Uncertainty factors:

Their use in human health risk assessment by UK Government

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The Interdepartmental Group on Health Risks from Chemicals aims to stimulate the development of new, improved approaches to the assessment of risks to human health from chemicals.

The Steering Committee of the Interdepartmental Group on Health Risks from Chemicals comprises participants from the Department for Environment, Food and Rural Affairs, the Department of Health, the Department of Trade and Industry, the Home Office, the Environment Agency, the Health and Safety Executive, the Food Standards Agency, the Medicines Control Agency, the Pesticides Safety Directorate, the Veterinary Medicines Directorate, the Biotechnology and Biological Sciences Research Council, the Medical Research Council, the Natural Environment Research Council and the Institute for Environment and Health.

The Secretariat is based at the Medical Research Council's Institute for Environment and Health.

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Foreword

This document has been produced by the Interdepartmental Group on Health Risks from Chemicals (IGHRC) as part of its current work programme. Following initial drafting by a working group of the IGHRC, consultation was undertaken with Government departments, agencies and their advisory committees in order to obtain a broad input and consensus. The following advisory committees were consulted as part of this process.

- Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
- Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment
- Advisory Committee on Pesticides
- Veterinary Products Committee
- Working Group on the Assessment of Toxic Chemicals

While these advisory committees support the general principles on the handling of toxicological uncertainty and the use of uncertainty factors described in this document, it is intended, primarily, to indicate the view of the IGHRC. Furthermore, this document is intended only to lay out the principles used in the UK, and the advisory committees are not constrained by its content, if in their expert judgement, alternative approaches are necessary.

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Introduction

A number of UK Government departments and agencies are involved in assessing the risks to human health posed by chemicals used in different situations, for example, exposures arising at work, from use in consumer products, from food, or from exposures arising from environmental pollution in air, soil water or waste. The general principles involved in chemical risk assessment are well established, being based on assessment of the inherent ability of the chemical to cause adverse health effects (its toxic properties) together with the estimated human exposure. The assessment of the hazard is nearly always based largely on toxicity data obtained from animal studies. The uncertainties in extrapolating data to estimate the likely hazard to humans due to interspecies variability is recognised. In addition the human population is far more diverse than the inbred strains of laboratory animals used in safety evaluation studies, and there is a need to take into account the variability that may be expected in the human population.

When estimating what is likely to be a 'safe' level of exposure to humans, these uncertainties are taken into account by the use of what are generally known as 'uncertainty factors'. Until now there has been no single UK Government document on the use of uncertainty factors in human health hazard assessment. The aim of this report is to provide an outline as to how government departments and agencies, and their respective expert advisory committees, address this issue of uncertainty, and to provide a framework that should facilitate greater rationalisation of the values used as uncertainty factors in specific cases.

The report considers approaches that have been used to deal with toxicological uncertainties in risk assessment in the past, and in other countries. The approaches taken by various UK regulatory departments and agencies are then considered in some detail with case examples given.

What are uncertainty factors?

When estimating what is likely to be a human exposure that will not produce any adverse health effects (i.e. a safe level), uncertainty factors are used to make allowance for a lack of full information on the chemical being assessed. The factors selected are numbers such as 10 or 100, and they are applied to the most relevant dose level in safety evaluation studies in animals on the chemical in question, usually the highest level producing no adverse effects in the most sensitive species. So if the most informative study on a particular effect of a chemical has been conducted in laboratory rats, and this has established that none of the animals had any adverse effects from the chemical when given a dose of 1 mg/kg per day, then this would be used as the starting point. Depending on the uncertainty factor judged to be appropriate, the human standard for exposure might be set at 0.1 mg/kg per day (if a factor of 10 were applied) or 0.01 mg/kg per day with a 100-fold factor.

Uncertainty factors have been used in health risk assessment for many years, and were originally established on the basis of experienced judgement and intelligent guesswork rather than on any real knowledge of the most accurate factor to choose. Traditionally an uncertainty factor of 100 has been applied. A factor of 10 has been shown to be appropriate to allow for differences that might affect the way the chemical behaves in humans rather than in the animal species tested, and another factor of 10 is adequate to allow for differences in the way the chemical might affect different people, to allow for the most sensitive

individuals. It is considered safest to assume that these two processes might operate in totally independent ways, so rather than sum them (and here reach a total of 20), the accepted method is to multiply the individual factors, in this case giving a composite factor of 100.

The interspecies and interindividual variation mentioned earlier are the main sources of uncertainty and it is difficult to imagine how we could ever have enough information about a chemical that no allowance need be made for them in a health risk assessment. However there are other shortfalls for which allowance must be made. A database of information may exist on the chemical with which we are concerned so such that it would be difficult to justify a further study in animals, but the studies done may not have used the same route of exposure (we may want to know about inhalation rather than dietary intake), or may not have looked at the same time scale that we now need to consider. Or we may know that there are particularly serious health effects from an exposure that exceeds the standard, such as carcinogenic or irreversible developmental effects. Some of these matters can also be allowed for by including extra uncertainty factors. However, most authorities that set standards consider that once the composite factor reaches a certain level, usually of above 10 000, then uncertainty is so high that it is not possible to conduct a meaningful risk assessment.

Uncertainty factors, then, are intended to provide a level of reassurance of safety from the harmful effects of exposure to chemicals in the face of limited information. As more information becomes available it may be possible to refine the default values (usually 10×10) by scientifically derived values that reduce the uncertainty in the human health hazard assessment. Finding a safe and scientifically sound way of doing this is a current subject of debate.

How uncertainty factors are used by UK Government for health risk assessment

In the UK there are many Government departments and agencies involved in assessing the risk of exposure to chemicals on human health. The chemicals that cause concern are those that could be found in food, beverages and drinking water, household products, human medicines, the environment or the workplace.

Some UK Government departments and agencies involved in health risk assessment

Biotechnology and Biosciences Research Council

Department for Environment, Food and Rural Affairs

Department of Health

Department of Trade and Industry

Environment Agency

Food Standards Agency

Health and Safety Executive

Home Office

Laboratory of the Government Chemist

Medical Research Council

Medicines and Healthcare Products Regulatory Agency

Pesticides Safety Directorate

Veterinary Medicines Directorate

The fact that different Government bodies have developed their own methods for establishing safe levels of exposure, and have come up with similar figures, is a reason for faith in the system. There are, however, a few important differences in the way some Government bodies operate when assessing uncertainty. For instance, the regulation of human medicines has to take into account that the chemicals used *should* have an effect — a health *benefit* — and there are complex considerations undertaken to weigh any health risk against the benefit. Another area of regulation that doesn't follow the normal pattern is occupational health, where identifiable uncertainty factors have not been used in standard setting, and less allowance for uncertainty is made in occupational exposure.

Government bodies are making strong efforts to rationalise some of the differences in approach to the use of uncertainty factors. They have agreed to exchange information on how they assess chemicals and select uncertainty factors, so it's easier to compare methods and share knowledge and experience. They also plan to work together to investigate some exciting new developments in techniques that could make a fundamental difference to the use of uncertainty factors. The establishment of the Interdepartmental Group on Health Risks from Chemicals is one outcome of these efforts.

Improving health risk assessment in the future

The use of uncertainty factors has been subject to comment and analysis over the past few years, and the simplicity of the system and the use of composite default factors have been criticised. Some adverse comment has been deflected by studies that show the traditional ten-fold factors are really rather good estimates, and have effectively protected our health over a long period of time.

However, there are good reasons for investigating approaches that may reduce uncertainty. There are existing techniques available that can supply information to help make risk assessment more accurate. These include, for example, *in vitro* tests, which use animal or human cells grown in the laboratory to investigate the variability between species and individuals. At present it is difficult to know how to apply new information on specific chemicals, because composite uncertainty factors encompass such a broad range of effects. The International Programme on Chemical Safety is developing a new framework in which chemical-specific adjustment factors can be incorporated more easily.

Advances in modelling and computer simulations also offer new opportunities to reduce uncertainties. Mathematical modelling based on knowledge of physiology and biochemistry should help to reduce the need for uncertainty factors in at least some aspects of risk assessment. Probabilistic approaches, which attempt to quantify variability and uncertainty, may be useful either as an alternative to simple multiplication in combining a number of uncertainty factors or as the basis for a new approach.

There are other new and exciting techniques under development. Genomics and proteomics could offer the possibility of understanding, and perhaps even predicting, the toxic properties of a chemical by looking at changes that occur in gene expression following exposure. These techniques are still at the development stage, but they should, at the very least, increase our understanding of interspecies variability.

Executive summary

In general the risk assessment of chemicals for threshold effects on human health is approached in two ways, both of which fundamentally include a comparison of the hazardous properties of the chemical with a measure or estimate of human exposure. For both approaches, the starting point is normally the identification of a critical effect (or effects) and the experimental dose level at which that effect is not detected (NOAEL), or at which the effect is found to be minimal in incidence and severity (LOAEL). These may be identified from studies in human populations, but, in the vast majority of cases, reliance has to be placed on data from studies in experimental animals and other test systems. In the case of experimental animal studies, a mathematically derived value, the benchmark dose, may be used as an alternative to the NOAEL or LOAEL, although this has seen little use in the UK. Whichever is available or chosen, this starting point can then be used to derive directly a standard considered to represent a level of exposure or intake at which it is believed there is little, if any, likelihood of developing ill-health effects. This standard is then compared directly with the measure or estimate of exposure. Alternatively, the starting point (NOAEL, LOAEL) can be compared directly with the measure or estimate of exposure through the calculation of the ratio of one to the other and a judgement made about the magnitude of this ratio and the likelihood of the development of adverse health effects. This latter approach also requires a consideration of the uncertainties in exposure estimates when interpreting the ratio.

Although these are two distinct approaches, they are essentially similar, not only in the comparison of hazard and exposure information but also in that both have to deal with many uncertainties in terms of the available toxicological information. These uncertainties generally include the need to extrapolate between species (i.e. from an experimental animal species to humans) and the need to account for variability in the potentially exposed human population, but may also include uncertainties due to limitations in the database (e.g. no long-term studies, not a full exploration of the range of potential toxic properties). Not all of these uncertainties may be met in all situations but it is very rarely the case that sufficient information from human experience will be available to address all the uncertainties that arise in a risk assessment. Thus, over the years, approaches have been developed to address these uncertainties in a systematic and generally consistent manner. The fundamental approach has been to use factors, referred to here as uncertainty factors, to allow for these uncertainties, and these are applied either directly to the NOAEL or LOAEL (in the derivation of standards) or as a framework against which to judge the adequacy of a derived hazard or exposure ratio.

When knowledge of the hazardous properties in question is at a basic level (e.g. a basic set of experimental information, which would include long-term studies in animals and information on reproduction and development but little on toxicokinetics, modes or mechanisms of action or knowledge of human variability), then the approach in many areas of regulatory decision-making has been to apply default uncertainty factors. These have usually been of the numerical order of 10 each to allow for uncertainties in interspecies extrapolation and intraspecies variability, in order to generate a position deemed to offer the required degree of confidence in health protection that is being sought. This approach was originally adopted in the USA in the 1950s, but has since become a well-established international practice used widely in many regulatory contexts and in many fora. These factors are intended to provide a level of reassurance of safety from the harmful effects of exposure to chemicals in the face of limited information; more information would

help the risk assessor to make a more accurate prediction of the true level of risk. Although the original derivation of these default factors of 10 is somewhat uncertain, they were initially based on very limited evidence and arguably had little scientific basis. However, over the years since their introduction, and particularly since the 1980s, there have been an increasing number of scientific analyses presented on various aspects of these factors, such that in general they are now supported scientifically as providing a default position deemed to match the degree of reassurance sought when information is limited. As indicated above, these default factors have been adopted internationally in a number of fora where the human health risk assessment of chemicals is conducted, and the same approach has been adopted across most but not all UK Government departments, agencies and their advisory committees which are responsible for such risk assessments.

As well as the defaults used to allow for the uncertainties in interspecies extrapolation and intraspecies variability, other default factors have been developed and used for situations where other uncertainties arise because of deficiencies in the available database, for example the lack of a long-term study, the use of a LOAEL instead of a NOAEL, data gaps or the need to make allowance for especially severe or irreversible effects. In general, default uncertainty factors of up to 10 have been used in such situations. Alternatively, analyses of aggregated existing experimental data have been used to derive more specific factors (e.g. when comparing the ratio of experimental NOAELs over varying exposure periods), but these analyses have fundamental flaws as they are reflective of, for example, dose selection rather than any true factor that reflects the relationship between the values being compared. Although defaults or these database-derived factors can be used in the sense that they represent a standardised and consistent approach, the use of expert judgement in such situations is also helpful, since in many cases the unthinking use of a standard factor may lead to its inappropriate application.

The use of default uncertainty factors in risk assessment is well established in the UK regulatory setting in those situations where the general population is exposed to chemicals from a variety of potential sources, whether such exposure is intentional or otherwise. In contrast to this situation, risk assessment in the occupational setting both in the UK and internationally has neither employed a clear framework for formally addressing areas of uncertainty, nor has used identifiable standardised numerical factors as defaults in the face of limited information. The occupational area, particularly in relation to standard setting, has developed separately within a particular economic and socio-economic context. There are also some particular technical features to take into account in occupational risk assessment. Taken together, these considerations have led to the acceptance of lower numerical uncertainty factors when seeking to control exposure to levels considered appropriate in the occupational setting. In the future it is intended to improve transparency in the use of uncertainty factors in this context, leading to a clearer portrayal of the similarities and differences between the occupational and other arenas in terms of any conclusions reached about accommodating uncertainty.

Recent years have seen a considerable move forwards in the thinking, development of technologies and the generation of data that may help to significantly improve our knowledge and approaches to dealing with toxicological uncertainties. It is important that these avenues are followed in order to improve chemical risk assessment. The replacement of default uncertainty factors in risk assessment may be possible where chemical-specific information can be used in frameworks designed to accommodate such information, such as that developed internationally under the auspices of the International Programme on Chemical Safety for the use of chemical-specific adjustment factors. Such information may also be used in more advanced approaches such as physiologically-based modelling, reducing the need for uncertainty factors in at least some aspects of risk assessment. Probabilistic approaches may be useful either as an alternative to simple multiplication in combining a number of uncertainty factors, or as the basis for an approach that differs from the traditional risk assessment paradigm.

Despite limitations that remain to be overcome, the use of *in vitro* systems derived from both animal and human tissues is beginning to be useful in some aspects of hazard and risk assessment. These systems may be useful in determining the variability in cellular metabolism of a chemical between species and individuals. The continued development of such *in vitro* systems is therefore essential, both in order to reduce the need for studies in animals and to secure their longer-term role in contributing to risk assessment. While it remains necessary to use the information from animal studies, the use of the benchmark dose potentially provides a statistically more robust value than the NOAEL, and thus reduces the uncertainty in the starting point for a risk assessment.

A novel but increasingly important development is the establishment of genomics and proteomics. These technologies offer the possibility of understanding, and ultimately predicting, the toxic properties of a chemical through changes in gene expression. Although there is still much development work to be undertaken, these approaches should increase our understanding of how the expression of toxicity varies between and within species. Placed in the context of the information emerging from the Human Genome Project, the possibility of reducing the uncertainties in accounting for human variability in risk assessment is likely to be increased.

1 Introduction

Chemicals (both natural and man-made) and their products and technologies are essential to most manufacturing and many service operations, and to all of us in our daily lives. But chemicals from all sources can harm human health, and so risks from their use have to be assessed to enable exposures to be properly controlled. A number of UK Government departments and agencies have a responsibility for assessing risk to human health from potentially toxic substances, such as may be found in food, beverages and drinking water, household products, human medicines, the environment or the workplace (Risk Assessment and Toxicology Steering Committee, 1999a).

Reliable data from human populations exposed to known levels of a substance are rarely available, except in the case of human medicines. Hence, the risk assessment process usually has to rely on data generated in experimental systems using species other than humans. The standardised experimental systems used also have other characteristics that limit their ability to be representative of the full range of real-life circumstances that might need to be addressed within regulatory considerations. Therefore, risk assessments developed on this basis inherently involve varying degrees of uncertainty, for example the need, often in the absence of particularly informative data, to extrapolate from animals to humans, from high to low dose, from one type of population member (e.g. fit, young people) to another (e.g. infirm, elderly people) and from one route of exposure to another. The conventional approach adopted to compensate for lack of knowledge in accommodating such extrapolations has been the use of uncertainty factors.

The uncertainties inherent in current risk assessment approaches are widely recognised (WHO, 1994, 1999), as is the frequent absence of scientific knowledge to facilitate more accurate extrapolations. Advances in scientific techniques, such as the use of novel biomarkers, *in vitro* toxicology, molecular modelling and computer simulations, may offer new opportunities to reduce these uncertainties. Government departments and agencies, together with the relevant research councils, decided to make a coordinated drive to pursue these important opportunities. Their commitment was set out in the 1995 UK Government *Forward Look of Government Funded Science, Engineering and Technology* (HMSO, 1995) and resulted in the establishment in 1996 of the Government/Research Councils Initiative on Risk Assessment and Toxicology. The outcome of the work of this Initiative was published in 1999 (Risk Assessment and Toxicology Steering Committee, 1999a). This report highlighted a number of recommendations covering a broad range of activities related to human health risk assessment as practised by UK Government departments and agencies. An important activity was a detailed mapping of the procedures used by Government departments and agencies in the human health risk assessment of potentially toxic chemicals (Risk Assessment and Toxicology Steering Committee, 1999b). This document describes the way in which UK Government approaches the risk assessment process. A particular recommendation in the report states:

> "It is recommended that an agreed Government view and guidance be developed on the size and application of uncertainty factors for interspecies and interindividual differences, based on the available science and appropriate for the general and the working populations. This would not only facilitate harmonisation of risk assessment practices in the UK but would also assist in ongoing international discussions on this topic."

The Risk Assessment and Toxicology Steering Committee was succeeded by the Interdepartmental

Group on Health Risks from Chemicals (IGHRC), which published its forward plan of work until 2002 (IGHRC, 2000). In considering the range of recommendations made by the Risk Assessment and Toxicology Steering Committee, the IGHRC adopted for action the above recommendation through the publication of this current document.

Until now, there has been no single UK Government document on the use of uncertainty factors in human health chemical risk assessment. The aim of this document is to develop an agreed framework detailing how UK Government departments, agencies and their advisory committees address the issue of uncertainty in the toxicological aspects of human health risk assessment, including the application of the factors they use in allowing for the uncertainties inherent in the process. The document thus provides guidance to both those outside and within Government on the way in which toxicological uncertainty is addressed in the regulatory setting in the UK, while helping to increase transparency, coherence and consistency.

It is important to note that this document addresses only the 'toxicological hazard' aspects of uncertainty in the human health risk assessment of chemicals through the use of uncertainty factors. As explained in more detail below, risk characterisation requires not only the consideration of hazard (toxicity) information but also knowledge of human exposure to the substance(s) of concern. The process of exposure assessment is itself subject to considerable uncertainties, but it is not the remit of this document to address these issues. IGHRC, however, is planning to undertake further work in the important area of exposure assessment (IGHRC, 2000). Furthermore, this document does not address issues of uncertainty in the use of analytical measurement (e.g. in the assessment of compliance with a regulatory standard) or in the apportionment of exposure to a substance from various routes of intake.

