (for example, mg kg^{-1}, mg m^{-3} or mg L^{-1}).
False negative	A test result that is erroneously negative.
First-pass metabolism	The metabolism of a chemical that occurs during its first pass through the gut and liver following oral ingestion. Nutrients and **xenobiotics** absorbed from the gut are transported in the blood via the hepatic portal vein to the liver before circulation around the rest of the body. First-pass metabolism thus reduces the **bioavailability** of a chemical and the **systemic dose** achieved.
Gavage	Administration of materials directly into the stomach by oesophageal intubation (stomach tube).
Genotoxic carcinogen	A chemical that induces tumours via a mechanism involving damage to the genetic material.
Genotoxin	A chemical capable of causing damage to genetic material.
Germ cell	An ovum (egg) or a sperm cell or one of its developmental precursors. Also known as ‘sex cells’.
Gut microflora	The microorganisms that live within the gastrointestinal tract and contribute to the digestion of foodstuffs and also **xenobiotics**.
Hazard	The set of inherent properties of a substance or mixture of substances that makes it capable of causing adverse effects to humans, other organisms or the environment.

Health Criteria Value	A generic term used in this report to describe a benchmark level of exposure to a chemical derived from available toxicity data for the purposes of safeguarding human health (e.g. a tolerable daily intake).
Hepatotoxicant	A substance capable of causing damage to the liver.
Independent action	See **simple dissimilar action**.
Index Dose	The term used in this report to refer to an estimate of the amount of a chemical soil contaminant (expressed as a daily intake **dose**) that can be experienced over a lifetime with minimal cancer risk.
Inhalable particle	A particle the size of which dictates that when inhaled it only reaches the upper respiratory tract. These particles generally have an **aerodynamic diameter** of 10–100 μm. Following deposition in the lung, they may be subject to **mucociliary clearance**, swallowing and oral absorption (cf. **respirable particle**).
Inhibition	An interaction in which one chemical acts to reduce the toxicity of another but is itself unaffected. The overall effect is therefore weaker than would be predicted from additivity.
Intake	The amount of a chemical entering the human body at the point of entry (that is, mouth, nose or skin) by ingestion, inhalation, or skin contact.
Interaction	The affecting of a chemical's behaviour by another chemical. Any effect of exposure to multiple chemicals that is not **simple similar action** (**dose addition**) or **simple dissimilar action** (**response addition**). The overall effect of an interaction may be one that is either stronger or weaker than would be predicted based on additivity, and the mechanism underlying the interaction may be at the chemical or biological level.
Interspecies variability	The variability (in chemical/toxic sensitivity) between members of different species, for example humans and other animals.
Intraspecies variability	The variability (in chemical/toxic sensitivity) among members of the same species. For example, variability within the human population (that results from factors such as genetic diversity, age, health status, personal habits, diet and smoking habits).
In vitro	Within an artificial environment such as a test tube (literally, "in glass").
In vivo	Within a living organism (literally, "in life").
Kinetics	See **toxicokinetics**.
Lowest-observed adverse effect level	The lowest concentration or amount of a substance, found by experiment or observation, which causes an **adverse effect** in the target organism distinguishable from normal (control) organisms of the same species and strain under the same defined conditions of exposure.
Local toxicity	Adverse effects of a chemical that are confined to the tissue(s) at the site of contact with the chemical. For example, lung cancer caused by inhaling asbestos fibres, or contact dermatitis caused by nickel.
Margin of Exposure	Ratio of the experimental point of departure (e.g. the critical NOAEL) to the theoretical, predicted, or estimated human exposure.