From the viewpoint of the toxicological aspects of risk assessment, this document considers the way uncertainty is addressed for those effects where a threshold for response may exist (see below for further discussion of the threshold concept). It does not attempt to address the process of hazard identification or risk assessment for those substances that are considered to possess 'non-threshold' properties, for example genotoxic carcinogens. The UK approach for the risk assessment of such carcinogens has previously been laid out (HMSO, 1991) and has been supplemented by recent IGHRC documentation (IGHRC, 2001).

Ideally, there should be sufficient reliable and relevant data to characterise the toxicity of a chemical adequately, so that those assessing human risk can start from a position of knowledge gained from scientific analysis, even though there may still be uncertainty about the relevance of that knowledge to exposed humans. Uncertainty related to extrapolation from the experimental or toxicological database to the exposed population is usually an unavoidable component of a toxicological risk assessment, and should be distinguished from the ignorance that results from incomplete characterisation of the toxicity of a chemical. For some chemicals, such as medicines and pesticides, available data on toxicity (hazard) characterisation enable as complete a characterisation of toxicity as possible. However there remain many chemicals for which little is known about their biological effects, and any risk assessment must start from a position of relative ignorance. The degree to which ignorance can be addressed depends on the balance between the need for reliable data and the resources available for their provision. While both ignorance and uncertainty must be taken into account in any risk assessment, this document concentrates on the latter, particularly through the application of uncertainty factors.

The following chapters therefore attempt to:

- describe the principles of the chemical risk assessment process;
- introduce the areas of uncertainty relating to toxicological hazard;
- describe how these are addressed, including historical and international perspectives, and the approaches used by UK Government departments, agencies and their advisory committees; and
- provide an overall summary and indication of future directions for this field.

2 Risk assessment

2.1 The risk assessment paradigm

As described previously, a basic framework for the process of risk assessment for human health effects has evolved through national (Risk Assessment and Toxicology Steering Committee, 1999b) and international consensus and is now well accepted (WHO, 1987, 1994). The process generally involves the following four steps: hazard identification, hazard characterisation, exposure assessment and risk characterisation (hazard identification and hazard characterisation are sometimes merged). Subsequent to and dependent upon the outcome of the risk assessment, risk management may be required. Risk management is the evaluation of alternative options and the actions taken to reduce potential risks in light of an adverse risk assessment. Although not considered further in this document, it should be recognised that the risk management approaches available may influence the risk assessment approach adopted (Risk Assessment and Toxicology Steering Committee, 1999c).

Hazard identification[1] is the identification of the inherent properties of a substance (based on structure–activity relationships, *in vitro*, animal and human studies), that *may* lead to adverse health effects in exposed humans.

Hazard characterisation is the evaluation of the effect of relevant factors on the qualitative and quantitative response to a chemical. Relevant factors include mechanism of action, species differences in response, route and level of exposure. Hazard characterisation is usually carried out through dose–response assessment of adverse effects (sometimes called assessment of dose–concentration–response relationships).

Exposure assessment is the measured, estimated or predicted intake of or exposure to a substance, in terms of its magnitude, duration and frequency for the general population, specific subgroups of the population or for individuals.

Risk characterisation is the integration of hazard identification, hazard characterisation and human intake or exposure assessment in order to determine an acceptable level of intake or exposure, to predict whether or not effects in humans are likely to occur, or to predict the nature and severity of adverse effects which may occur in a given population exposed to a given concentration.

At the outset, it is important to emphasise a crucial point. Biological systems and their response to external influences exhibit great variability. Even with a complete and adequate data set it is not possible to predict the precise influence of a chemical exposure on each and every member of an exposed human population. In most cases, as explained below, the data sets available on individual substances are not complete. The aim of most toxicological risk assessment is not to arrive at the best estimate of the magnitude of any risk (with an equal chance of underestimation and overestimation of the risk involved), but rather to determine whether or not there is sufficient reassurance of little or negligible risk under the relevant exposure situation (often of a worst case nature): in such cases an overestimation of risk is much more acceptable than underestimation. Hence, where there is an absence of knowledge with its inherent uncertainty, the approach *defaults* to securing such reassurance, rather than using the most probable estimate of the risk based on statistical inference.

[1] Implicit in these definitions is that the hazard is a property of the chemical, and that the extent to which the hazard is expressed (the risk) is dependent on the dosage. It should be noted that, in relation to food, the *Codex Alimentarius* defines hazard identification as "identification of biological, chemical or physical agents capable of causing adverse health effects". Under this definition it is the agent (substance) rather than the property of the agent (substance) that is defined as the hazard.

2.2 The concept of threshold in the dose–response relationship

From a toxicological perspective the hazardous properties of substances have generally been separated into two discrete sets — those considered likely to possess a threshold for their dose–response relationship and those where it is considered that a threshold may not exist, whether or not one exists in reality. The large majority of toxic properties possessed by substances including, for example, acute toxicity, irritation, non-carcinogenic effects of prolonged exposure and effects on reproduction, are considered to show thresholds in their dose–response relationships. It should be noted that this includes effects which may lead to expression of carcinogenicity through a non-genotoxic mode of action (e.g. sustained cell proliferation). The most well recognised examples of non-threshold effects are genotoxicity *in vivo* and carcinogenicity induced through a direct genotoxic mode of action.

From an historical and regulatory perspective, this dual grouping has been driven by the need to ensure that adequate protection is afforded to exposed human populations. From a scientific perspective, it is plausible that the so-called 'non-threshold' effects may in fact possess a biological threshold, taking into account the influence of toxicokinetics, and defence and repair processes at the molecular, cellular and tissue levels. However, thresholds, if they exist, cannot be identified with any confidence with the techniques currently available, in order to support a less-stringent regulatory position for the control of such serious health outcomes. Thus in general for 'non-threshold' effects the UK regulatory system adopts a prudent approach to risk management, the aim of which is either to prevent exposure or reduce it to very low levels, generally as low as reasonably practicable (Risk Assessment and Toxicology Steering Committee, 1999b). This approach assumes that any level of exposure could result in an increase in risk (IGHRC, 2001). However, it should be noted that decisions on what actions are taken to prevent exposure and what is regarded as 'as low as reasonably practicable' are made on a socio-political basis rather than on purely scientific or technical grounds. Therefore, in the UK, the major risk assessment consideration in these cases is the control of exposure; discussion of toxicological uncertainty is essentially confined to consideration of the relevance of non-human data to the human situation rather than to its quantitative extrapolation.

Although this prudent approach remains the cornerstone for the way non-threshold effects are regulated, there are some recent examples of this being modified in light of appropriate information or interpretation. For example, on a few occasions the Expert Group on Air Quality Standards (EPAQS), in deriving air quality standards for non-threshold air pollutants, has used uncertainty factors to allow for interindividual variability. The basis for this decision was a pragmatic estimate of a level at which an increased risk cannot be detected in a reasonably sized epidemiological study; this is a level which represents a small risk and is an appropriate point of departure for setting a standard (Maynard *et al.,* 1997). The way this approach has been applied is illustrated in Example 1.

Example 1
Recommended ambient air standards for benzene and 1,3-butadiene[1]

Benzene and 1,3-butadiene are air contaminants, produced by human activity such as combustion of petrol and diesel, industrial activity and smoking. Both substances are considered to be genotoxic human carcinogens. In developing recommendations for ambient air standards for these two substances, EPAQS reviewed the available animal and epidemiological data. For each substance, from the available epidemiological data studies in workers, EPAQS identified a level of exposure over a working life (500 ppb (1.6 mg/m^3) for benzene, 1000 ppb (2.21 mg/m^3) for 1,3-butadiene) at which it would be unlikely that any increased risk to workers could be detected in any feasible study. This was used as a point of departure for establishing a standard, and these values were divided by a factor of 100 (10 to allow for the difference in exposure over a working life compared to a whole lifetime, multiplied by another 10 to allow for variation in the whole exposed human population). This gave recommendations of 5 ppb for benzene and, in principle, 10 ppb for 1,3-butadiene. However, EPAQS noted that as both substances are genotoxic carcinogens then exposures should be kept as low as practicable and not allowed to rise. Thus in the case of 1,3-butadiene, where ambient levels were already at 1 ppb as a running national average, it was recommended that this should not be exceeded and a similar level was recommended for benzene.

[1]EPAQS (1994, 2002)

Similarly, for substances that are mutagenic *in vivo,* a linear dose–response relationship is assumed, so that exposure at any level is considered to be associated with some damage to DNA and thus an

increased risk of mutation, albeit that this may be small. However, recently the Committee on Mutagenicity (COM, 2001) has reviewed two mechanisms for mutagenicity where sufficient evidence is available for identification of a threshold for mutagenic activity. These are aneugenicity induced by tubulin inhibitors (see Example 2), and the rapid detoxification of two substances, hydroquinone and phenol, following oral dosing (COM, 2001). In such cases the regulatory approach can then be based on the identification of a critical NOAEL and the use of uncertainty factors.

Example 2
Threshold mechanisms for mutagenicity[1]

The chemicals of the methyl benzimadazole carbamate (MBC) class are widely used as fungicides in approved pesticide products and also in veterinary medicines. These chemicals act by interfering with microtubule formation during mitosis. In 1993 the COM agreed that it was reasonable to assume that aneuploidy-inducing chemicals (particularly those that function by interfering with the spindle apparatus of cell division) have a threshold of action. The safety evaluation of aneuploidy-inducing chemicals (aneugens) acting by inhibition of microtubule formation is based on the identification of a threshold dose below which aneuploidy does not occur. In 1996, the Committee considered the results of experiments undertaken with the MBCs benomyl and carbendazim and concluded that the studies had been satisfactorily conducted and the data indicated that NOELs (no observed effect levels) could be estimated for these two chemicals. It was noted that that it would be difficult to define precise thresholds for activity from these data and the mathematical models that had been used for their analysis.

[1] http://www.doh.gov.uk/comivm.htm

Another property for which it has not generally been possible to define a threshold is sensitisation. In contrast to mutagenicity and carcinogenicity, the assumption that any level of exposure could result in an increase in risk is not necessarily made for sensitisation. However, until recently it has not been possible with the experimental techniques available to define thresholds either for induction of the hypersensitive state or elicitation of an allergic response in a sensitised individual. Example 3 illustrates how this problem has been addressed from a World Health Organization (WHO) regulatory perspective in relation to the development of a maximum residue limit (MRL) for penicillin. There is, though, increasing evidence

Example 3
Establishment of an MRL for penicillins[1]

Hypersensitivity reactions were the most common adverse effects noted in humans exposed to penicillins. The overall prevalence of allergy to penicillin in the human population appears to be in the region of 3–10%. There was no evidence of sensitisation caused by consumption of penicillin residues in food.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated the available data on allergic reactions caused by penicillin residues. Only four cases were considered to be adequately documented to demonstrate that hypersensitivity reactions could be caused by ingestion of less than 40 µg of the drug.

In the absence of adequate data to establish a NOEL, the Committee recommended that the daily intake from food be kept as low as practicable, and in any case below 30 µg of the parent drug. The risk associated with the occurrence of mild hypersensitivity reactions at this level was considered to be insignificant.

[1] WHO, 1991

that thresholds exist in the induction of skin sensitisation, particularly from the development of newer methodologies (Kimber *et al.,* 1999).

For the majority of other hazards it is widely accepted that there is a level of exposure below which no biologically significant effect is induced, that is to say, there is a threshold. Slob (1999) has argued that dose thresholds cannot exist in a strict quantitative sense (i.e. as a discrete step-function in the dose–response relationship), but that thresholds can be defined in relation to the magnitude of any change in a continuous variable, which would be considered not to be adverse. For an individual, the threshold concept makes the assumption that exposures up to some finite amount can be tolerated without the induction of adverse effects. The position of the threshold will vary from one person to another, meaning that there will be a distribution of individual thresholds within any given population. The presence of a threshold cannot be demonstrated readily from experimental data because any experimental dose–response relationship (whether or not it has a threshold) may include doses without a measurable (or statistically significant) biological effect in the test system. Thus the proof of the presence or absence of a threshold for these effects remains a matter of debate and the possibility of a level of exposure that does not

produce an effect has to be based on experience and expert judgement of the underlying biology of the test system (Edler *et al.*, 2002).

2.3 Determination of dose–response relationships for threshold effects

A critical point in the risk assessment for threshold effects is the determination of a dose that can be used as a *surrogate* for the 'true' threshold for the critical effect of concern in the population of interest, that is, a dose at which no adverse effect is observed. This is achieved by consideration of the available dose–response data from studies in humans (rarely) or, more often, from the use of data from studies in experimental animals, human response data being unavailable.

2.3.1 Data from human studies

Dose–response data in humans may be available either from epidemiological studies or, very rarely, by direct experimentation (e.g., the effects of substances on the activity of enzymes such as cholinesterase, or the determination of sensory irritation responses on exposure to airborne substances). There are ethical issues relating to the direct administration of non-therapeutic compounds to human volunteers, although response measurements using biomarkers of minor and reversible changes (such as those indicated above) can provide valuable human data.

The dose–response relationships available from epidemiological studies may involve estimates of levels of exposure of humans at the time of the study (although often retrospective exposure estimates are made), and the contemporary incidence or risk of adverse effect of concern. Such a relationship does not generally provide a reliable estimate if there was an interval between exposure and development of the adverse effect, as, for example, in chronic renal damage. Cumulative exposure estimates may be available in some rare cases, usually from workplace studies, although often the monitoring will have been relatively recent with back-extrapolation for past exposures. Exposure assessment in epidemiological studies is usually imprecise and often non-existent. A further problem may be the potential for the study population to have been contemporaneously exposed to other harmful agents, which could contribute to an observed adverse effect (van den Brandt *et al.*, 2002). Although data from studies in humans are used whenever available, limitations in their extent and quality mean that the majority of risk assessments involve the interpretation of studies in experimental animals and the extrapolation of data across species.

Studies at non-toxic doses do not provide evidence of the dose–response relationship in humans. They can, though, supply data on the metabolism and fate of the chemical in humans (toxicokinetics). Chemical-specific toxicokinetic data, and information on the metabolic and other processes involved in the fate of the chemical, can be used to refine the interspecies extrapolation and human variability aspects of hazard characterisation.

2.3.2 Data from experimental animal studies

In the absence of appropriate information from studies in humans, data from studies in experimental animals are employed. However, not all effects detected in animal studies are predictive of possible adverse health effects in humans. It is normal practice to administer higher doses in hazard identification and characterisation studies in animals compared with human exposures because of the relatively small numbers of animals studied and to ensure observation and measurement of critical effects. The high doses often used in standard animal studies may produce nutritional imbalances or adaptive responses that would not be relevant at the lower levels of intake normally associated with human exposure. In addition, some adverse effects in animals are not relevant to humans, for example the nephropathy induced in male rats by light hydrocarbons (Capen *et al.,* 1999), and the proliferation of peroxisomes induced in the rodent liver (Ashby *et al.,* 1994) by a range of compounds. Therefore an important initial decision, requiring expert judgement, is needed in the available animal studies to define the 'critical effect(s)'. This is the relevant adverse effect(s) that has been detected at the lowest exposure level, and therefore is the most sensitive endpoint. It is assumed that any risks related to other hazards detected at higher doses will be lower than those relating to the critical effect(s). The starting point for identifying the threshold is the definition of a dose level that can be used as a surrogate for the 'true' threshold dose for the effect in the species used.

The no observed adverse effect level (NOAEL) is a level of exposure at which treated animals do not differ appreciably from untreated animals in measurements related to toxic effect(s) recognised at higher doses (see Figure 1). The NOAEL is not simply the highest exposure that does not show a statistically significant difference from controls; the dose–response relation is taken into account,

usually without fitting a mathematical model, in defining whether the response at each dose is a part of the dose–response curve or is a NOAEL. The NOAEL is a dose without measurable adverse activity, and therefore can be considered to be at or below the threshold in animals. The validity of the NOAEL as a surrogate for the threshold is dependent on three main factors of the study design: group size, test sensitivity and dose spacing. The larger the group size the greater the chance of detecting an effect, with the group sizes currently recommended in testing guidelines representing the best compromise between sensitivity and animal welfare considerations. In relation to test sensitivity, the more sensitive the method of detection of adverse effects (e.g. by using specialised rather than general staining techniques in histopathological examination) then the lower the NOAEL may be. Inadequate or poor methods will result in a higher NOAEL, that is, the tendency is to reward poor studies. Dose spacing is a major determinant in defining the NOAEL. Since the NOAEL is the next dose down from the minimal effective dose, the experimental NOAEL may be a gross underestimate of the true threshold if dose spacing is large (e.g. if there are factors of 10 between doses). Modern studies use lower spacing intervals (three to five-fold) in order to reduce this problem. These different aspects (group size, test sensitivity and dose spacing) affect the relationship between the NOAEL and the true biological threshold in different directions and may, to some extent, cancel each other out. In practice the NOAEL should be interpreted in light of the whole dose–response relationship (Edler *et al.*, 2002).

If all test groups produce a significant effect compared to control then a NOAEL cannot be established and a lowest observed adverse effect level (LOAEL) is used instead. In this situation, the LOAEL reference point is an unknown distance above the true threshold, and this adds an extra level of uncertainty to the risk assessment (this issue is addressed further in Section 3.2.1). The LOAEL, like the NOAEL, is an experimental observation and is dependent on both the design of the study and the toxicity of the chemical, as discussed above for the NOAEL.

An alternative method to the NOAEL/LOAEL approach is the benchmark dose, BMD (Crump, 1984; Faustman & Omen, 2001), although this has seen little application in UK regulatory activities. This method uses the full dose–response data to determine the dose associated with a pre-defined low level of response. The numerical value of the BMD is derived by fitting a mathematical model to the experimental data in the observed range and selecting either the central tendency or the 95th percentile lower confidence limit on the dose causing a particular magnitude of response (see Figure 1). It is considered in the United States that the BMD is more suited for quantal (discrete) variables, such as the incidence of a histopathological lesion, for which a particular incidence of effect (e.g. 1% or 5% incidence) can be selected as the BMD. This approach is more

Figure 1 Comparison of the no observed adverse effect level (NOAEL) and the 5% benchmark dose (BMD)

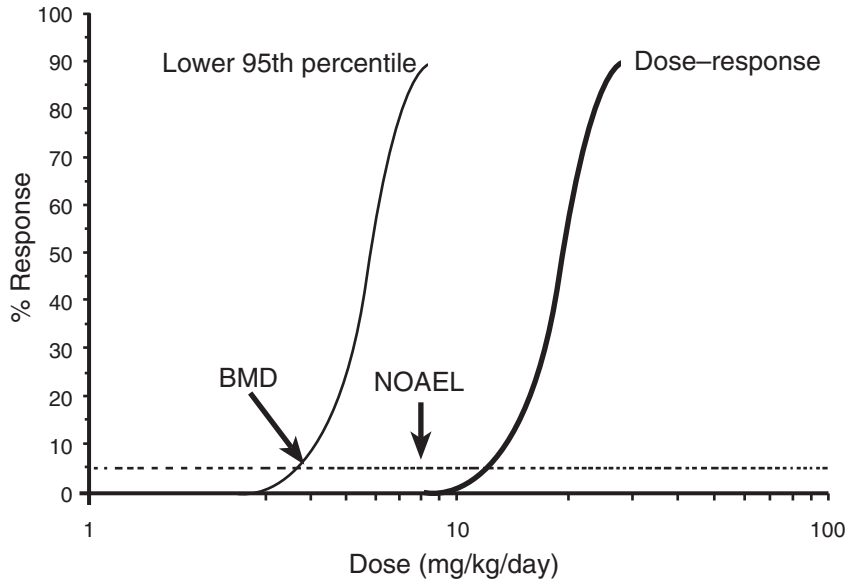


Figure courtesy of Prof AG Renwick, University of Southampton

problematical for continuous variables, such as organ weight, where, for example, a 5% difference may be within the background biological variability seen in control animals and therefore may not represent a true adverse effect. The BMD based on reprotoxicity data is close to the experimental NOAEL and may be either above or below it. The calculation of a BMD for a continuous variable requires the selection of a critical effect size that is considered to represent an adverse response; the dose calculated from the mathematical model to produce this level of response is taken as the BMD (Edler *et al.*, 2002). Advantages of the BMD are that it rewards good dose–response data because this will result in narrower confidence intervals; it is not subject to the limitation of the NOAEL as discussed above; it can be derived from studies that do not show a NOAEL; and it can be derived using smaller numbers of animals in each treatment group. Disadvantages of the BMD are that it cannot be calculated when none of the experimental observations produces an adverse effect; it is very approximate when the adverse effect(s) are only seen at the highest dose in a study; and it requires that graded adverse effects are produced in two or more treatment groups and therefore may result in an increase in the number of animals experiencing distress. The NOAEL gives a deterministic point estimate as the basis for hazard characterisation and cannot be used for probabilistic approaches; the BMD provides a dose estimate with associated uncertainty, and this can be used as the starting point for a probabilistic hazard characterisation (Edler *et al.*, 2002).

2.4 Integration of toxicity data into the risk assessment paradigm for threshold effects

In order to consider the issues of the assessment of toxicological uncertainty in relation to the risk assessment of threshold effects it is useful to understand in general terms the risk assessment activities of UK Government departments, agencies and their advisory committees. Figure 2 summarises the approaches used by UK Government in applying the risk assessment paradigm to substances exhibiting threshold toxicity (Risk Assessment and Toxicology Steering Committee, 1999b). Hazard identification, hazard characterisation and exposure assessment are common stages in all activities. Variation occurs, though, in the way in which the exposure assessment and hazard information are integrated in the risk characterisation step.

2.4.1 Standard setting

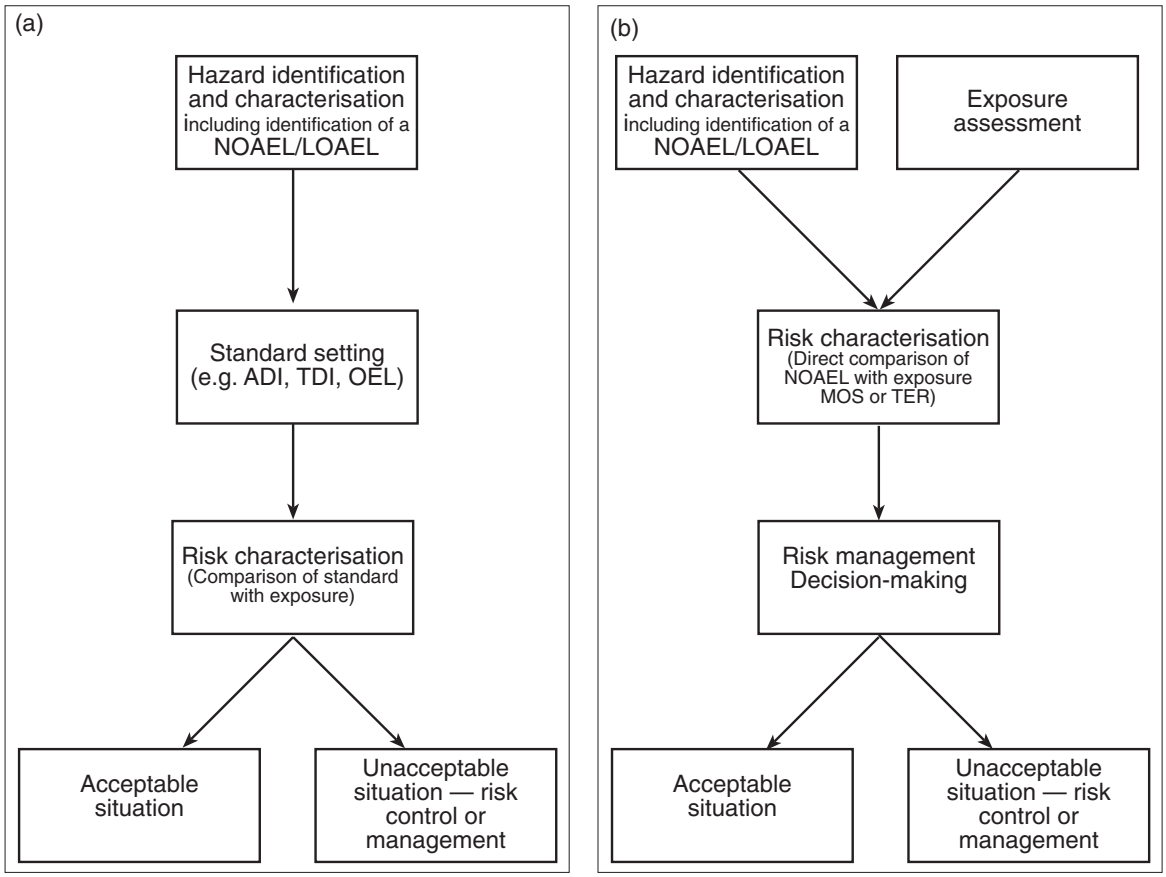
Often the output of the hazard assessment (e.g. the NOAEL for the critical effect) leads directly to the establishment of a regulatory standard or position, for example an acceptable or tolerable daily intake (ADI, TDI), as in Figure 2a.

This regulatory standard is then compared with the exposure assessment. The risk characterisation is conducted by comparing the standard with the estimated exposure. Regulatory decisions on the need for further risk management action are then made on the basis of this comparison. In effect this form of risk assessment is based on the concept of defining a level of dose (the derived standard) expressed usually on a temporal basis (e.g. daily, weekly, yearly) which is considered to offer sufficient reassurance of protection of human health, and then comparing this with an assessed level of exposure. If consideration of exposure indicates a level above the standard then further regulatory intervention may be needed. In this approach the toxicological uncertainties are addressed as part of hazard characterisation and standard setting (i.e. a dose is established that offers sufficient reassurance of absence of adverse response in humans), and are incorporated before considerations of exposure.

For most classes of chemical, standard setting is based solely on risk assessment, and any perceived benefits of the substance, either to the individual or society, are not taken into account. (They are normally taken into account during risk management.) An exception to this is therapeutic substances, where both the risk and the benefit apply to the same individual. In the case of medicines there is an extensive database of information required before registration can be completed (see Section 5.8), and a knowledge-based risk–benefit analysis may be undertaken for the individual patient under clinical supervision, or an approved dosage can be established for medicines obtainable without prescription. In addition, post-marketing surveillance may be used to check the appropriateness of the regulatory decision.

For micronutrients, such as vitamins and minerals, adverse effects could be produced if the intake were too low, due to deficiency, or too high, due to toxicity. For most micronutrients there is a good nutritional database, but toxicological information may be inadequate, with numerous deficiencies in the database. In some cases, application of the normal uncertainty factors discussed below, especially those related to database shortcomings,

Figure 2 Application of the risk assessment paradigm for the human health risk assessment of chemicals by UK Government departments, agencies and advisory committees: (a) as used in standard setting; (b) as used to obtain a ratio between exposure and effect



ADI, acceptable daily intake; LOAEL, lowest observed adverse effect level; MOS, margin of safety; NOAEL, no observed adverse effect level; OEL, occupational exposure limit; TDI, tolerable daily intake; TER, toxicity exposure ratio

might result in an intake that was nutritionally inadequate. Therefore the risk assessment and advice to risk managers about micronutrients represent a balance between the desirability of minimising toxicity while at the same time allowing an adequate intake.

2.4.2 Derivation of a toxicity exposure ratio

An alternative approach, shown in Figure 2b, is to make a direct comparison between the output of the hazard assessment (e.g. NOAEL for critical effect in experimental animals) and the exposure assessment. This approach leads to the establishment of a ratio between, for example, the experimental NOAEL and the estimate of exposure (e.g. the margin of safety, MOS, or toxicity exposure ratio, TER). The interpretation of the significance of the magnitude of the derived ratio in terms of the possible risk of adverse consequences for the health of the exposed population is the key aspect of this approach. The magnitude of the ratio will determine the ultimate regulatory position that is adopted: either regulatory action or acceptance of the existing situation. In this approach the toxicological uncertainties, which are essentially similar to those involved in standard setting (2a), are addressed as part of the risk characterisation step (i.e. by considering whether the ratio is sufficiently large to give the degree of confidence that the exposure situation will not threaten human health).

A further feature has emerged as experience has been gained in the interpretation of MOS/TER values and their relation to the role and treatment of exposure estimates. As indicated in Section 1, exposure assessment is an important and integral part of risk assessment. Where a 'standard setting' approach is used (Figure 2a) in the application of uncertainty factors to a NOAEL/LOAEL, the standard is established by taking into account the biological and toxicological uncertainties that are encountered but not the uncertainties in exposure assessment (these feature later in the process). However, in the interpretation of the MOS/TER one needs to consider whether or not the derived ratio is adequate, taking into account not only the biological and toxicological uncertainties but also the uncertainty involved in the exposure assessment. This is an important issue, particularly

when exposure values are presented as 'worst-case' scenarios. Uncertainties in exposure assessment can be as great as those in the toxicological aspects, since it is often difficult to obtain data sets of exposure information that accurately portray realistically representative exposure estimates of the potentially exposed population. Thus the MOS/TER approach has to allow for these uncertainties when interpretation of the ratios is made. The difficulties in exposure assessment have been recognised and further work within IGHRC is being undertaken to start to address them (IGHRC, 2001).

2.4.3 The problem of uncertainty

The same uncertainties exist in moving from hazard assessment to the development of a standard, or in applying the hazard information to assessing the significance of a derived ratio. In both cases allowance is often made for these uncertainties by the application of numerical factors. In the case of the standard-setting approach, this is directly applied to the hazard assessment/characterisation output (i.e. the NOAEL or LOAEL) in order to derive the standard. In the ratio approach it is part of the consideration of the magnitude of the ratio between hazard assessment output and exposure (i.e. by considering whether the ratio is large enough to accommodate the numerical factors that are used to allow for uncertainties). Other, more sophisticated approaches may be adopted when sufficient data of appropriate quality are available.

The uncertainties that are addressed further in this document, therefore, relate to the use of the hazard output in establishing the regulatory standard (Figure 2a) or interpreting the toxicological aspects of a derived ratio (Figure 2b). These uncertainties are fundamentally related to the biological and toxicological processes and principles involved in the likely expression of a toxic response following exposure to a chemical.

On occasion the risk management philosophy being used will dictate that additional factors may be applied. For example, extra factors may be used because the severity of the ultimate outcome is of particular concern (e.g. irreversible effects on development, or cancer arising through non-genotoxic modes of action), even though the underlying toxicological processes are likely to possess similar threshold and extrapolation characteristics to those of other forms of adversity. Such considerations may be influenced by the risk management scheme under which the risk assessment is being performed (Risk Assessment and Toxicology Steering Committee, 1999c). An analysis of the historical use internationally of such factors showed that they were applied inconsistently and, in some cases, incorrectly (Renwick, 1995). The aim of this current publication is to consider only those areas of uncertainty that are scientific in nature and not to attempt to address those that are influenced by non-scientific issues.

3 Toxicological uncertainties in risk assessment

The toxicological database available for risk assessment varies widely from chemical to chemical. For example, the legal requirements for the approval of a new pesticide or food additive include completion of a relatively comprehensive set of studies, performed to modern regulatory standards, for consideration by the regulatory authorities. In contrast there may be very limited information on many existing industrial chemicals and environmental contaminants, but risk assessments may still need to be performed.

In principle, an ideal database for risk assessment would hold a full range of information from known exposures in a human population, including investigations on all potential health-related outcomes. In some cases data from studies in humans may be available (see Section 2.3.1) and, depending upon the endpoint of interest, may provide enough suitable information for use in risk assessment. Example 4 shows how human data have been used to establish an occupational exposure limit (OEL). Data from experimental human studies for this endpoint would form the basis for the risk assessment. The uncertainties here relate to how reliable the experimental no observed adverse effect level (NOAEL) or benchmark dose (BMD) is as a surrogate for the true threshold, and how representative the data from a small number of human individuals are for a potentially much larger exposed population.

Example 4
Establishment of an occupational exposure limit using human data[1]

Triethylamine (TEA) is used extensively throughout UK industry as an intermediate for a number of products, including agrochemicals and pharmaceuticals, and in the foundry industry in the production of moulds and cores. The critical health effect from exposure to TEA is visual disturbance and local irritation to the eyes, nose and respiratory tract. There are reliable data from two human volunteer studies, which were considered to provide the most suitable basis for an occupational exposure standard (OES). These studies together indicate that 2 ppm as an 8-hour time-weighted average (TWA) OES is appropriate to prevent visual disturbance and eye irritation. This value is also below the animal NOAEL for systemic toxicity of 50 ppm for repeated exposure by a factor of 25. In view of the irritancy of TEA and the possibility that visual disturbances may be caused by short-term peak exposures, a 15-minute short-term exposure limit (STEL) OES of 4 ppm was also considered appropriate. This was based on the lack of symptoms of irritation in one of the human volunteer studies and the results from studies in occupationally exposed workers where such effects have only been associated with airborne TEA concentrations of above about 5 ppm.

[1] HSE, 2002a

In general, though, it is rarely the case that enough relevant data relating to human experience are available. For most substances, risk assessment relies on the information obtained from studies in experimental animals and other test systems covering a range of endpoints. For the majority of chemicals subject to licensing or approval, information on toxicokinetics (absorption, distribution, metabolism and excretion), general toxicity from single and repeated dose administration, reproductive toxicity (fertility and developmental), genetic toxicity and carcinogenicity are often required. For some chemicals, information on skin and eye irritation and skin sensitisation may also be required (sometimes for formulations as well as the parent chemical entity). These studies may be supplemented by more detailed examination of, for example, neurotoxicity, endocrine modulating activity or information on mode and mechanism of action underlying any of the effects seen.

Clearly as the amount of information available from such experimental work increases then the degree of understanding of the hazards expressed in experimental animals also increases, and the uncertainties due to lack of this type of information decrease. However, even with complex experimental databases, uncertainties usually still remain. Table 1 summarises the key areas of uncertainty when using data from experimental animal and other systems in risk assessment.

Table 1 Sources of toxicological uncertainty in risk assessment

Category	Uncertainty
Extrapolation	From non-human species to humans
Extrapolation	Variability in the human population
Extrapolation/ database related	Route-to-route
Database related	Duration of exposure
Database related	NOAEL not established or not firmly established
Database related	Gaps or other deficiencies in database

As can be seen, the uncertainties fall into two broad categories. Firstly, there are the uncertainties related to the extrapolation of the key data from experimental animal species to the 'average' human, and then from the 'average' human to other members of the population with different characteristics (i.e. those with greater sensitivity). There are then a number of uncertainties related to the available database.

It is clear that increased knowledge of the mechanisms of toxicity helps to reduce uncertainties in extrapolation, and increased amounts of information help to reduce the uncertainties related to the database (e.g. in studies where there are gaps in the database or further work is required on different routes of exposure).

3.1 Uncertainties relating to extrapolation

3.1.1 Animals to human

The relevance of effects detected in animal studies to human health depends on:

- the presence and importance within human cells and tissues of the critical target affected in animals;
- the presence and relative amount of the ultimate toxicant in the target tissue of experimental animals compared with humans;
- the presence and relative efficiency of protective mechanisms; and
- the relative sensitivity of the target to the active chemical entity in animals compared with humans.

The few data that are available on the inherent sensitivity of human tissues to foreign chemicals (toxicodynamics) suggest that in general (but with specific exceptions such as peroxisome proliferation) this is not an important source of species differences compared with differences in the toxicokinetics of a chemical (Renwick, 1993). Species differences in the fate of the chemical in the body (toxicokinetics) arise from differences in the rate and extent of metabolism, and physiological differences such as heart rate, cardiac output and renal and hepatic blood flows. For example, hepatic and renal plasma flows are 3–4 times lower in humans than in rats, so that humans are likely to have higher body loads for a comparable daily intake on a mg/kg body weight basis (Renwick, 1993). When differences in liver weight and enzyme activity are taken into account there may be larger differences in clearance, half-life and body burden. Hence there are reasonable grounds for expecting quantitative differences in sensitivity between humans and experimental animals. Unless detailed information is available on the relative toxicokinetics and toxicodynamics between humans and the key experimental species there is uncertainty when extrapolating from data obtained in the key animal to the human, and this needs to be accounted for in conducting a risk assessment.

3.1.2 Human variability

Variability in the human population may result from genetic differences (including enzyme polymorphisms), age, gender and environmental and other lifestyle factors, for example nutrition. The human population may include potentially sensitive sub-groups of individuals, for example those with particular enzyme deficiencies. Variability in sensitivity at the site of action could occur as a result of genetic predisposition, age (e.g. in developing organ systems), pre-existing disease, or co-exposure to environmental agents (the effects of which could be synergistic, simply additive or antagonistic). Variability in homeostatic mechanisms could occur as a result of genetic or environmental factors, disease or old age. With the exception of therapeutic responses (Renwick & Lazarus, 1998) few data are available on the

variability in the sensitivity of human tissues to foreign compounds, particularly for systemic effects, since it is difficult to separate the contributions of kinetics and dynamics to *in vivo* variation in the ultimate response (Renwick, 1993). For some compounds it may be known that a particular group of the population could be more sensitive to the effects, possibly due to deficiencies in detoxification pathways, as happens for example where there is polymorphism in the enzymes involved in xenobiotic biotransformation. This should be taken into account if the deficiency could lead to a marked change in either bioavailability or clearance of the parent compound or a change in the extent of the formation of a toxic metabolite. In addition, some life stages may be more sensitive than others because of toxicodynamic differences, for example in the developing embryo or elderly people.