Masking	An **interaction** in which two or more chemicals produce functionally competing effects on the same organ system or the effects of one override the effects of another.
Mean daily intake	The average **intake** of a soil contaminant from other, non-soil, sources, expressed as an amount per day (e.g. µg day^{-1}). The mean daily intake is estimated for each **route of exposure** (oral and inhalation) and arises principally from exposure to the contaminant in food, water and air.
Mechanism of action	The detailed molecular and biochemical pathways and events initiated or altered by a chemical that give rise to its observed adverse effect(s) (cf. **mode of action**).
Mesothelioma	A malignant tumour (cancer) of the tissue membrane lining the chest cavity or abdominal cavity.
Minimal risk level	1. A level of exposure to a non-threshold carcinogen (expressed as a daily intake **dose**) that is considered to be associated with a negligible risk of cancer. Minimal risk levels are derived using non-quantitative risk assessment methods employing expert judgement. 2. An **ATSDR** estimate of daily human exposure to a hazardous substance at or below which that substance is unlikely to pose a measurable risk of harmful (adverse), non-cancerous effects. MRLs are calculated for a route of exposure (inhalation or oral) over a specified time period (acute, intermediate, or chronic).
Mode of action	The collective key biochemical events initiated or altered by a chemical that result in the observed adverse effect (cf. **mechanism of action**).
Monotonic	Designating a sequence in which successive values either consistently increase or consistently decrease; they do not oscillate in relative value. Each member of a monotone increasing sequence is therefore equal to or greater than the preceding member; each member of a monotone decreasing sequence is equal to or less than the preceding member.
Mucociliary clearance	A process by which inhaled particles that have deposited on the mucous surface of the airways are removed with the mucous by the action of cilia (tiny hairs on the surface of the airways), often then becoming swallowed.
Mutagen	A chemical that can produce permanent heritable change in the amount or structure of the genetic material of cells or organisms (see **mutation**).
Mutation	A permanent change in the amount or structure of the genetic material of an organism, which may result in a heritable change in the characteristics of the organism. These alterations may involve individual genes, blocks of genes, or whole chromosomes. Mutations involving single genes may be a consequence of effects on single DNA bases (point mutations) or of larger changes, including deletions and rearrangements of DNA. Changes involving chromosomes as entities may be numerical or structural. A mutation in the **germ cells** of sexually reproducing organisms may be transmitted to the offspring, whereas a mutation that occurs in **somatic** cells may be transferred only to descendent daughter cells. Mutagenic chemicals may present a hazard to health since exposure to a mutagen carries the risk of inducing germ-line mutations, with the possibility of inherited disorders, and the risk of somatic mutations including those leading to cancer.
Negative synergy	See **antagonism**.

No-observed adverse effect level	The greatest dose, concentration or amount of a substance, found in experiment or observation, which causes no detectable **adverse effects** in the target organism under defined conditions of exposure.
Non-genotoxic carcinogen	A chemical that induces tumours via a mechanism that does not involve direct damage to **DNA**.
Parent compound	The chemical entity to which initial exposure occurs, before any biochemical or other process metabolises or otherwise alters it following intake into the body.
Peroxisome	Organelles within the cells of **eukaryotes** that participate in the metabolism of fatty acids and other metabolites.
Point of departure	The dose or concentration selected from a toxicity or epidemiology study as the basis for derivation of a **Health Criteria Value** or a **Margin of Exposure**. Examples include the **NOAEL**, **LOAEL** and **BMDL**.
Potency	The intrinsic strength or ability of a substance to cause a particular type of harm to health.
Potentiation	An **interaction** in which one chemical acts to enhance the toxicity of another, but is itself unaffected. The overall effect is therefore stronger than would be predicted from additivity.
Prokaryotic	Pertaining to a prokaryote – a single-celled organism lacking a membrane-bound nucleus (e.g. a bacterium).
Pulmonary	Of or pertaining to the lungs.
Receptor	1. An entity receiving an exposure to a chemical from a particular source. In this report, the source is contaminated land and the critical receptor is the human population potentially affected. Other receptors include wildlife and plant life, groundwater, and buildings/structures. 2. A molecular protein structure present in a surface membrane of a cell or organelle to which complementary molecules, such as hormones, neurotransmitters, antigens or antibodies, may become bound and 'activate' the receptor.
Reference concentration	An **HCV** derived by USEPA for inhalation exposure to a chemical. Defined as: an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of non-cancer deleterious effects during a lifetime.
Reference dose	An **HCV** derived by USEPA for oral exposure to a chemical. Defined as: an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of non-cancer deleterious effects during a lifetime.
Respirable particle	A particle that is able to reach the deep lung and **alveoli**. For humans, respirable particles generally have an aerodynamic diameter of <10 µm (cf. **inhalable particle**).