There is currently particular concern about the sensitivity of infants and children. For example, in the USA the 1996 Food Quality Protection Act (FQPA) specifically sets stricter standards for infants and children in relation to pesticides residues in foods, in order to address concerns relating to potentially higher intakes and sensitivity in these age groups. The immaturity of hepatic metabolism and low clearance rates in pre-term infants mean that they may represent a vulnerable sub-group in the population because of the potential for increased systemic levels of the parent compound. In contrast, a recent review on the differences in kinetics between adults and children indicated that young children often eliminate drugs more rapidly than adults through enhanced metabolism and excretion (Renwick, 1998). Thus on toxicokinetic considerations alone children may be at lower risk of adverse effects (assuming that the parent compound is the active entity), compared with adults. Little information is available on the quantitative differences in intrinsic sensitivity (i.e. toxicodynamic rather than kinetic aspects) in target organ response between adults and neonates or children. The limited data from studies in children on therapeutic drugs that used mathematical models to separate the contributions of kinetics and dynamics indicate no significant difference in inherent sensitivity compared with adults. There appears to be no general, evidence-based case for treating children as a particularly sensitive sub-group on the basis of information currently available, providing that adequate developmental studies have been undertaken in animals (Renwick *et al.,* 2000) and differences in exposure are taken into account. Clearly there is a need for adequate developmental toxicity studies to investigate effects on developing organs, such as the immune and endocrine systems. In specific cases the nature of the toxic effect (e.g. post-natal developmental neurotoxicity) or the exposure situation may indicate that infants should be considered as a special sub-group for risk characterisation, and an uncertainty factor may be required in the absence of an adequate developmental study.

Clearly there is the potential for a population to vary in its response to a chemical exposure. In many cases it is unlikely that the data available for a risk assessment will provide enough information to determine the nature and extent of such variability, and thus this uncertainty needs to be accounted for in undertaking the risk assessment.

3.2 Uncertainties relating to deficiencies in the database

There are well-established guidelines on the extent and design of toxicity studies needed to gain approval for use of a chemical such as a food additive, pesticide or medicinal product, both in the UK and internationally (Risk Assessment and Toxicology Steering Committee, 1999b). However, in other cases a risk assessment may have to be undertaken using an inferior database, as is often the case for chemicals that may be environmental or workplace contaminants. This situation introduces extra uncertainties into the assessment, as indicated in Table 1 and outlined below. However, it should be noted that this is not an exhaustive list of the uncertainties relating to limitations in the database. There can be many sources of uncertainty associated with a limited database, for example, the rate at which the dose is delivered (e.g. as a bolus as opposed to in the diet), the vehicle in which it is delivered, the form in which it is delivered (e.g. solid particles as opposed to a solution in droplet form in inhalation studies), the uncertainties in identification of the NOAEL (as described earlier) and the differences in life span between experimental animal species and humans. However, those listed in Table 1 and described briefly below are considered to be particularly important. They have been studied with a view to developing appropriate uncertainty factors.

3.2.1 Absence of a NOAEL

In some cases the lowest dose used in the key experimental animal study may have resulted in the critical effect being observed, albeit sometimes at a low level of expression. This precludes identification of a NOAEL in that species. As indicated in Section 2.3.2, in this situation a lowest observed adverse effect level (LOAEL) may be used

as an alternative to a NOAEL. Since a LOAEL represents a dose level at which an adverse effect is observed, then the NOAEL could only be determined in such a study had lower dose groups been included. However, the dose interval between the LOAEL and what would have been a NOAEL is often unclear, and this uncertainty needs to be accounted for in the risk assessment. An alternative and more scientifically credible approach in such situations would be to calculate the BMD, although as indicated previously little or no use of this has been made in UK regulatory activity.

3.2.2 Route-to-route

It may be the case that the data generated in experimental animal studies involved the dosing of animals by one particular route of exposure (e.g. orally through the diet) whereas a subsequent risk assessment may focus on the exposure of humans by another route (e.g. inhalation). Arguably this may be considered an issue of extrapolation rather than a deficiency in the database. It may be addressed by correcting the exposure to allow for differences in internal dose (body burden) based on knowledge of relative absorption by different routes of exposure if this information is available. However, in such cases there is the need to consider the uncertainty in applying data from the route of experimental exposure to the route of interest. Uncertainty exists in both a qualitative sense (e.g. whether the experimental data provide information about potential local effects in the portal of entry) and in a quantitative sense (e.g. whether the systemic dose levels and the shapes of the concentration–time curves achieved by each route of dosing would be the same, or would differences occur due, for example, to differences in uptake and/or first-pass effects following oral dosing). If the toxicokinetic information available on a substance is relatively meagre then there might be considerable uncertainty involved in estimating route-to-route comparisons in response. Physiologically-based pharmacokinetic (PBPK) modelling may provide a method by which this issue can be addressed in the cases where enough information is available.

3.2.3 Duration of exposure

Ideally the duration of exposure in the animal study reflects potential human exposures expressed as a proportion of life span, or in relation to a known mechanism of toxicity. In certain cases a lifetime or chronic study may not be available and it will be necessary to use data from a shorter duration study (e.g. a 90-day study). This may not pose a real problem in situations where the expected human exposure to be considered in the risk assessment is of limited duration, for example in seasonal work lasting only two or three months per year, or for occasional use by a consumer of a product.

However, where human exposure is likely to be long term and regular (including lifetime exposure) then the lack of data from a long-term study needs to be accounted for in the assessment. For some chemicals, if adequately performed long-term studies are not available, then data on the extent of accumulation in the body and the rate of excretion found in shorter-term studies may be valuable in assessing the need to compensate for potential tissue build-up over a lifetime (Rubery *et al.*, 1990).

3.2.4 Gaps or deficiencies in the database

The available studies on a chemical may be inadequate to cover the whole range of toxic properties that a substance may potentially possess. For example, data might not be available for particular life stages, such as effects on reproduction (fertility or development). For some chemicals the database that is available may be relatively old, and the analytical techniques employed limited compared with modern standards. In such cases there is uncertainty as to whether or not all potential toxic effects have been studied and identified (e.g. older inhalation studies may not have considered effects in the respiratory tract; modern staining techniques for neuronal damage may not have been employed in older studies). In cases such as these the risk assessment has to account for the uncertainties generated by these gaps in knowledge.

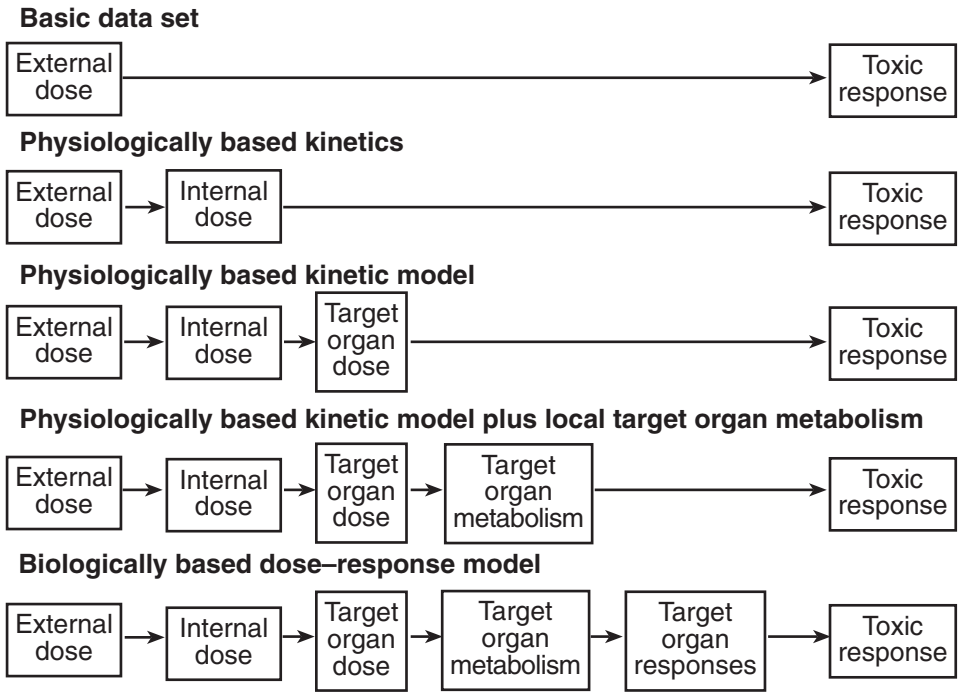
4 Dealing with the uncertainties

The various sources of uncertainty in the risk assessment process have, over the years, been addressed with increasing sophistication as more information and new approaches and techniques have become available. Figure 3 shows how increased availability of information can improve extrapolation from a basic data set. The figure illustrates a continuum of approaches to addressing interspecies differences and human variability.

At one time the information available only allowed the approach adopted in the first row of Figure 3, but as more information became available then more complex and predictive approaches were adopted (this issue is addressed in more detail in Section 4.2.4). The approach adopted for any specific substance is determined by the amount of available relevant data. In turn the amount of data available is, to a large degree, determined by the extent of human exposure, the type of substance and its economic importance: the more important the substance the greater the amount of data likely to be available.

When extensive information is not available, the basic approach normally used in chemical risk assessment has been to apply numerical factors to allow for the uncertainties in the assessment. The terms used for the numerical factors vary depending upon the context and the country where they are employed. So, for example, the terms 'safety', 'assessment', 'extrapolation' and 'uncertainty' factors (and this is certainly not a comprehensive listing) have been used over the

Figure 3 Increasing levels of sophistication in the relationship between external dose and toxic response



From Renwick *et al.*, 2001, reprinted with permission from Amherst Scientific Publishers

years in different contexts. Essentially all are employed to allow for the uncertainties in the risk assessment process. In the context of the present document the term uncertainty factor is used, since this document specifically addresses uncertainties in the risk assessment process.

4.1 Historical perspectives

Although their history is somewhat unclear, the use of numerical factors in risk assessment can largely be traced back to the mid 1950s and the USA's response to the introduction of legislation in the area of food additives. The US Food and Drug Administration (USFDA) proposed that a safe level of an additive or contaminant in food could be derived from a chronic no observed adverse effect level (NOAEL; expressed as mg/kg in diet) from animal studies, divided by a 100-fold 'safety' factor. The original rationale for the 100-fold factor was based on a consideration of the contemporary knowledge of the toxicity of fluorine in rats and arsenic in dogs, each compared with their perceived toxicity in humans (Lehman & Fitzhugh, 1954). Although this was an interspecies comparison, the factor was also considered to cater for variability within a population (allowing for there being more-sensitive people in the human population due to illness), and also possibly for synergism with other substances to which some people would be exposed. It is interesting to note that in their paper Lehman and Fitzhugh state:

> "The '100-fold margin of safety' is a good target but not an absolute yardstick as a measure of safety. There are no scientific or mathematical means by which we can arrive at an absolute value. However, this factor of 100 appears to be high enough to reduce the hazard of food additives to a minimum and at the same time low enough to allow some use of chemicals which are necessary in food production or processing".

This statement is still applicable today, although there have been various attempts over the years to justify and rationalise this basic 'default' position, as well as to develop a more scientific approach to allow suitable information to be used quantitatively in the risk assessment process. However, it remains the case that originally the 100-fold factor was an essentially arbitrary value based on little scientific evidence. It was adopted with the aim of providing 'sufficient' reassurance of safety but, interestingly, there is also something of a cost–benefit balance in this original statement.

The factor of 100 as originally proposed by Lehman and Fitzhugh was discussed at, and considered adequate by, the Joint FAO/WHO (Food and Agriculture Organization/World Health Organization) Expert Committee on Food Additives (JECFA) in 1958. This approach was formally adopted in 1961 by JECFA at its sixth meeting, where it was used in the establishment of the first acceptable daily intake (ADI), although in fact case-by-case margins from 10 to 500 were used for the individual substances examined at that meeting (JECFA, 1962). The practice of using this overall factor of 100 to allow for the uncertainties in extrapolating from experimental animal studies to the real-life human situation was subsequently widely adopted (as demonstrated below for various national and international activities) and is still used today. In many cases the value has been used, with subdivision, usually in the context of the setting of (safety) standards (e.g. ADI or tolerable daily intake, TDI), and has become established as the 'default' position when only the basic, minimally required information is available. An uncertainty factor of 100 would be adopted as the default in the situation described in the top row of Figure 3. Where more data are available (e.g. comparative toxicokinetic and mechanistic studies) then there has been an increasing tendency to use such data wherever possible rather than rely solely on the default position (i.e. moving progressively down through the rows of Figure 3).

Subsequent to the adoption of the 100-fold factor, various authors have attempted to provide a scientific rationale for this choice. For example, Bigwood (1973) provided an expanded rationale for the 100-fold factor, assigning a portion of it to each of the following five sources of variation (experimental animal versus human): body size; food consumption patterns; water balance; hormonal function and their effect on food intake; and differences in inherent sensitivity to toxic effects. Based on an analysis of the then available toxicological data, the first four were considered to be sufficiently accounted for by a factor of about 60, with the fifth (differences in inherent sensitivity) being essentially unquantifiable but taken as being allowed for by the extension of the factor to 100. Vettorazzi (1976) rationalised the use of 100-fold on the basis of possible differences in susceptibility to toxicants between animals and humans, possible variation in sensitivity within the human population, the small size of the groups of animals used in toxicological testing compared with the size of the human population that is potentially exposed, the difficulty in estimating human intake and the possibility of synergistic action among chemicals within the human diet. The factor of 100

has been used for nearly 40 years in the derivation of ADIs for food additives by the JECFA (WHO, 1987; Lu, 1988).

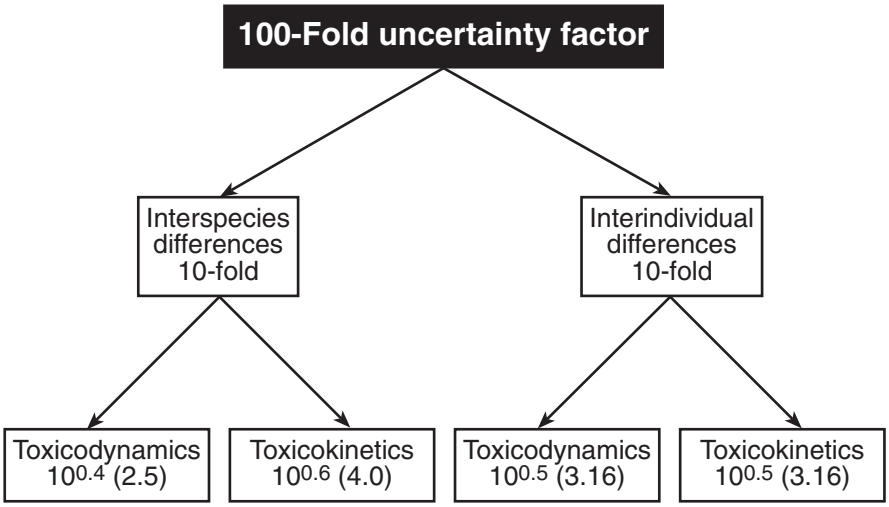
In general this 100-fold factor has been seen as allowing for the uncertainty in deriving a human equivalent sub-threshold dose from an animal NOAEL in a chronic dosing animal study using relatively small numbers of animals (WHO, 1987; Dourson *et al.*, 1996), accommodating the possibility of interspecies and intraspecies variations both operating in the direction of increasing sensitivity, compared with the experimental animal data. Where experimental human data are the basis for defining the NOAEL, a factor of 10 is normally used. Thus the 100-fold default has been seen as allowing for the possibility of a 10-fold increase in sensitivity in extrapolating from animals to humans and a 10-fold difference in sensitivity between the threshold dose for an average person in the population to a (lower) threshold dose for a sensitive human in the population (WHO, 1987). The 10-fold factors are multiplied on the assumption that they are independent variables (i.e. that human variability and species differences are independent even when they relate to the same process). In turn, each of these 10-fold factors can be thought of as covering the possibility of differences (between animals and humans) and variation (within a human population) in how substances are taken in, metabolised, distributed and excreted by the body (toxicokinetics) and how they interact with target sites and the subsequent reactions leading to adverse effects (toxicodynamics). This concept of further subdivision of each factor into toxicokinetics and toxicodynamics is considered further below. It is important to emphasise that the factors are used not in the sense of accurate predictors of the situation. For example, it is not a generally established fact that humans are more sensitive to all toxicants than are experimental animals. Rather, the factors are used to allow for the possibility (in the absence of knowledge) that the above statement is true for the substance in question.

The validity of this approach has been the subject of investigation by a number of scientists and the subject of numerous reviews (Dourson & Stara, 1983; Calabrese, 1985; Hattis *et al.,* 1987; Lewis *et al.,* 1990; Sheehan & Gaylor, 1990; Calabrese *et al.,* 1992; Renwick, 1993; Naumann & Weideman, 1995; Dourson *et al.,* 1996; Renwick & Lazarus, 1998; Burin & Saunders, 1999; Vermeire *et al.,* 1999; Walton *et al.,* 2001). In general, these reviews have been post-hoc analyses of the validity of the uncertainty factors that were selected in the 1950s.

As described by Dourson *et al.* (1996), the same 100-fold default approach has been applied and continues to be applied to a wide range of situations in which risk assessment is undertaken (see Section 4.2 and Chapter 5), and on a broad range of substances with diverse chemical structures, metabolic fates and target organ effects. The approach has been open to criticism because of its simplicity, and the appropriateness of a single default approach has been questioned (Calabrese, 1985; Hattis *et al.,* 1987). The analysis of human variability by Renwick & Lazarus (1998) demonstrated that the 10-fold factor was adequate to cover most known examples of interindividual variation, but that situations could be envisaged in which a compound might be metabolised in such a way that there would be greatly increased human variability. Recent analyses, based on the variability in the metabolism and excretion of foreign compounds (mostly therapeutic drugs), indicate that the default uncertainty factor for toxicokinetics ($10^{0.5}$ or 3.2 — see below) will cover at least 99% of the adult population for some metabolic pathways (Dorne *et al.*, 2001a, 2001b, 2002, 2003a, 2003b). Where appropriate data have been compared, a similar picture has emerged for animal-to-human extrapolation; that is to say, a 10-fold factor seems to accommodate most recognised cases of variability. Overall, in general, the analyses that have been performed indicate that the 100-fold default position provides a high degree of confidence in safety.

As increasing amounts of new information, both generally and for specific chemicals, have become available on various aspects of these areas of uncertainty, it has led to further developments in approach. Over the years a number of approaches have been proposed for substituting scientifically derived uncertainty factors for these standard defaults. Lewis *et al.* (1990) described a methodology (LLN model) for establishing guidelines for determining atmospheric emissions, although it is applicable to standards for other routes of exposure. This methodology attempts to separate out the scientifically based factors involved in 'uncertainty' from those believed to be related to policy issues. Renwick (1993) proposed the division of the two 10-fold factors into sub-factors to allow for differences in toxicokinetics and toxicodynamics (see Figure 4). The 10-fold factor for interspecies differences was subdivided into 4.0 for kinetics and 2.5 for dynamics, because a value of four is necessary to allow for basic physiological differences in organ blood flows between rats (the most common animal model) and humans. The 10-fold factor for human variability was subdivided similarly by Renwick (1993) into 4.0 for kinetics and 2.5 for dynamics, but this was revised at an

Figure 4 Subdivision of the normal 100-fold default uncertainty factors as proposed by Renwick (1993) and modified by IPCS



From WHO, 1999; reprinted with permission from WHO

International Programme on Chemical Safety (IPCS) meeting (WHO, 1994) into an even 3.2 to 3.2 split. The aim of this approach is to allow for the introduction of chemical-specific data for one or more of the aspects of toxicokinetics and toxicodynamics. Thus, where data are available on specific chemicals, these can be used to replace the default values in this model. The ultimate approach to the replacement of default uncertainty factors has been the development of physiologically-based toxicokinetic/toxicodynamic (PBTK/TD) modelling (the last row of Figure 3), where all default positions are replaced with mathematical models, based on normal physiology, which describe and predict how a chemical is handled and may react with the body (Risk Assessment and Toxicology Steering Committee, 1999d). These chemical-specific approaches have been adopted by the IPCS (WHO, 1994, 1999) and have been expanded upon recently (WHO, 2001[1]). This is considered in more detail in Section 4.2.4.