Response additivity	The effect seen on exposure to two or more chemicals with **simple dissimilar action**. The effect is that which would be expected based on combining the responses seen with each individual chemical (cf. **dose additivity**).
Risk	The possibility that a harmful event (death, injury or loss) arising from exposure to a chemical or physical agent may occur under specific conditions.
Risk management	Intervention steps taken to limit exposure to a chemical and thereby mitigate the risk or reduce it to an acceptable level.
Route of Exposure	The way a chemical enters an organism after contact (for example, ingestion, inhalation or **dermal absorption**).
Route-to-route extrapolation	The prediction of the total amount of a substance administered by one route of exposure that would produce the same toxic endpoint or response to that obtained for a given amount of that substance administered by another route.
Safety factor	See **uncertainty factor**.
Sigmoidal	S-shaped. The start of a sigmoid dose-response curve nearest the origin has a low gradient that gets progressively steeper until (sometimes) reaching a short period of linearity before slowing and levelling off again as the maximum response is approached.
Simple dissimilar action	Two or more chemicals causing (possibly different) effects via different **modes of action**, resulting in response addition (**response additivity**).
Simple similar action	Two or more chemicals causing the same effect via the same **mode of action**, resulting in dose addition (**dose additivity**).
Soil Guideline Values	Non-statutory, scientifically based generic assessment criteria for assessing the risk to human health from chronic exposures to chemicals in soil.
Somatic cell	A cell of the body, with the exception of the **germ cells**.
Steady-state	The situation where the kinetic processes of absorption and **elimination** are essentially in dynamic equilibrium and the overall **body burden** is stable.
Sub-additivity	An **interaction** in which the combined effect of two or more chemicals is less than would be predicted from **additivity**. (See **antagonism**, **inhibition**, **masking**, **negative synergy**.)
Supra-additivity	An **interaction** in which the combined effect of two or more chemicals is greater than would be predicted from **additivity**. (See **potentiation**, **synergy**.)
Synergy	An **interaction** in which two or more chemicals affect the toxicity of each other and the toxicity of both chemicals is enhanced (cf. **potentiation**).
Systemic	Relating to the body as a whole.

Systemic circulation	The part of the blood system that transports blood from the heart to and from the rest of the body, except for the lungs which have their own circulatory system (the pulmonary circulation). In toxicology, the term is usually used to describe the main blood circulatory system that is reached by a chemical (or the proportion of a chemical dose) after being absorbed and successfully bypassing **first-pass metabolism**.
Systemic dose	The amount of a chemical that reaches the **systemic circulation** unchanged following absorption.
Systemic effect	An effect of a chemical that is either of a generalised nature or that occurs at a site distant from the site of entry of the chemical.
Systemic toxicity	An adverse **systemic effect**.
T25	The daily dose resulting in a tumour incidence of 25% at a specific site, after correction for spontaneous incidence, within the standard life span of the study species.
Target	The cells, organ(s) or system(s) where a chemical actually causes an adverse health effect. For example, target organs such as kidneys or lungs or target systems such as the lymphatic or reproductive systems.
TD_{50}	The daily dose of a chemical estimated to halve the probability of remaining without tumours at the end of a standard life span.
Teratogen	An agent capable of causing malformation of an embryo or foetus.
Tolerable daily intake	Originally defined as an estimate of the amount of a chemical contaminant, expressed on a bodyweight basis (e.g. mg kg^{-1} bw day^{-1}), that can be ingested daily over a lifetime without appreciable health risk, the term has been expanded to also apply to exposure via inhalation and dermal contact.
Tolerable daily soil intake	The portion of the **tolerable daily intake** for a contaminant that is allocated to exposure from soil, once background exposure from other sources (the **mean daily intake**) has been accounted for.
Topical	Of or pertaining to the exterior body surface.
Toxicity	The inherent property of a substance to cause injury or an adverse effect in a living organism.
Toxicodynamics	The sequence of events (and their determination and quantification) at the cellular and molecular levels leading to a toxic response to a chemical, i.e. the effect of the chemical on the body. (Also referred to as pharmacodynamics.)
Toxicokinetics	The time course of absorption, distribution, metabolism and excretion of a chemical by the body, i.e. the effect of the body on the chemical. (Also referred to as pharmacokinetics.)
Transcutaneous	By way of or through the skin.
Tumourigenicity	The ability to cause tumours.
Uncertainty	A lack of knowledge about specific factors in a risk assessment.

Uncertainty factor	A value used in the extrapolation of toxicity data from a test or study to a target population (such as from experimental animals to man, or from selected individuals to the general population); for example, a value applied to a **NOAEL** to derive a **TDI**. The value depends on the size and type of population to be protected and the quality of the toxicological information available. If the target population is *known* to be more sensitive than the test population, and this can be quantified, a **chemical-specific adjustment factor** may be applied.
Uptake	The amount of a contaminant that enters the body having been absorbed through the skin, the gastrointestinal system and/or the pulmonary system (lungs).
Variability factor	See **uncertainty factor**.
Xenobiotic	A chemical within an organism that is foreign to (i.e. not produced by) that organism. Medicines and environmental contaminants are examples of xenobiotics.