Alternatives, such as probabilistic methods, have been proposed (Baird *et al.,* 1996; Price *et al.*, 1997; Slob & Pieters, 1998; Vermeire *et al.*, 2001). Probability-based approaches require knowledge about the uncertainty associated with the starting point, that is, the benchmark dose (BMD), combined with assumptions about the nature of the distribution of uncertainty factors (Edler *et al.*, 2002), some of which are more well-founded than others (Vermeire *et al.*, 2001). Probabilistic approaches, while not having been used in the UK regulatory context in terms of toxicological assessments, may offer a potentially useful tool in the future and IGHRC is further investigating this potential (IGHRC, 2000).

Alongside the adoption of the 100-fold factor to account for uncertainties in inter- and intraspecies extrapolation issues, the other areas of uncertainty relating to limitations in the database (see Section 3.2) have also been addressed. As is the case for the inter- and intraspecies extrapolations, the approach generally used has been to adopt default uncertainty factors to allow for limitations in the database (Dourson *et al.*, 1996). These factors have again generally been of the order of 10-fold, although attempts have been made to analyse available databases in order to provide a scientific underpinning for these or other numerical values.

The sub-chronic (or sub-acute) to chronic factor is based on the assumption that an effect seen after shorter durations will also be seen after a lifetime of exposure but at lower dose levels of exposure. There have been a number of analyses of data where comparison has been made between NOAELs and/or LOAELs from sub-chronic and chronic studies, and ratios between the two developed (McNamara, 1976; Dourson & Stara, 1983; Wouterson *et al.*, 1984; Lewis, 1993; Baird *et al.*, 1996; Kalberlah & Schneider, 1998; Vermeire *et*

[1] WHO (2001) *Draft Guidance Document for the Use of Data in Development of Chemical-Specific Adjustment Factors (CSAFs) for Interspecies Differences and Human Variability in Dose/Concentration Response Assessments* IPCS, World Health Organization, Available [June 2003] at http://www.who.int/pcs/harmon_site/harmonize/uncert_variab.htm

al., 1999). In general these analyses have indicated that ratios lower than 10 (~2–5) apply in moving from a reference point (e.g. a NOAEL) for one time period to the same reference point in a study of the next higher duration (e.g. sub-acute to sub-chronic; sub-chronic to chronic). However, these analyses have a number of difficulties. Because they are based on comparisons of NOAELs and/or LOAELs, which are defined essentially by pre-selected doses (doses in longer-term studies are often based on the preceding shorter duration study), the analyses are influenced by dose selection rather than being solely an estimate of the true difference in the biological threshold. Also, studies of different durations may focus on different endpoints and effects, so that some endpoints may not be investigated as thoroughly in one study as another. The concern here is that the less comprehensive study might have missed important findings. Thus these analyses at best provide an indication of the possible extent of change in NOAEL with variation in exposure duration, rather than providing robust support for any particular value reflecting the true difference due to differences in dosing period.

A similar approach has been used in those cases where only a LOAEL is available as a starting point. Analyses of several databases have suggested that dividing the LOAEL by a factor of 10-fold or lower is sufficient to allow for the lack of a NOAEL (e.g. Dourson *et al.*, 1996; Vermeire *et al.*, 1999). However, as for the exposure duration analyses above, any value for a LOAEL/NOAEL ratio determined from published studies will be dependent to a certain extent on dose selection, and thus is as much a reflection of experimental dose spacing as an accurate toxicological value. It is arguable that expert consideration of the data, including assessment of the shape of the dose–response curve and the magnitude of the effect at the LOAEL, is a better solution in such cases (Vermeire *et al.*, 1999). As indicated previously, where only a LOAEL is available, an alternative approach is the use of the BMD, although this has yet to be adopted in the UK.

The other areas of database-related uncertainty are those situations where key data may not be available (e.g. a lack of information on reproductive toxicity). The historical default approach to this situation has been to apply an uncertainty factor of up to 10 to the NOAEL from the studies performed, and the endpoint investigated to allow for a lack of potentially important information (WHO, 1994; Dourson *et al.*, 1996).

The default (and more developed) approaches outlined above have generally been adopted in many situations where chemical risk assessment and the setting of exposure standards is performed. One notable exception has been in the occupational arena. Formal toxicological risk assessment (Figure 2b) for substances in the occupational setting, usually based on experimental animal data, has been a relatively recent development (particularly in the UK and the EU), largely stimulated in the 1990s by the requirements under EU regulatory programmes such as the Notification of New Substances (NONS) and the Existing Substances Regulation (ESR). The development of workplace airborne exposure standards (i.e. the situation described by Figure 2a) has a longer tradition. In this activity there has been no attempt to apply default factor approaches. In most cases the procedure for setting occupational airborne exposure standards has involved deriving the standard directly from the NOAEL (or LOAEL), usually involving judgement from an expert committee, without any clear definition of the specific factor(s) that may have been used, and with a poor record of the basis for the judgement. Retrospective analysis of 24 occupational exposure standards (OES) established in the UK between 1990 and 1993 indicated that assessment factors in the range 1–10 emerged for most substances where the critical data were available from animal studies alone, with higher factors sometimes being evident where the critical effect was of particular concern, such as developmental effects (Fairhurst, 1995). Factors of 1–2 were used where the database contained key human evidence, normally for effects such as sensory irritation. It should be noted, however, that the UK occupational exposure limit (OEL)-setting process has to accommodate other considerations in addition to those discussed above, such as the reasonable practicability of controlling exposure to the standard, and the ability to monitor exposure at the level of the standard (Fairhurst, 1995). These considerations, and the socio-economic traditions surrounding the assessment and control of risk in the workplace relative to risk in other aspects of life, have meant that uncertainty has been dealt with rather differently in the occupational setting, with smaller margins between the toxicological reference point (e.g. NOAEL) and exposure levels deemed to be acceptable. This attitude has prevailed not just in the UK but also in most OEL-setting systems around the world (e.g. American Conference of Government and Industrial Hygienists (ACGIH), MAK Commission).

4.2 Approaches used outside the UK

Before considering in more detail the way uncertainty is currently addressed by UK

Government departments, agencies and their advisory committees, it is useful to reflect on the approaches used by some authorities and bodies outside the UK. This is not intended to be a comprehensive review of all the approaches used worldwide but rather illustrates approaches used and highlights contemporary emerging ideas and initiatives. It also serves to illustrate the general consistency of approach that has developed across the international toxicological risk assessment community as indicated in the previous section. It should be noted that the focus here is on the application of uncertainty factors within a particular context, and not the broader issues of these contexts themselves, or related issues such as weight of evidence that may be influential upon a specific assessment. In some cases risk assessments carried out at an international level (e.g. as part of EU or WHO activities) are either used directly by, or receive input from, the UK. These situations are covered in Chapter 5 as they illustrate the way uncertainty factors are used by the UK, even though the UK input may be part of a wider international activity. As described above, the use of uncertainty factors, particularly the default values used for inter- and intraspecies extrapolation, emerged from international activity such as by JECFA and related bodies (e.g. Joint (FAO/WHO) Meetings on Pesticides Residues, JMPR); these activities are not discussed further but are recognised as being important international influences.

4.2.1 United States Environmental Protection Agency

Since the 1980s the United States Environmental Protection Agency (USEPA) has been prominent in developing approaches to the handling of uncertainty in toxicological risk assessment. The approach adopted by USEPA is also generally representative of the way in which other US authorities address uncertainty, although the terminology and choice of uncertainty factors may differ. For example, USEPA uses the terms uncertainty factor and reference dose or concentration (RfD, RfC), whereas the US Food and Drug Administration (USFDA) uses the terms safety factor and ADI. Nevertheless, the principles and approaches used are fundamentally similar.

The USEPA derives RfDs from the application of uncertainty factors to the NOAEL or LOAEL of the critical effect (Dourson, 1994). The approach used is as in Figure 2a, where application of factors leads to the development of a standard against which exposures can be compared. In general, the following standard default uncertainty factors are employed.

- A factor of 10 is used when extrapolating from valid experimental results in average healthy humans where prolonged exposure has occurred, to account for the variation in sensitivity among members of the human population (an intraspecies factor).

- A factor of 10 is used when extrapolating from valid results of long-term studies on experimental animals, when human data are not available or are inadequate (an interspecies factor).

- If long-term toxicity data are not available in experimental animals or humans then a factor of 10 is employed to account for the uncertainty involved in using a shorter term NOAEL rather than one from a chronic study (a shorter term to longer term exposure factor).

- If it is not possible to identify a NOAEL and a LOAEL is used instead, then an extra factor of 10 is employed to account for this (a LOAEL to NOAEL factor). If a BMD approach is used then this issue is less significant and this default uncertainty factor is not required.

As well as the factors used above, an extra modifying factor (MF) may also be used. This is greater than zero and less than or equal to 10, and is based on professional judgement in assessing the scientific uncertainties in the database over and above those addressed above. For example, a factor may be introduced to allow for the lack of completeness in the overall database (e.g. no data on reproductive toxicity). The default value for the MF is 1.

The final value of the uncertainty factor is the product of all the above specific factors employed, including the MF (e.g. for a chemical with a full data set, including a NOAEL from a chronic bioassay and a MF of 1, then the overall uncertainty factor is likely to be 100). However, in undertaking an assessment the USEPA may consider substances with less extensive data sets. In these cases the overall uncertainty factor would be substantially greater — 1000, for instance. In cases where the product of the specific factors would be greater than 10 000 the USEPA considers the database to be too limited to serve as the basis for a risk assessment based on numerical data.

As indicated in Section 3.1.2, the Food Quality Protection Act (FQPA) explicitly requires USEPA

to address risks to infants and children in relation to pesticide residues in food. This allows for an extra uncertainty factor of up to 10 (less if reliable data show that a different factor is supportable) for infants and children. The UK's Advisory Committee on Pesticides (ACP) has taken the approach that the routine application of higher uncertainty factors, as used in the USEPA risk assessment for children, is not justified. Use of additional factors would be considered on a case-by-case basis, taking into account all the relevant data, and must have a sound scientific basis if used (ACP, 2001[1]).

The default values of 10 are adopted from the established historical convention of using these values supported by the post-hoc analyses, as described in Section 4.1. It should be noted that USEPA views the RfD as an estimate that has an uncertainty associated with it of up to perhaps 10-fold.

The situation for RfCs for airborne substances is similar, but differs in one important aspect: it incorporates dosimetric adjustments to allow for species-specific differences in the relationship between exposure concentration and deposition or delivered dose in the respiratory tract (Jarabek, 1994, 1995). The default uncertainty factor for interspecies extrapolation using this approach is about three-fold rather than 10-fold. This reduction is based on the approach used taking into account interspecies differences in delivery to and uptake by the airways and lungs, although this would relate largely to local rather than systemic effects. An RfC would not be developed if the total database did not extend to at least a sub-chronic inhalation study (Jarabek, 1994).

More recently, where the data have become available, USEPA has employed the use of PBPK modelling in the development of a risk assessment (EPA, 1999[2]).

4.2.2 Health Canada

The approach adopted by Health Canada in determining a TDI or TC (tolerable concentration) for threshold effects in relation to environmental exposures is again to use the NOAEL or LOAEL (or, if appropriate, a BMD) for the critical endpoint as a starting point (Meek *et al.,* 1994). TDIs or TCs are not normally developed on the basis of acute or short-term studies, although sub-chronic data may be used if no adequate chronic study is available. Normally the TDI/TC is developed on data from the appropriate route of human exposure, but exceptionally, where a NOAEL or LOAEL cannot be identified in studies by the appropriate route, data from another route of exposure may be used, incorporating relevant toxicokinetic data in the route-to-route extrapolation.

Uncertainty factors are derived on a case-by-case basis, depending largely on the quality of the available database. Generally a factor of one to 10 is used to account for interspecies differences and for intraspecies variation, with 10×10 being the usual default. Where data are available these factors are modified in light of toxicokinetic or toxicodynamic information as suggested by IPCS (WHO, 1994, 1999, 2001[3]). An additional factor of one to 100 is used to account for inadequacies of the database, such as a lack of data on developmental toxicity, fertility or chronic toxicity, use of a LOAEL or limitations in the critical study. An additional uncertainty factor of between one and five may be used where there is sufficient information to indicate a potential for interaction with other chemical substances commonly present in the general environment. Overall, numerical values of the uncertainty factor normally range from one to 10 000. Uncertainty factors of greater than 10 000 are not applied since the limitations in the database are such that they are judged to preclude development of a TDI or TC.

4.2.3 Netherlands approach for new and existing substances

The method used by the Netherlands for the risk assessment of new and existing industrial chemicals when meeting their obligations under the EU regulatory programmes was developed using information published by the European Commission and various published sources (Hakkert *et al.,* 1996; Vermeire *et al.,* 1999). The method was originally devised with worker risk assessment in mind and involved the development of so-called health-based occupational reference values (HBORV). Subsequently, the term HBORV has been replaced with the term 'minimal MOS' (margin of safety), although the principles and uncertainty factors used are the same. The starting point is that workers may be exposed

[1] ACP (2001) *Final Minutes of the 281st Meeting of the Advisory Committee on Pesticides (ACP) on 18th January 2001,* Item 3.3.1. Available [February 2003] at: http://www.pesticides.gov.uk/committees/acp/acp%2D281%5Fmins.htm

[2] EPA (1999) US Environmental Protection Agency IRIS Substance file – *Ethylene glycol monobutyl ether (EGBE) (2-Butoxyethanol)*. Downloaded [2001] from http://www.epa.gov/IRIS/

[3] See http://www.who.int/pcs/harmon_site/harmonize/uncert_variab.htm

predominantly, but not exclusively, by two routes: dermal and inhalation. Minimal MOSs are assessed for both routes separately and for every effect (if possible) as defined in the technical guidance documents.

The hazard characterisation serves as the starting point for the derivation of the minimal MOS with the identification of the NOAEL or LOAEL. To translate the selected NOAEL or LOAEL into the minimal MOS, factors are applied that allow for the uncertainties inherent in extrapolation of experimental (animal) data to a given human situation, and for uncertainties in the toxicological database. The assessment factors are derived allowing for the toxicity profile of the substance. If no conclusions can be drawn then a default factor is used. The standard default factors are presented in Table 2. The overall factor is established by multiplication of the separate factors, unless the data indicate another method to be used. The authors state that one should be aware that, in practice, it is not possible to distinguish all factors in Table 2, and that some factors are not independent of each other. Therefore straightforward multiplication may lead to unreasonably high factors. Discussion and weighing of individual factors are considered essential in deriving a reliable and justifiable overall assessment factor. Of particular interest are the metabolic scaling factors that are used for conversion of dose between species. As indicated in Table 2, these are based on a consideration of the basal metabolic rate in different species and are used when converting an oral dose in experimental animal species to an equivalent oral dose in humans. This therefore makes the default assumption that all substances are metabolised at a rate equivalent to normal basal metabolism.

The use of metabolic scaling in such a way has been considered previously by, for example, the JECFA (Lu, 1988) but was not adopted on the grounds that metabolism of xenobiotics is not necessarily well correlated with general body metabolic rates. It should also be noted that a factor of one is used for extrapolation for the inhalation route of exposure since it is argued that respiratory rate is dependent upon metabolic rate and thus automatically corrects for interspecies differences. Another point to note is that a default factor of three is used to allow for variability in the worker population, compared to the traditional default of 10. The justification for this lower default is that the worker population does not include very young, elderly or infirm people and thus it is assumed that the intraspecies differences are smaller in the worker population than in the general public (Hakkert *et al.,* 1996). However, no data or analyses are presented to support either this assumption or the value of three that is adopted.

Table 2 Assessment (uncertainty) factors applied for the calculation of minimal MOS values in The Netherlands

Aspect	Assessment factor (default value)
Interspecies differences	
Mouse	$7^a \times 3^b$
Rat	$4^a \times 3^b$
Rabbit	$2.4^a \times 3^b$
Dog	$1.4^a \times 3^b$
Intraspecies differences	3^c
Differences between experimental conditions and exposure pattern for workers	
chronic to chronic exposure	1
sub-acute to semi-chronic exposure	10^d
semi-chronic to chronic exposure	10^d
other aspects	1
Type of critical effect	1
Dose–response curve	1
Confidence of the database	1
Route-to-route	No default: if no relevant data on toxicokinetics and metabolism are available, worst case assumptions with respect to absorption % have to be made

[a] a calculated adjustment factor to allow for differences in basal metabolic rate (proportional to the 0.75 power of body weight)
[b] the extra factor of three is used to allow for the remaining uncertainty in extrapolating between species after adjustment for toxicokinetic differences
[c] a factor of three is used for workers, a factor of 10 for the general population
[d] the actual factor applied is often lower than that indicated, and is derived from the toxicological profile of the test substance

4.2.4 International Programme on Chemical Safety

The IPCS was developed to establish the scientific health and environmental risk assessment basis for safe use of chemicals and to strengthen national capabilities for chemical safety. The United Nations Environment Programme (UNEP), the International Labour Organization (ILO) and the WHO cooperate in IPCS. The WHO Programme for the Promotion of Chemical Safety (PCS) is responsible for the overall management and coherence of the IPCS and for risk assessments for food safety. Therefore there is a close connection between the JECFA and IPCS, and much of this section is also relevant to Section 5.1.

As described above, traditionally in relation to the general population the application of a 100-fold uncertainty factor, comprising the product of two 10-fold factors for inter- and intraspecies extrapolation, has been adopted by the IPCS (WHO, 1987). Extra uncertainty factors may also be incorporated to allow for deficiencies in the database (WHO, 1994). However, as indicated in Figure 3, there are a range of options potentially available, from application of default values through to a fully developed biologically-based model. In the vast majority of cases there is rarely the information available to enable significant movement away from the use of default uncertainty factors even for those chemicals where a reasonably robust database exists, and thus the default values have remained a key tool in risk assessment. Increasingly though, data are being generated on a substance-specific basis, and if this information is to contribute to risk assessment then some account needs to be taken of it, even if it is not sufficient to enable full biologically-based modelling.