Appendix A – Sources of toxicological information

The sources included in this appendix are not intended to be exhaustive and would be expected to constitute the minimum requirements of a literature search used for the risk assessment of chemical soil contaminants in the UK.

UK agencies and expert groups

Drinking Water Inspectorate (DWI)

DWI regulates public water supplies in England and Wales. Information on drinking water legislation and standards for chemicals in drinking water can be accessed at:

http://www.dwi.gov.uk/

Food Standards Agency (FSA)

FSA is a non-ministerial government department set up by an Act of Parliament in 2000 to protect the public's health and consumer interests in relation to food. As part of its role, FSA conducts food surveys of contaminants in food and total diet and nutrition surveys of the population's eating habits, from which oral mean daily intake values may be estimated.

http://www.food.gov.uk/

Health Protection Agency (HPA)

HPA is an agency established in 2005 to protect the health and wellbeing of the population. HPA is accountable to the Secretary of State for Health and has a role in protecting people from infectious diseases and in preventing harm when hazards involving chemicals, poisons or radiation occur. The Chemical Hazards and Poisons Division (CHaPD) of HPA publishes a Compendium of Chemical Hazards, which may be accessed via the HPA website at:

http://www.hpa.org.uk/

Health and Safety Executive (HSE)

The Health and Safety Commission (HSC) is responsible for health and safety regulation in Great Britain. The Health and Safety Executive (HSE) and local government are the enforcing authorities who work in support of the Commission. HSE is responsible for setting Workplace Exposure Limits (WELs) for chemicals.

http://www.hse.gov.uk/

Health and Safety Laboratory (HSL)

HSL is an agency of HSE, that supports HSE's mission to protect people's health and safety by ensuring risks in the changing workplace are properly controlled.

http://www.hsl.gov.uk/

Pesticides Safety Directorate (PSD)

PSD is an Executive Agency of Defra. PSD is responsible for the risk assessment and monitoring of pesticides used in the UK.

http://www.pesticides.gov.uk/

Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC)

Sponsored by the Department of Health (DH) and FSA, COC is an independent advisory committee that provides advice to government departments and agencies on matters concerning the potential carcinogenicity of chemicals, ranging from natural products to new synthetic chemicals used in pesticides or pharmaceuticals. COC statements and reports may be accessed at:

http://www.advisorybodies.doh.gov.uk/coc/index.htm

Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM)

Sponsored by DH and FSA, COM is an independent advisory committee that provides advice to government departments and agencies on matters concerning the potential mutagenicity of chemicals, ranging from natural products to new synthetic chemicals in pesticides or pharmaceuticals. COM statements and reports may be accessed at:

http://www.advisorybodies.doh.gov.uk/com/

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT)

Sponsored by DH and FSA, COT is an independent advisory committee that provides advice to government departments and agencies on matters concerning the toxicity of chemicals, ranging from natural products to new synthetic chemicals used in pesticides or pharmaceuticals. COT statements and reports may be accessed at:

http://cot.food.gov.uk/

Committee on the Medical Effects of Air Pollutants (COMEAP)

Sponsored by DH, COMEAP is an advisory committee of independent experts that provides advice to government departments and agencies on all matters concerning the potential toxicity and effects upon health of air pollutants. COMEAP statements and reports may be accessed at:

http://www.advisorybodies.doh.gov.uk/comeap/index.htm

Expert Panel on Air Quality Standards (EPAQS)

Sponsored by Defra, EPAQS was established in 1991 to provide independent advice to Defra on air quality issues, in particular the levels of pollution at which no or minimal health effects are likely to occur. EPAQS publications and reports can be accessed at:

http://www.defra.gov.uk/environment/airquality/panels/aqs/index.htm

In 2007, it was announced that EPAQS is to be merged with COMEAP (see above).

European agencies and industry groups

European Chemicals Bureau (ECB)

ECB is the focal point for data and the assessment procedure on dangerous chemicals. The ECB provides scientific and technical support for the conception, development, implementation and monitoring of EU policies related to dangerous chemicals. It co-ordinates the EU risk assessment programmes covering the risks posed by existing substances and new substances to workers, consumers and the environment. EU chemical risk assessment reports (RARs) can be accessed via the ECB website at:

http://ecb.jrc.it/

European Food Safety Authority (EFSA)

EFSA, established in 2002, is the keystone of European Union (EU) risk assessment regarding food and feed safety. In close collaboration with national authorities and in open consultation with its stakeholders, EFSA provides independent scientific advice and clear communication on existing and emerging risks.

EFSA's Scientific Committee, its Scientific Expert Panels and other expert groups provide risk assessments on all matters linked to food and feed safety, including the presence of chemical contaminants in food. EFSA Expert Panel Opinions and Reports can be accessed via the EFSA website at:

http://www.efsa.europa.eu/en.html

Before 2002, the Scientific Committee on Food (SCF), established in 1974, was the EU committee responsible for the risk assessment of chemicals in food.

http://ec.europa.eu/food/fs/sc/scf/index_en.html

European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC)

ECETOC was established in 1987 as a scientific, non-profit organisation financed by leading companies with interests in the manufacture and use of chemicals. A list of ECETOC technical reports and Joint Assessment of Commodity Chemicals (JACC) reports is available via the ECETOC website at:

http://www.ecetoc.org/

International

International Agency for Research on Cancer (IARC)

In 1969, IARC initiated a programme to evaluate the carcinogenic risk of chemicals to humans, involving the production of critically evaluated monographs on individual chemicals. In 1980 and 1986, the programme was expanded to include evaluations of carcinogenic risks associated with exposures to complex mixtures and other agents.

IARC monographs are critical reviews of data on carcinogenicity for agents to which humans are known to be exposed. IARC classifies chemicals according to their carcinogenic potential, i.e. hazard, as indicated by the available data.

http://inchem.org/pages/iarc.html

International Programme on Chemical Safety (IPCS)

IPCS, established in 1980, is a co-operative programme of the World Health Organization (WHO), the International Labour Organisation (ILO), and the United Nations Environment Programme (UNEP), running activities relating to chemical safety.

http://www.who.int/ipcs/en/

IPCS INCHEM is a web-based tool produced through co-operation between IPCS and the Canadian Centre for Occupational Health and Safety (CCOHS). It provides access to internationally peer-reviewed information on chemicals commonly used throughout the world, which may also occur as contaminants in the environment and food. It consolidates information from a number of intergovernmental organisations.

http://inchem.org/

IPCS Concise International Chemical Assessment Documents (CICADs)

CICADs provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are based on selected national or regional evaluation documents or on existing Environmental Health Criteria monographs. CICADs undergo extensive peer review by internationally selected experts before publication by IPCS.

The primary objective of CICADs is characterisation of hazard and dose-response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterisation of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn.

http://inchem.org/pages/cicads.html

IPCS Environmental Health Criteria (EHC) Monographs

EHC chemical monographs are based on a comprehensive search of available original publications, scientific literature and reviews, and examine: the physical and chemical properties and analytical methods; sources of environmental and industrial exposure and environmental transport; biokinetics and metabolism including absorption, distribution, transformation and elimination; short and long-term effects on animals (carcinogenicity, mutagenicity, and teratogenicity); and finally, an evaluation of risks to human health and the effects on the environment.

http://inchem.org/pages/ehc.html

IPCS Pesticide Data Sheets (PDSs)

PDSs are prepared by WHO in collaboration with the Food and Agriculture Organization (FAO) and give basic toxicological information on individual pesticides. The data sheets are prepared by scientific experts and peer reviewed.

http://inchem.org/pages/pds.html

IPCS Poisons Information Monographs (PIMs)

PIMs are prepared for chemicals, pharmaceuticals, poisonous plants, and poisonous and venomous animals commonly involved in cases of poisoning. They are prepared by collaborating poisons information centres and other experts throughout the world and are subjected to individual and peer review. PIMs summarise the physical-chemical and toxicological properties of the substance, the medical features of the effects produced by various routes of exposure to the substance, the patient management, and the supporting laboratory investigations.

http://inchem.org/pages/pims.html

Joint Expert Committee on Food Additives (JECFA)

JECFA is an international scientific expert committee that is administered jointly by FAO and WHO. Established in 1956 to evaluate the safety of food additives, its work now includes the evaluation of contaminants, naturally occurring toxicants and residues of veterinary drugs in food.