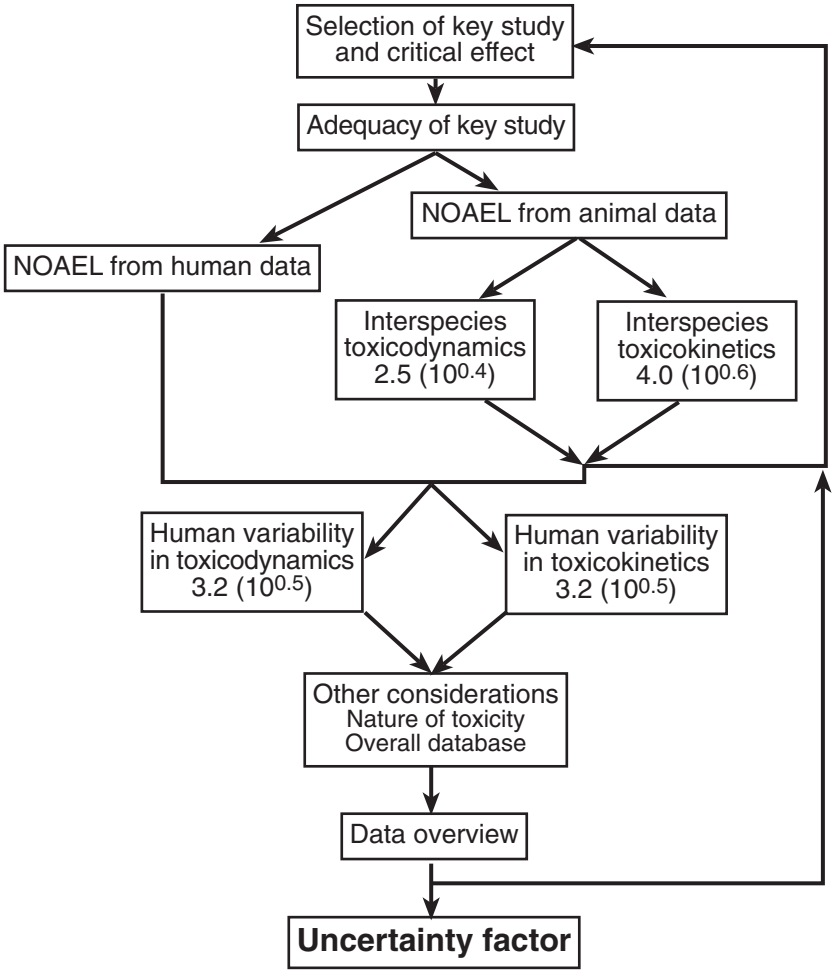
In an attempt to promote the ability to move away from the standard default values in cases where more incisive data are available, Renwick (1993) analysed data (largely for pharmaceuticals) on a limited number of substances for interspecies differences and human variability in toxicokinetics and toxicodynamics. This analysis consisted of subdividing each of the 10-fold default uncertainty factors for inter- and intraspecies variation into subfactors covering toxicokinetics and toxicodynamics. Based on an analysis of this limited database, Renwick proposed that each of the 10-fold factors could be subdivided into a factor of $10^{0.6}$ (a factor of 4) for toxicokinetics and $10^{0.4}$ (2.5) for toxicodynamics. Subsequently this general approach was adopted by a WHO task group on environmental health (WHO, 1994) with some modifications (see Figures 4 and 5). The task group considered that the data were not sufficient to warrant an uneven subdivision between toxicokinetics and toxicodynamics for humans, and thus the values were adjusted to give an equal subdivision or $10^{0.5}$ (3.16). This subdivision for the human interindividual aspects of variability was supported following a more extensive analysis of data (Renwick & Lazarus, 1998). The critical aspects of this approach are that it allows toxicokinetics and toxicodynamics to be considered separately, and also allows the introduction of substance-specific and issue-specific data. The scheme described by IPCS (WHO, 1994, 1999) is based on the subdivision of the traditional 10-fold factors. It reverts back to the 100-fold default in the absence of appropriate data, but has the potential for chemical-specific quantitative information on any aspect of the flowchart to be introduced where it is available. The defaults may be replaced either by data relating to a single chemical entity or for categories of chemical. Recent analysis has suggested that this approach for classes of chemicals may be of limited use for the replacement of the interspecies defaults (Walton *et al.*, 2001) but may be of more practical value for the replacement of the intraspecies default in some cases (Renwick *et al.*, 2001).

Clearly this approach may result in a modification of the overall 'composite factor' (CF) such that it becomes greater or less than the 100-fold default, depending upon the influence of any data introduced to replace a specific toxicokinetic or toxicodynamic default. Where this would result in a CF of less than the default of 100, then a different toxic effect with a higher NOAEL or NOAEC (no observed adverse effect concentration) than that originally chosen as the critical effect, would need to be considered to ensure that these effects are also appropriately accommodated by the application of the chemical-specific adjustment factor to the original NOAEL or LOAEL (see Figure 5).

Thus with the application of more information, the procedure becomes iterative and the ultimate critical effect would be that which gives the lowest derived exposure level after application of appropriate factors to the appropriate reference (starting) point for each effect seen experimentally.

The term 'data-derived uncertainty factors' was used originally to describe this approach of introducing data to replace defaults (Renwick, 1993; WHO, 1994, 1999). Recently, under the auspices of the IPCS project on the harmonization of risk assessment, this approach has been explored

Figure 5 General procedure for the derivation of chemical-specific adjustment factors



From WHO, 1994, more extensive guidance is given in WHO, 2001; reprinted with permission from WHO

further at an international workshop (WHO, 2001)[1]. The term 'chemical-specific adjustment factor' (CSAF) was adopted at this workshop in preference to data-derived uncertainty factor because it was considered to better describe the nature of the refinement to the usual default approach. Also, it avoids confusion with factors that may be based on analysis of databases on a group of chemicals possessing common characteristics, such as similar physicochemical parameters, common metabolic pathways (e.g. Renwick *et al.,* 2001; Walton *et al.,* 2001) or the databases used to extrapolate from LOAEL to NOAEL.

The IPCS workshop on CSAFs held in Berlin in May 2000 considered in much greater detail the elements of the interspecies and intraspecies toxicokinetic and toxicodynamic defaults and the chemical-specific data that would be required to replace them, using case studies to help explore, develop and illustrate these issues. Detailed guidance was produced that provides the risk assessor with logical pathways by which to consider derivation of CSAFs to replace the toxicokinetic and toxicodynamic components of the inter- and intraspecies defaults (WHO, 2001)[1]. Furthermore, guidance was also developed on the type, quality and quantity of data that would be required in order to support replacement of a specific default with a CSAF. The updated scheme still defaults to the usual 100-fold factor if appropriate and adequate data are not available to support robust CSAFs. This workshop represents a significant advance in this field internationally, and provides valuable guidance to risk assessors as well as to researchers on the type of data required for the generation of CSAFs.

[1] See http://www.who.int/pcs/harmon_site/harmonize/uncert_variab.htm

5 Approaches used in UK Government Regulatory Decision-Making

This chapter reviews the uncertainty factors used by UK Government departments, agencies and their advisory committees in human health risk assessment. Table 3 provides a summary of the default values for uncertainty factors that are used in risk assessment across UK Government. It should however be noted that many risk assessments are conducted at an international level (e.g. by the European Union (EU) or WHO); this is indicated where appropriate.

5.1 Food additives and contaminants

5.1.1 Substances covered

Food additives include anti-caking agents, emulsifiers and stabilisers as well as sweeteners, colours, flavouring agents, antioxidants and preservatives. Contaminants include aerosol propellants and solvents used in food processing, components of packaging materials, mycotoxins, and inorganic and organic environmental pollutants that enter the food chain.

Table 3 Default values for uncertainty factors used in UK Government chemical risk assessment

Chemical sector	Animal to human factor	Human variability factor	Quality or quantity of data factor	Severity of effect[a] factor
Food additives and contaminants	10	10	2–10	1–10
Agricultural pesticides	10	10	2–10[b]	2–10
Non-agricultural pesticides (biocides)	10	10	2–10	2–10
Veterinary products	10	10	2–5	2–10
Air pollutants[c]	10	10	–	–
Industrial chemicals	NS	NS	NS	NS
Consumer products	10	10	2 or greater	2 or greater
Drinking water contaminants	1–10	1–10	1–10	1–10
Soil contaminants	1–10	1–10	1–10	1–10
Medical devices	1–10	1–10	1–100	–
Human medicines[d]	NA	NA	NA	NA

NA, not applicable; NS, not specified.
As indicated in Section 5.10, specific default uncertainty factors for risk assessment or standard setting in the workplace have historically not generally been applied. Uncertainty factors are used in the occupational sector but have been set on a case-by-case basis, and generally at a lower level than the default factors of 10 used in other sectors
[a] An extra uncertainty factor may be applied because of the risk management philosophy being used, for example because the severity of the outcome is of particular concern (see Section 2.4.3)
[b] Normally a full data set would be available, but for reviews on existing chemicals, and on a case-by-case basis, an extra factor may be used in order to make a decision on whether to revoke an approval or gather further information
[c] When setting ambient air standards only human data have been used, and factors of 10 or greater have been employed. Where the risk from environmental exposure to industrial chemicals is assessed, for example under the Existing Substances Regulation, then the use of animal data and the range of factors indicated may be employed
[d] Human medicines are evaluated on a case by case basis to balance the therapeutic benefit against possible toxicity/side effects

It is common practice to distinguish additives from contaminants. Additives are added intentionally in order to produce some desired technical effect on the food, are approved onto a 'positive list' with possible definition of permitted use levels, and can therefore readily be controlled. In contrast, chemical contaminants are unwanted, but may be unavoidable. They may be introduced as a result of environmental contamination, by contact with packaging materials or equipment used in processing, or may be generated during cooking or processing. The intake of additive that is not expected to produce harmful effects is referred to as 'acceptable', whereas the intake of contaminants is commonly designated as 'tolerable' (i.e. permissible). A caveat to this general distinction between the approach to additives and contaminants exists in the case of chemical migration from plastic materials and articles in contact with food for which, in the EU, a positive list of chemicals permitted for use in such materials exists. This allows chemicals to be approved for use in plastics on the basis of toxicological and migration data.

5.1.2 Processes and procedures

The processes for evaluation of additives and contaminants are similar. For additives, the manufacturers are expected to provide a complete dossier of toxicological studies and to demonstrate absence of harm. However no single organisation would have responsibility for a food contaminant, and it is therefore necessary to compile a review of published studies to evaluate tolerable intake levels.

Within the EU, a legislative framework has now been established to allow the introduction of food safety standards by submission either at the national level or to the EU. Until 2003, EU-wide legislation on additives and contaminants required an assessment of the relevant substances by the Scientific Committee on Food (SCF), which was initially established in 1974 (as the Scientific Committee *for* Food) and re-constituted in 1997. The SCF's mandate was to provide advice on any problem relating to consumer health and food safety associated with food consumption, particularly on issues relating to nutrition, hygiene and toxicology. In the case of a new food additive, or a packaging additive, the SCF evaluated a dossier of information provided by the manufacturers, which included information on toxicity data and details of the proposed usage. If the SCF was satisfied with the data it established an ADI or, in cases where exposure was likely to be limited, simply concluded that the proposed uses of the substance were 'acceptable'. Based on the SCF's advice, the European Commission (EC) developed draft legislation for presentation to the member states. In most cases the legislation is also subject to agreement by the European Parliament. The end result has been either an EC directive that required all member states to make the necessary changes to their national legislation, or a regulation that has direct effect across the EU. However, with the establishment of the European Food Safety Authority (EFSA) in 2003, the work of the SCF and other EU committees dealing with food safety is to be taken on by eight new scientific expert panels. These will advise EFSA on the following.

- Food additives, flavourings, processing aids and materials in contact with food
- Additives and products or substances used in animal feed
- Plant health, plant protection products and their residues
- Genetically modified organisms
- Dietetic products, nutrition and allergies
- Biological hazards
- Contaminants in the food chain
- Animal health and welfare

The manufacturers of food additives may also apply for national authorisation in one or more of the EU's member states for an interim period while applying for EU approval. Within the UK this procedure involves evaluation using procedures similar to those used by the SCF and the Joint FAO/WHO (Food and Agriculture Organization/World Health Organization) Expert Committee on Food Additives (JECFA). The evaluation is conducted by the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), taking advice from its sister committees on mutagenicity (COM) and carcinogenicity (COC) where appropriate. If an acceptable daily intake (ADI) is established, the additive may be approved for marketing within that member state for a period of two years while an application is made to the EU. The application is then considered by EFSA and, if approved, the additive is subsequently incorporated into an EU directive. If the application is not accepted by EFSA the additive must be withdrawn.

Legislation relating to approved food additives contains 'positive lists' of permitted additives

(approved by the SCF), including technical specifications such as on purity, particular technological purposes for which the additives may be used, and any restrictions in place, such as the maximum use levels in food or special labelling requirements.

Tolerable daily intakes (TDIs) or other tolerable intakes proposed for contaminants in foods are also used as the basis for establishing maximum levels, applied internationally, and defined in EU regulations or in the *Codex Alimentarius*. In addition there may be a need for national assessment of contaminants in order to provide the basis for regional risk management options.

As part of their remit, COT, COM and COC advise the UK Food Standards Agency and the Department of Health about possible health implications of chemicals in food, water supply and other sources of human exposure.

5.1.3 Risk assessment and dealing with uncertainties

The basic approach to establishing acceptable and tolerable intakes has already been described in Sections 4.1 and 4.2.4. Essentially this entails identification of the most sensitive toxicological endpoint that is relevant to human dietary exposure, and application of safety (uncertainty) factors to the no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL) for that effect. A complete data set for a new additive should include a wide range of specified studies conducted to current guidelines in order to characterise the hazardous properties, and would include identification of a NOAEL. The data set for contaminants is frequently much less comprehensive, and it may not be possible to identify a NOAEL.

The ADI is defined as "an estimate of the amount of a food additive, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk". A body weight basis is used in order to allow both for differences in body weight between test animals and humans and the variability in human size (e.g. children compared with adults). The ADI relates to daily ingestion, because acceptable additives should not accumulate in the body.

Some expert committees consider it appropriate to use a longer reference period for contaminants that do accumulate in the human body. In addition, JECFA considers the evaluation of contaminants to be tentative because of the inevitable paucity of reliable data on the consequences of human exposure at the levels anticipated to occur from food. Consequently the term provisional tolerable weekly intake (PTWI) is used. Recently JECFA established a provisional tolerable monthly intake for dioxins and dioxin-like polychlorinated biphenyls (PCBs), using this measure because of their very long half-lives. For contaminants of natural occurrence that do not accumulate in the body, JECFA establishes provisional maximum tolerable daily intakes (PMTDI). This category may include trace elements, such as iodine, that are essential nutrients as well as unavoidable food constituents, in which case a range is indicated with the lower value corresponding to the essential level. Other expert committees and regulatory bodies may use the term TDI for contaminants.

The ADI (or TDI) is normally established by application of the default uncertainty factor of 100 to the NOAEL but, as described in Section 4.2.4, there are a number of situations that may lead an expert committee to recommend a different factor (e.g. see Example 5). In addition, if the database is considered inadequate, a temporary ADI may be allocated while further studies are conducted, and an additional uncertainty factor (e.g. a factor of two) may be incorporated to allow for the added uncertainty. In the case of contaminants the database may show gross deficiencies, and an additional uncertainty factor of five or 10 may be applied in establishing the TDI.

Example 5
An evaluation where a default uncertainty factor was not used[1]

The COT evaluation of dioxins and dioxin-like PCBs provides a recent example of an expert committee using other than the default uncertainty factors. The tolerable intake was derived from the body burden in the key rat study, scaled across to give an estimated human intake. Therefore there was no need for an uncertainty factor to allow for interspecies differences in toxicokinetics (i.e. uncertainty factor = 1). The strain of rat used in the key study was considered to be particularly sensitive, and therefore uncertainty factors of one were also appropriate for interspecies or interindividual differences in toxicodynamics. However, a factor of 3.2 was required for the uncertainty with respect to interindividual differences in toxicokinetics of the different PCB congeners. A additional factor of 3 was used to allow for the absence of a NOAEL in the key study. Thus a total uncertainty factor of 9.6 ($1 \times 1 \times 1 \times 3.2 \times 3$) was applied.

[1] http://www.food.gov.uk/multimedia/pdfs/cot-diox-full

Some authorities use an additional uncertainty factor for substances shown to produce irreversible developmental effects or carcinogenic effects of potential relevance to humans, even by an assumed threshold-based mechanism. However, the application of this factor is considered to be related more to risk management than to risk assessment and its use is not generally advocated by scientific expert committees.

A number of different categories of ADI are applied by JECFA and the SCF. For some additives of low potential toxicity, evaluation of the available data may lead to the conclusion that the total maximum potential intake from all possible sources does not represent a hazard to health. In this situation, it may be considered unnecessary to specify a numerical value for the ADI, and the term 'ADI not specified' is used, as for example with the modified celluloses. However, this does not mean that the additive may be used at any level. The principles of good manufacturing practice should then be applied, that is to say, it should be used at the lowest level required to produce the desired technological effect.

Another variation of the ADI has been mentioned above in relation to the need for a higher safety factor if the database is not adequate. A temporary ADI may be allocated for a defined period when new questions are raised about an approved food additive and additional studies are being conducted. A temporary ADI does not imply that consumers are at increased risk, but that a larger safety factor (e.g. two-fold higher than otherwise) is being applied as a precautionary measure because of the greater uncertainty. The new data would then be reviewed, resulting either in re-establishment of a full ADI, a request for further work while extending the temporary ADI, or withdrawal of the ADI. If a temporary ADI is granted, it is considered that the relative short exposure to the substance is unlikely to result in harm, but that safety cannot be assured with lifetime exposure.

The ADI normally specifies the maximum acceptable intake for a single chemical substance, but there are a number of situations in which a modified approach is considered appropriate. A group ADI may be set for compounds that are expected to have additive effects because of similar chemical structure or toxicity. If 10 such compounds were all consumed at the level specified by an individual ADI, the combined result would be equivalent to consuming ten times the ADI of just one of them, with the possibility of producing harmful effects. It is therefore considered necessary to control the overall intake of the group. The group ADI may be derived from an average of the NOAELs for all of the compounds, but usually, and more conservatively, the group ADI is based on the lowest NOAEL of any member. Alternatively the NOAEL may be based on the toxicity of a common metabolite. For example the assessment of allyl esters is based upon the toxicity of the hydrolysis product, allyl alcohol, and its metabolites.

5.2 Pesticides and biocides

5.2.1 Substances covered

'Pesticides' is a general term that includes all chemical and biological products used to kill or control pests by chemical or biological but not physical means. This includes products designed to act as animal and bird repellents, food storage protectors, insecticides, plant growth regulators, anti-fouling products, rat and mouse poisons, weed-killers and biocides.

Under the current UK system for approval of pesticides each product is classified as agricultural or non-agricultural according to the purpose for which it is used. Agricultural pesticides include those used in agriculture, horticulture, the home, garden or forestry, and weed-killers for use in and around watercourses, lakes or on non-crop land such as roads and railways. Non-agricultural pesticides (also called biocides) include those used in wood preservation, as masonry biocides, as public hygiene or nuisance insecticides, and as anti-fouling products.