http://www.who.int/ipcs/food/jecfa/en/

http://inchem.org/pages/jecfa.html

Joint FAO/WHO Meeting on Pesticide Residues (JMPR)

JMPR is an international scientific expert group established in 1963 that is administered jointly by FAO and WHO. JMPR publishes toxicological evaluations of pesticides, which are used by the Codex Alimentarius Commission and national governments to set international food standards and safe levels to protect consumers.

http://www.who.int/ipcs/food/jmpr/en/

http://inchem.org/pages/jmpr.html

Organisation for Economic Co-operation and Development (OECD) Screening Information Data Set (SIDS) for High Production Volume Chemicals

OECD SIDS are published by UNEP to facilitate access to information needed for health and environmental risk assessment of chemicals. SIDS documents can be accessed via the IPCS website at:

http://inchem.org/pages/sids.html

WHO guidelines for drinking water quality

WHO produces international norms on water quality and human health in the form of guidelines that are used as the basis for regulation and standard setting, in developing and developed countries worldwide. These include guideline limits for many chemical contaminants. The guidelines, chemical fact sheets and the supporting background documents can be accessed via the WHO website at:

http://www.who.int/water_sanitation_health/dwq/guidelines/en/

WHO air quality guidelines for Europe

WHO air quality guidelines are intended to provide background information and guidance to (inter)national and local authorities in making risk assessment and risk management decisions. In establishing pollutant levels below which exposure – for life or for a given period of time – does not constitute a significant public health risk, the guidelines provide a basis for setting standards or limit values for air pollutants. The guidelines can be accessed via the WHO Regional Office for Europe website at:

http://www.euro.who.int/air/activities/20050222_2

Foreign national

Dutch National Institute for Public Health and the Environment (RIVM) Maximum Permissible Risk (MPR) levels

RIVM establishes Soil Intervention Values for priority chemical contaminants, based on Maximum Permissible Risk (MPR) values that quantify the human toxicological risk limit (tolerable daily intake, tolerable concentration in air, oral cancer risk, and/or inhalation cancer risk). Information on MPRs for contaminants can be accessed via the RIVM website at:

http://www.rivm.nl/en/

Health Canada Toxicological Reference Values

Toxicological reviews of priority contaminants and Toxicological Reference Values (TRVs) in the assessment of contaminated sites by Health Canada can be accessed via the Health Canada website at:

http://www.hc-sc.gc.ca/index_e.html

US Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles and Minimal Risk Levels

ATSDR is a federal public health agency of the US Department of Health and Human Services. It performs specific functions concerning the effect on public health of hazardous substances in the environment, including public health assessments of waste sites and health consultations on hazardous substances. Toxicological Profiles for priority contaminants and ATSDR minimal risk levels can be accessed via the ATSDR website at:

http://www.atsdr.cdc.gov/

USEPA Acute Exposure Guideline Levels (AEGLs)

Acute Exposure Guideline Levels (AEGLs) have been derived by USEPA for various chemicals, for various durations of acute exposure. The AEGLs database can be accessed via the USEPA website at:

http://www.epa.gov/oppt/aegl/pubs/chemlist.htm

USEPA Health Advisories

Health Advisories are derived by USEPA Office of Water for contaminants that can cause human health effects and are known or anticipated to occur in drinking-water. Health Advisories are guidance values based on non-cancer health effects. A table of Health Advisories and the supporting documents can be accessed via the USEPA website at:

http://www.epa.gov/waterscience/criteria/drinking/

USEPA Integrated Risk Information System (IRIS)

IRIS is produced by USEPA National Center for Environmental Assessment. It is a database of human health effects that may result from exposure to various substances found in the environment, with non-cancer health-based reference doses (RfDs) and reference concentrations (RfCs) proposed for each chemical. The IRIS database can be accessed via the USEPA website at:

http://www.epa.gov/iris/

Other online resources

Toxicology Data Network (Toxnet)

Hosted by the US National Library of Medicine, Toxnet is a collection of databases on toxicology, hazardous chemicals, environmental health, and toxic releases. These include IRIS, Toxline and the Hazardous Substances Data Bank (HSDB). Toxnet can be accessed at:

http://toxnet.nlm.nih.gov/

Entrez PubMed

A service of the US National Library of Medicine and National Institutes of Health, Entrez PubMed is an online search engine and database of biomedical journal citations. It can be accessed at:

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi

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