A distinction is also made between professional and amateur use. Professional products may only be used by people as part of their work and they must be competent in their use. The workplace risk for professional users is controlled through observance of statutory requirements such as formal control measures and the requirement for adequate training and supervision. The requirements for training in the use of pesticides by professionals are set out in the Control of Substances Hazardous to Health (COSHH) and Control of Pesticide Regulations (CoPR), and apply to both agricultural and non-agricultural pesticides.

In practice, all those using professional agricultural products must first obtain, or must work under the direct supervision of someone who has obtained a certificate of competence recognised by responsible ministers. The only exceptions to this rule are for those using such pesticides in certain specified fields of use, such as vertebrate control or food storage

practice, and people born before 31 December 1964 who are not using such pesticides in the course of a commercial service, for example farmers applying pesticides approved for agricultural use to their own land.

A similar scheme of recognised certificates of competence does not exist for non-agricultural pesticides. However, there is no less of a requirement for appropriate training in the safe use of non-agricultural pesticides. Training standards to meet the legal requirements have been developed in collaboration with trade associations (HSE, 1990), and many trade bodies provide training certification to branch-specific standards.

Products for amateur use may be used by the general public, who rely upon the product label for information on the safe use of the pesticide. There is an expectation, but no guarantee, that amateur users will comply with instructions for use of a product. There is no assumption of access to controls or formal personal protective equipment, although members of the public may be directed to use household protective equipment (e.g. gardening or kitchen gloves).

5.2.2 Processes and procedures

In the UK the systems for regulating pesticides have evolved progressively since the 1940s. They currently involve various government agencies, departments and their ministers, the independent Advisory Committee on Pesticides (ACP) and Biocides Consultative Committee, and now also committees and agencies within the EU (Defra/HSE, 2002). The approach described in Section 5.2.1 was originally used for the UK national approvals process. This has now evolved to be compatible with the EU scheme. For agricultural pesticides the final decisions are taken by the Standing Committee on Plant Health into which the UK has an input, and will affect the opportunity for the UK to give authorisations at the national level.

Before a new pesticide can be approved for sale and use, evidence is required first of its efficacy and secondly that it will not pose an unacceptable risk to human health or to wildlife. To this end, companies seeking approval for a new product are required to submit an extensive package of scientific data. The components of the package vary according to the nature of the pesticide and the uses to which it will be put, but as far as possible they are standardised. One of the main components of a data package addresses the potential toxicity to humans.

5.2.3 Risk assessment and dealing with uncertainties: Agricultural pesticides

One approach adopted to determine whether or not the proposed use of an agricultural pesticide may present a risk to human health is by the establishment of a standard, the ADI, against which exposure can be compared (see Figure 2a). The ADI is developed with the protection of consumers exposed through residues in food in mind. The ADI is the mean amount of the chemical that can be consumed every day for a lifetime in the practical certainty, on the basis of all known facts, that no harm will result. The starting point for the derivation of the ADI is usually the lowest relevant NOAEL that has been detected in toxicity studies. This is then divided by an uncertainty factor, which is normally 100 but can vary depending on the available data. The default uncertainty factor of 100 allows for the extrapolation from animals to humans and for variability in the human population. A factor of less than 100 may be used when there are appropriate human data, or a larger factor may be used for compounds producing severe effects, or as an interim measure when there is additional uncertainty surrounding an aspect of the data package (see Example 6).

Example 6
Establishing an ADI for Linuron

The ACP evaluation of Linuron provides an example of the use of an overall uncertainty factor greater than 100[1]. In long-term studies in rats there was evidence that Linuron induces hormonal interactions. Even at the lowest dose tested (25 ppm in the diet, equivalent to 1.3 mg Linuron/kg bw/day) there were effects seen that could be associated with an hormonal perturbation (reductions in the incidence of pituitary tumours). In establishing an ADI a factor of 10 was used for interspecies extrapolation and another factor of 10 was used to allow for variability within the human population. An additional factor of five was used because a NOAEL had not been established, giving an overall uncertainty factor of 500 and leading to an ADI of 0.003 mg/kg bw/day.

[1] DETR, 1995

In addition to the ADI, an acute reference dose (ARfD) is also derived if it is considered that a single dose of the compound via a food residue could elicit an adverse response. The ARfD of a chemical is an estimate of the amount of a substance in food or drinking water, normally expressed on body weight basis, that can be

ingested in a period of 24 hours or less without appreciable health risk to the consumer on the basis of all known facts at the time of evaluation. It is usually derived by applying an appropriate assessment factor to the lowest relevant NOAEL from studies that have assessed effects following short-term exposure or endpoints such as developmental toxicity that may be affected by a single dose at a critical time. The assessment factor chosen for the ARfD is selected in the same way as for an ADI. An important consideration is to ensure that the toxicological endpoint of concern is relevant to the consumer group under consideration. For example, depending on the effect, an ARfD derived from a developmental toxicity study will not be of relevance to infants but only women of childbearing age.

In addition to the ADI and ARfD, for agricultural pesticides an acceptable operator exposure level (AOEL) is also derived. This is intended to define a level of daily exposure that would not cause adverse effects in operators who work with a pesticide regularly over a period of days, weeks or months. Depending on the pattern of use of the pesticide, it may be appropriate to define a short-term AOEL (i.e. for exposures over several weeks or on a seasonal basis), a long-term AOEL (i.e. for repeated exposures over the course of a year) or both. AOELs are derived in a manner analogous to the ADI.

Maximum residue limits (MRLs) are also established for agricultural pesticides but differ from those developed for veterinary medicines (see Section 5.7.3). For pesticides an MRL is defined as the maximum concentration of pesticide residue (expressed as milligrams of residue per kilogram of commodity) likely to occur in or on food commodities and in cereals and products of animal origin after the use of pesticides according to good agricultural practice (GAP).

MRLs for pesticides are intended primarily as a check that GAP is being followed and to assist international trade in produce treated with pesticides. MRLs for pesticides are not safety limits, and exposure to residues in excess of an MRL does not automatically imply a hazard to health.

5.2.4 Risk assessment and dealing with uncertainty: Non-agricultural pesticides and biocides

In contrast to the approach for agricultural pesticides, the determination of whether or not the proposed use of a non-agricultural pesticide may present a risk to human health is by the establishment of the ratio of the NOAEL to the exposure estimate. This is termed the toxicity exposure ratio, TER (see Figure 2b). The approach is the same as was originally used for all pesticide products in the UK national schemes. It will evolve into the EU system for biocides when this system has been finalised: both the TER and AOEL approaches are being considered. In the EU system, the final decisions will be taken by the Standing Committee on Biocides into which the UK has an input, and will affect the opportunity for the UK to give authorisations at the national level. Currently the magnitude of the TER is used to determine whether or not approval is given for the proposed use in the UK. In general, the default position is that the ratio should be 100, derived from the standard default position allowing for inter and intraspecies extrapolation. In some cases the ratio may be less or greater than 100, and the assessment is treated on a case-by-case basis. Thus although the ratio may be less than 100, in some cases approval may still be given because the effects are judged as being of limited significance for human health. Alternatively it may be decided that a ratio of above 100 may not provide sufficient reassurance for the protection of human health and approval not given.

Assessment of shorter periods of operator exposure is also carried out for non-agricultural pesticides use in the same way as for agricultural pesticides. The calculation of a TER is used to judge risk to human health and usually the same default factor of 100 is applied.

Generally, database deficiencies are not addressed primarily by additional uncertainty factors for agricultural and non-agricultural pesticides. The regulatory schemes in place enable the authorities to request further information should there be significant gaps in the database. In the case of reviews of existing active substances, extra factors might be applied initially while making the decision either to obtain further information or revoke approval.

Thus in summary, although different versions of the risk assessment paradigm are used in the approval of pesticides and biocides, the standard 100-fold default to allow for interspecies extrapolation (factor of 10) and human variability (factor of 10) is usually employed. The decision not to use this factor can be made on a case-by-case basis if substance-specific data are available to allow this.

5.3 Air pollutants

5.3.1 Substances covered

Air pollutants are those substances released by human activity into the air that we breathe. In essence all substances released into our ambient air are included in this definition, but there are some key pollutants which are of particular concern and for which air quality standards (AQS) have been developed.

5.3.2 Processes and procedures

AQSs for a limited number of key air pollutants have been recommended by the Expert Panel on Air Quality Standards (EPAQS), an independent advisory body set up by the Secretary of State for the Environment in 1991. The work of EPAQS is administered by the Department for Environment, Food and Rural Affairs (Defra). The panel consists of independent experts, appointed for their medical and scientific expertise. EPAQS reviews the published and peer-reviewed evidence available on specific substances in order to provide the Government with recommendations for AQSs. The terms of reference of EPAQS have been updated recently (DETR, 2000).

5.3.3 Risk assessment and dealing with uncertainty

EPAQS has endeavoured to set AQSs on the basis of human epidemiological and volunteer studies, utilising if possible evidence obtained in vulnerable groups likely to be most affected by air pollutants (e.g. people with asthma); animal data are used only when human data are not sufficient. While such an approach reduces the uncertainty associated with interspecies extrapolation from animal toxicology studies, there are nevertheless other sources of uncertainty that need to be addressed in developing the AQSs, such as data quality and less than lifetime exposures.

Generally, EPAQS attempts to determine a NOAEL, or where this is not possible a LOAEL, from epidemiological data for the most sensitive individuals, often people with asthma or chronic lung disease. The group then uses expert judgement to identify an appropriate margin of safety or an uncertainty factor to apply to the NOAEL or LOAEL. Example 7 shows how EPAQS uses this approach.

Example 7
EPAQS recommendation for an air quality standard for sulphur dioxide

The standard for sulphur dioxide is based on effects in people with asthma, as these individuals are considered to be more susceptible to its effects than are healthy individuals. The Panel concluded that it was unlikely that clinically significant effects would occur in the majority of people with asthma exposed to concentrations below 200 ppb (0.52 mg/m^3). But, as concentrations can briefly double during a 15-min monitoring period and it is likely that some participants with asthma are more sensitive than those who took part in the volunteer studies, an uncertainty factor of two was applied to the NOAEL to take into account brief exposure peaks. A value of 100 ppb was subsequently chosen as the AQS. Here there was no need to apply uncertainty factors to take account of either interspecies differences or intraspecies variability[1].

[1]EPAQS, 1995

5.4 Drinking water contaminants

5.4.1 Substances covered

Contaminants in drinking water can come from a number of sources including industrial activity, farming and water treatment. Risk assessments and standards for each of these sources are considered below.

5.4.2 Processes and procedures: Statutory standards

Statutory standards for contaminants in drinking water are contained in the 1989 and 2000 issues of the UK Drinking Water Regulations (HMSO, 1989; SO, 2000). These values are transposed from those listed in relevant EC water quality directives and in most cases the values originate from drinking water guideline values published by the WHO (e.g. WHO, 1993).

UK regulatory bodies (e.g. the Drinking Water Inspectorate, a Defra agency, advised as appropriate by the Department of Health) participate in the standard-setting process through representation at technical meetings of the WHO and participation in EU technical committees.

5.4.3 Risk assessment and dealing with uncertainty: Statutory standards

To establish guideline values the WHO generally uses animal toxicity data. A NOAEL or, if not available, a LOAEL, is identified and divided by an uncertainty factor to give a TDI. The uncertainty factor is made up from a number of possible sources of uncertainty and the values used are shown in Table 4.

Table 4 Uncertainty factors applied for the calculation of TDIs

Aspect	Uncertainty factor
Interspecies variation	1–10
Intraspecies variation	1–10
Adequacy of study or database	1–10
Nature and severity of effect	1–10

In most instances factors of uncertainty of 10 each for inter- and intraspecies variation are used to give a total uncertainty factor of 100. The total uncertainty factor used should not exceed 10 000, as uncertainty above this level is considered to lack meaning. The drinking water guideline value is calculated from the TDI using a standard procedure and either default assumptions or values based on specific evidence of human behaviour.

5.4.4 Processes and procedures: Advisory values for pesticides in drinking water

The statutory level for individual pesticides in water is 0.1 ppb, a level based on analytical sensitivity and not derived from a health risk assessment. Pesticide levels in water above 0.1 ppb, while breaching the regulatory value, may not constitute a risk to human health, particularly if exposure is transient or the levels are below a health-based value. Such health-based values are called advisory values (AV) and have been established by the Department of Health to assist in this evaluation. Around 40 AVs have been published by the Drinking Water Inspectorate (1989). Where a WHO guideline value has been published for a particular pesticide these have been used as the AV.

5.4.5 Risk assessment and dealing with uncertainty: Advisory values for pesticides in drinking water

The lowest suitable NOAEL of a pesticide is identified from the available literature. This is divided by a total uncertainty factor to give a TDI. Standard uncertainty factors of 10 each are used for inadequacies in the basic data, uncertainties in the extrapolation from data on animals to humans, and to incorporate a margin of safety to protect against the possibility of effects in vulnerable groups, such as babies and elderly people. This normally produces a total uncertainty factor of 1000. The advisory value is calculated in the same way as the guideline value described above. However, since drinking water is not usually the sole potential source of human exposure to pesticides, exposure from all sources is taken into account in the development of the advisory value. This is achieved by apportioning a percentage of the TDI to drinking water. As defaults, these are either 10% (for herbicides) or 1% (for insecticides) of the TDI to derive a daily intake level allowable from drinking water.

5.4.6 Processes and procedures: Chemicals used in water treatment and provision

The Committee on Products and Processes for use in Public Water Supply (CPP) advises the Secretary of State for the Environment on the acceptability, on public health grounds, of commercial products used in the purification, treatment and distribution of public water supplies. A consequence of the use of these products is that substances may arise in drinking water at consumers' taps as a result of leaching, persistence or degradation, and the acceptability of such potential exposures is assessed by the CPP. The secretariat for the committee is provided by the Drinking Water Inspectorate, the Department of Health provides a toxicological assessor and there is also an independent toxicological advisor present.

5.4.7 Risk assessment and dealing with uncertainty: Chemicals used in water treatment and provision

A suitable NOAEL or LOAEL is generally identified from toxicological data for such potential contaminants, and uncertainty factors of 10 each for interspecies differences and intraspecies variability, and where appropriate, additional factors of 10 for deficiencies in the database and severity of toxic effect, are included to derive a value equivalent to a TDI. A comparison is made between this value and potential human exposure from drinking water, taking into account duration and variability of exposure, and a decision of acceptability is reached by expert judgement.

5.5 Soil contaminants

5.5.1 Substances covered

Statutory guidance on the health risks from contaminated land has been published by Defra (Defra/EA, 2002) to support the implementation of contaminated land regime under Part IIA of the Environmental Protection Act 1990. The guidance provides a basis for the setting of land use specific soil guideline values (SGV) for a number of commonly encountered environmental pollutants. These values are used to assess whether the presence of these substances in soil defines land as contaminated land, thus possibly presenting a human health risk and requiring remediation or restriction in land use. An SGV is generated by use of an exposure model which estimates potential human exposure, and that can then be compared with a toxicological input value: either the TDSI (the tolerable daily intake from soil sources, used for substances with threshold properties for which a TDI can be derived) or the index dose (a measure of intake from soil sources which presents minimal risk from non-threshold contaminants such as genotoxic carcinogens).

5.5.2 Processes and procedures

TDSIs are derived by expert judgement, based wherever possible on existing TDIs already published by national or international authoritative bodies (e.g. WHO, JECFA, SCF).

5.5.3 Risk assessment and dealing with uncertainty

The way in which TDIs are derived, including the use of uncertainty factors, has been described in Chapter 4.

In a case where COT was asked to derive a TDI for the ingestion of phenol as a soil contaminant (see Example 8), standard uncertainty factors of 10 for extrapolation from rodent data and 10 for variability within the human population were considered appropriate to apply to the NOAEL derived for the relevant toxicological endpoint in the critical study.

Example 8
Derivation of a TDI for phenol as a soil contaminant[1]

Phenol has been identified as a soil contaminant of possible concern. The COT assessed the toxicological data for this substance in order to define an oral TDI that could be subsequently used to derive soil guideline values. Taking note of the view of its sister Committee on Mutagenicity (COM, 2000) that, by the oral route only, there is potential for a threshold for mutagenicity, a NOAEL of 70 mg/kg bw/day for other endpoints was identified from the critical study in rats. It was also considered that standard uncertainty factors of 10 for extrapolation from rodent data and 10 for variability within the human population were appropriate to apply to the NOAEL, and an oral TDI of 0.7 mg/kg bw/day was derived.

[1] http://www.doh.gov.uk/cotnonfood/phenol.htm

5.6 Consumer products and cosmetics

5.6.1 Substances covered

Consumer protection legislation in the UK places the responsibility on industry for ensuring that consumer products are safe for the purpose intended, and there is no requirement for prior approval by Government. This category includes cosmetics, which are covered by an EU directive, implemented in the UK by DTI. The EU definition of cosmetics is wide, covering for example soaps, shampoos, deodorants, sunscreens, toothpaste and mouth washes.

5.6.2 Processes and procedures

Although there is no requirement for prior approval of such products, there is a requirement that ingredients used for certain purposes (e.g. colourants, preservatives, UV filters) can only be chosen from lists of permitted compounds. In order for compounds to be included on such lists, the EC's Scientific Committee on Cosmetics and Non-Food Consumer Products (SCCNFCP; in the 1990s this was called the Scientific Committee on Cosmetology) must give a favourable opinion on a compound's safety, after consideration of a dossier of data from industry provided through the EU Trade Association, COLIPA.

5.6.3 Risk assessment and dealing with uncertainty

In considering the acceptability of an ingredient the SCCNFCP uses a margin of safety approach (MOS; see Figure 2b), using exposure algorithms based on data agreed with COLIPA. The Committee invariably looks for an MOS of 100 or more in order to give a favourable opinion. This is equivalent to an uncertainty factor of 100.

The only other area where there is a formal risk assessment of exposure to chemicals in consumer

products is in the EU's new substance notification scheme, NONS, or on priority chemicals being considered under the Existing Substances Regulation (ESR; see Section 5.10 for further details). In both cases the Health and Safety Executive (HSE) leads on the health assessments in the UK. A margin of safety approach is employed, and values of 100 or more are in general considered appropriate for compounds with threshold effects. An overall uncertainty factor of 100 is thus used.

5.7 Veterinary products

5.7.1 Substances covered

Veterinary medicinal products (VMPs) are used to treat sick animals or to prevent disease in individual animals or herds and flocks. This category therefore includes a wide range of pharmacologically active substances, some of which may also be used in human medicines. The assessment process also covers administration devices that are an integral part of a particular product, but there is no European or national legislation in respect of medical devices used in veterinary medicine equivalent to that for medical devices in human medicine (see Section 5.9). Zootechnical feed additives (such as prophylactics, digestion/performance enhancers and substances altering the physiology of the animal) are assessed at European level. The processes and procedures involved are similar to those for VMPs and the Veterinary Products Committee (VPC) provides input into assessments for which the UK is responsible.

5.7.2 Processes and procedures

Assessments of risk to consumers from active substances used in VMPs for food-producing animals are conducted at a European level by the Committee for Veterinary Medicinal Products (CVMP), which establishes ADIs. Assessments of applications for Marketing Authorisations for specific products which include user safety assessments may be conducted either under the centralised procedure (in the case of active ingredients that are novel or produced using recombinant DNA technology) and assessed by the CVMP or the mutual recognition (or decentralised procedure) under which member states may recognise another member state's authorisation.

ADIs are not established for most genotoxic compounds due to the non-threshold nature of their effects, and these compounds are generally not permitted in products intended for use in food species. ADIs have no statutory standing, but are used to determine the statutory MRL. It should be noted that the MRLs developed for VMPs are not the same as those developed for agricultural pesticides (see Section 5.2.3). The MRLs for VMPs, along with data on residue depletion, are used to determine withdrawal periods for products containing these substances, during which time treated animals may not be slaughtered for food, or produce collected. Withdrawal periods may be set at national or European levels. The major risks to consumers are considered to be potential chronic (lifetime) low-dose toxic effects, including carcinogenicity and reproductive effects. It is also recognised that developmental effects can result from acute exposures, and pharmacological effects can also be important. For some veterinary medicines pharmacological and microbiological ADIs may be needed as well as toxicological ADIs, and the overall ADI and MRLs for the substance will be based on the lowest of these three endpoints.

5.7.3 Risk assessment and dealing with uncertainty

The risk assessment for VMPs is similar to that for pesticides, but it also involves some aspects that are unique to this sector. In considering the balance of risk to benefit in the use of a VMP, quality of the product, efficacy, and target species safety must be taken into account as well as human safety and environmental safety. An application for a marketing authorisation for a product to be used in food-producing animals may fail on any of these aspects, but must be acceptable in all to be successful. The two major considerations regarding the assessment of risks to humans are consumer and user safety. Consideration will also be given to whether environmental exposure may result in risks to human health.

The risk assessment for consumers relates to the risk from edible tissues (muscle, liver, kidney, fat and skin) and edible products (milk, other dairy products, eggs and honey) from food-producing animals (e.g. cattle, sheep, pigs, poultry, fish, bees). The approach adopted is the derivation of a standard (see Figure 2a). The standard, the ADI and the MRL have to be determined for all active ingredients and pharmacologically active excipients used in VMPs within the EU.

A pharmacological ADI would be established for substances where its pharmacodynamic activity is likely to be of greater biological significance than other endpoints, for example tranquillisers or hormones. The ADI is based on the most relevant NOEL or LOEL for the primary (i.e. the intended therapeutic activity) and secondary (other) pharmacodynamic effects of the substance. A toxicological ADI should be established based on

the most appropriate NOAEL or LOAEL in the most sensitive species.

Pharmacological and toxicological ADIs are determined using the standard 10×10 uncertainty factor approach, plus, where necessary, an additional factor of between 2 and 10 depending on the quality of the data and the nature and severity of the critical effect. In the case of non-genotoxic carcinogens an ADI could be determined if a mechanism can be identified for any carcinogenic effect observed. This would be based on the NOEL for the most sensitive indicator of that mechanism, with a standard 100-fold uncertainty factor. If the mechanism is unclear, an extra 10-fold uncertainty factor may be introduced to give an overall factor of 1000. This is illustrated in Example 9, for the anthelmintic drug nitroxinil.

In the case of aneugenic substances, the CVMP has used a similar approach to that recommended to the UK Pesticides Safety Directorate by COM. This is illustrated in Example 10.

The standard default of a 100-fold uncertainty factor is therefore employed, as for pesticides and biocides. Variation from this standard may occur on a case-by-case basis depending upon the available data. In cases where the overall ADI has been determined from human data a factor of less

Example 9
Derivation of an ADI for the anthelmintic drug nitroxinil[1]

Nitroxinil gave negative results in a series of *in vitro* and *in vivo* mutagenicity studies, except for an increase in structural chromosome aberrations at its limit of toxicity in an *in vitro* cytogenetics assay in cultured human lymphocytes. In a two-year rat carcinogenicity study, increases in thyroid gland carcinomas and pituitary gland adenomas were observed at the highest dose used in the study (320 mg/kg diet).

In the absence of *in vivo* mutagenic effects, and taking into account that the substance contains iodine, it was concluded that the increase in tumours was due to a non-genotoxic mechanism related to its goitrogenic properties.

An ADI of 0.005 mg/kg bw was established based on the NOEL of 0.5 mg/kg bw/day for effects on T_3 and T_4 levels and thyroid morphology in male rats in a 90-day study, using an uncertainty factor of 100. This ADI gives a margin of over 500 for the tumorigenic effects seen in the two-year study.

[1] http//www.emea.eu.int/pdfs/vet/mrls/045298en.pdf

Example 10
Development of an ADI for the spindle inhibitor Mebendazole

Mebendazole is a benzimidazole anthelmintic[1]. A toxicological ADI of 0.0125 mg/kg body weight was determined based on the NOEL of 2.5 mg/kg bw/day from a 13-week repeated dose toxicity study in dogs, and developmental toxicity studies in rats and mice. A series of mutagenicity studies was conducted, including *in vitro* studies using human peripheral lymphocytes and *in vivo* bone marrow micronucleus studies in mice that utilised fluorescence *in situ* hybridisation (FISH). These studies indicated that although Mebendazole is not a direct-acting mutagen or clastogenic, it is aneugenic in mammalian somatic cells. It was not possible to identify a NOEL for aneugenicity from the *in vivo* data due to the lack of sensitivity of the method, but a threshold concentration and a no effect concentration of 85 ng/ml was identified from the *in vitro* FISH studies. Human pharmacokinetic studies indicated that plasma concentrations of Mebendazole were 2–3 times lower than the *in vitro* NOEC, and 3–4 times lower that the threshold concentration for aneugenicity at an oral dose 2000 times higher than the ADI. It was therefore concluded that potential aneugenic effects were sufficiently covered by the ADI.

[1] http://www.emea.eu.int/pdfs/vet/mrls/078101en.pdf

Example 11
Use of pharmacological data in humans to establish an ADI[1]

Clenbuterol is used as a bronchodilator in horses and as a tocolytic in cattle and horses; it is also used as a human medicine for the treatment of chronic obstructive airway diseases. A NOEL of 2.5 µg/person/day was identified in a pharmacological study to examine the acute bronchospasmolytic effects in patients with chronic obstructive airway disease, who were shown to be more susceptible than 'normal' patients to the bronchodilatory effects. An uncertainty factor of 10 was used to derive a pharmacological ADI of 0.25 µg for a 60 kg adult. This factor was used to allow for variation in the human population, recognising that asthmatics may be particularly sensitive to the bronchodilatory effects of β-agonists such as Clenbuterol.

[1] http://www.emea.eu.int/pdfs/vet/mrls/072399en.pdf

than 100 may be used, depending on the nature of the effect and quality of the data. In such cases the ADI is derived from pharmacological data; Example 11 shows how such data may be used.

In addition to carcinogenicity, other effects that may be non-threshold, or where a threshold may be difficult to identify or a dose–response difficult to define may prove to be pivotal in a risk assessment. As discussed in Chapter 2, sensitisation is such an endpoint and Example 3 shows how JECFA established MRLs for penicillins that were subsequently adopted by the CVMP.

Based on pharmacokinetic and tissue residues studies, the distribution of the residues of the substance between the various edible tissues and products can be determined. Based on a 'standard' food basket, MRLs can be allocated to the different food items in appropriate proportions such that residue intake of a 60 kg adult should not exceed the ADI.

User risk assessment involves the identification of the toxicological endpoints relevant to user safety, dependent on likely exposure from administration of the product and contact with treated animals. There is no provision for setting AOELs for VMPs under EU legislation. It may be necessary, on a case-by-case basis, for applicants to provide evidence that user exposure will not exceed levels considered to be acceptable from the risk assessment. Where exposure to VMPs occurs in an occupational setting (e.g. in veterinary surgeries or feed manufacturers), the user should conduct a workplace exposure risk assessment that may involve consideration of AOELs for components of the VMP (e.g. volatile solvents) set under other legislation.

User safety is generally managed by avoiding unnecessary exposure and by giving advice on safe storage, handling and disposal of the product. Product literature should include directions on safe administration and advice on suitable protective clothing and removal of contamination. Engineering controls are used to avoid exposure during the incorporation of medicated pre-mixes into feed. Appropriate dosing devices may be required, such as multi-dose syringes, shielded needles, oral-dosing pumps, coated tablets, single dose applicators and sachets. In some cases, warnings to seek medical attention and advice to doctors may be included in the literature. In the case of sensitising agents, users may be advised to avoid contact when a known sensitivity or allergy exists. Operator training may also be required, for example certification of competence for sheep dipping operatives.

5.8 Human medicines

5.8.1 Substances covered

A human medicine is defined in European legislation as a product for the treatment and prevention of disease, for administration to make medical diagnosis, or for restoring, correcting or modifying physiological functions in human beings.

5.8.2 Processes and procedures

The safety evaluation of medicines differs from that of most other chemicals to which humans are exposed because there is a direct benefit to the exposed individual, and therefore there is a need to balance any risks against the clinical benefits gained from the use of a medicine. The task of evaluating the risk–benefit ratio (evaluation of the possible harmful effects of the medicine against the beneficial effects) is complex. Evaluation takes into account several factors e.g. the nature of the disease or condition to be treated, the effective dose to be administered, the type of patient (e.g. age, gender) and the duration of treatment. A high risk to benefit ratio may be acceptable in the treatment of terminally ill patients where the quality of life might be enhanced, whereas a very low risk to benefit ratio would be expected in the treatment of patients with self-limiting diseases, for prophylactic treatment (e.g. vaccines) and for those requiring life-long treatment for their illness. There is no general default safety margin expected in medicines, and the risk–benefit ratio is considered on a case-by-case basis for each medicine, based on the quality, safety and efficacy of the compound in relation to a specific therapeutic indication.

There are some aspects of risk assessment of human medicines that are almost unique to this sector. For example, medicines are intentionally administered to humans, for a beneficial effect. The administered dose and thus the exposure can be controlled. Safety and pharmacokinetic data are available on humans from direct experimentation (clinical trials). This means that it is possible to compare the biological properties of the product as predicted from studies in animal models and the data gained from humans. Thus the risk assessment involves not only the extrapolation of data across species from studies in animals in relation to the potential toxic effects in humans, but also the evaluation of human data. The safety assessment of medicines is not based on the application of a standard uncertainty factor to the NOAEL from

animal studies, but the findings from such studies are important in assessing the adequacy of the safety assessment based on the results of clinical trials.

Safety, quality and efficacy are the only criteria on which legislation to control human medicines is founded within the UK and the EU. Safety issues encompass potential or actual harmful effects, quality relates to development and manufacture, and efficacy relates to the beneficial effect of the medicine to the patient.

Establishing the quality, safety and efficacy of a medicine in its intended therapeutic indication is a lengthy, stepwise process necessary for obtaining a marketing authorisation (MA). There is a sequence of three clinical testing phases, designed to gain increasing experience of use in humans. The clinical trials start with Phase I — exploratory investigations in a small number of human volunteers or patients, typically 20 to 100, for safety and dose-range finding. Phase II trials investigate safety and efficacy in a larger number of volunteer patients, typically 100 to 300, followed by Phase III trials, which involve extensive investigations of safety and efficacy in typically 1000 to 3000 patients. If the results are satisfactory in terms of quality, safety and efficacy then a submission may be made for a MA. Even after an MA is granted, further studies (Phase IV) take place on the newly authorised medicine to monitor the product in order to identify rare and unanticipated adverse effects, which are likely to emerge only after extensive clinical use.

No medicinal product can be considered to be completely risk free. Therefore there is a need for a robust system to regulate the quality, safety and efficacy of medicines in order to safeguard public health. This is achieved largely through a system of authorisation and subsequent monitoring of medicines after they have obtained a MA. In the UK the mandatory control of human medicines operates in the legal framework provided by the Medicines Act 1968 and its various codes and regulations, and the relevant EU directives from 65/65/EEC onwards. In the EU a medicine can be marketed only when the applicant has been granted either a national or an EU MA. The current EU authorisation system is based on two procedures in which member states' regulatory bodies undertake the scientific work associated with the two procedures, either on their own account or on behalf of the EC body responsible, the European Medicines Evaluation Agency (EMEA). The two procedures are:

- a centralised authorisation procedure for products derived from biotechnology or other innovative techniques; and

- a decentralised authorisation procedure, under which member states' regulatory bodies carry out the scientific work and a company holding a MA issued by one member state is issued with an identical MA on the basis of mutual recognition (MR).

When the UK is the reference member state in the MR procedure, or is the (co)-rapporteur in the centralised procedure, the opinion of a national expert advisory committee (Committee on the Safety of Medicines; CSM) is routinely sought before submitting the assessment report to the relevant member states or the Committee for Proprietary Medicinal Products (CPMP). The CSM is one of the independent advisory committees established under the Medicines Act 1968, which advises the UK Licensing Authority (Government health ministers) on the safety, quality and efficacy of medicines on the UK market.

In the area of human medicines there has been wide international agreement on the regulatory requirements under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This conference, representing the Commission of the EU, the USFDA and the Japanese Ministry of Health and Welfare, together with representatives of European, USA and Japanese pharmaceutical industries, harmonised many of the regulatory requirements between the three regions. The ICH guidelines completed to date have been adopted by the CPMP.

5.8.3 Risk assessment and dealing with uncertainty

A variety of non-clinical (*in vitro* and animal) studies are also conducted, both preceding and running concurrently with the clinical trials programme. Guidelines on non-clinical studies are based on EU directives and notes for guidance published by the CPMP, which is the EU advisory body for human medicines. The package of studies required depends on many factors, including the chemical nature of the product, its biological activities, the intended patient population, the nature and severity of the disease and the nature and duration of the product's clinical use. The key functions of the non-clinical studies relate to protection of clinical trial patients and assessment of safety endpoints not amenable to clinical

evaluation. The non-clinical tests should show the following:

- The potential toxicity of the product and any dangerous or undesirable effects that may occur under the proposed conditions of use in humans. These should be evaluated in relation to the pathological condition concerned.

- The pharmacological properties of the product, in both qualitative and quantitative relationship to the proposed use in humans. In addition, clinicians should be given information about the therapeutic potential of the product.

The animal models should be relevant: they should be pharmacologically responsive to the compound and have a similar pharmacokinetic profile to humans. The data should identify toxic effects and target organs and establish a dose–response relationship for these effects. The data should help to predict a safe level of exposure in humans. The frequency, duration and dose given to animals provide a basis for the dose levels used in the early stages of clinical trials. The therapeutic index, which is the ratio of the dose level that produces adverse effects to the dose level that produces the therapeutic benefit, is an important consideration. Some of the main factors to be considered in relation to potential concerns over safety are:

- the validity and relevance of safety margins in terms of comparative systemic exposure in the test species and humans;

- the correlation (if any) between adverse effects seen in animal models and those found in humans;

- the significance of toxic effects that are irreversible;

- the need to impose conditions on the clinical use of the product because of non-clinical findings;

- the relevance of the non-clinical data to target populations of patients, for example elderly or renally impaired patients;

- the significance of any metabolites found in humans but not in the animal models; and

- the implications of any genotoxic or carcinogenic potential or reproductive toxicity as a risk for humans.

The use of pharmacokinetic approaches is of considerable benefit in understanding the toxicity profile of a medicine. Comparative pharmacokinetic data are very useful in extrapolation and safety assessment roles. Pharmacokinetic data can be used to define adequate dosage in toxicity tests of experimental animals, and also may explain differences in pharmacological and toxicological responses between species.

As a clinical development programme progresses, the animal toxicity data are superseded once there are sufficient data from human clinical trials. This is an aspect almost unique to human medicines. However for practical and ethical reasons, some endpoints, such as genotoxicity, carcinogenicity and reproductive toxicity, can only be investigated in animal studies.

In summary, on the three principles of quality, safety and efficacy, a risk–benefit ratio is considered on a case-by-case basis for each medicine.

5.9 Medical devices

5.9.1 Substance covered

A medical device is defined here as any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of diagnosis, prevention, monitoring, treatment or alleviation of disease, diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or handicap, investigation, replacement or modification of the anatomy or of a physiological process, control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

It is necessary to balance any risks with the clinical benefits arising from the use of a medical device when judging its suitability for a particular use. This also applies to substances which may leach out of the medical device and which could be harmful to the health of any person in contact with the device.

5.9.2 Processes and procedures

A series of European directives, transposed into UK legislation, sets out essential requirements for the safety and performance of all medical devices placed on the European market. More detailed provisions for safety assessment are contained in

European standards, including a series of standards (EN/ISO 10993) that provide methods for assessing the biological safety of medical devices. One document in this series (ISO, 2002) presents an international consensus on the way allowable limits should be set for residues of toxic chemicals that can leach out of medical device materials.

5.9.3 Risk assessment and dealing with uncertainty

Toxicological assessment of medical devices is complicated by the fact that their materials typically comprise a complex mixture of chemicals, and the route and duration of exposure to these materials varies widely. Moreover, it is rare for toxicity of the chemical constituents to be adequately characterised in relation to the anticipated exposure conditions. Limits can be based on local or systemic, immediate or delayed effects. The approach used in this methodology is the establishment of a standard (see Figure 2a), and also considers the potential for local toxicity at the site of use of the device.

Leachable substances from medical devices can be introduced into the body by differing routes, ranging from skin absorption to direct systemic administration. In addition devices are, for convenience, placed into three categories according to their duration of use. In theory each material can have multiple limits based upon multiple duration categories and routes of exposure. To achieve this, tolerable intake values (TIs) are calculated individually for each route of exposure within each applicable use category. In practice the lowest TI value for a category of use or a route of entry may be chosen to best represent the toxicological effects of the leachable substance.

An individual TI is calculated by taking the NOAEL or LOAEL and dividing it by a modifying factor (MF), which is the product of all the uncertainty factors employed. (It should be noted that the term MF is used in a different way here than in Section 4.2.1.) The uncertainty factors employed are intended to cover the range of uncertainties described above, with factors of between 1 and 10 being chosen to take account of possible differences between species and within the human population. Interspecies extrapolation tends to be a significant area of uncertainty because toxicokinetic data relevant to medical device materials are rarely available. It can therefore be difficult to justify the use of a value less than the default of 10 for this uncertainty factor. Because mismatches between experimental data and intended use are comparatively common (e.g. when data are available only from short-term studies on oral routes and the compound is present in a material intended for implantation), considerable uncertainty may be introduced by extrapolation from one route or duration category to another. Thus an uncertainty factor of between 1 and 100 is used to account for the quality and relevance of the experimental data, chosen on the basis of professional judgement that takes into account the quality of the data and the design of the studies. Other situations that may give rise to greater uncertainty relating to data quality include the availability of a LOAEL instead of a NOAEL, the absence of supporting studies and the use of inappropriate animal models, routes or rates of exposure for the endpoint being assessed.

The resulting factors are multiplied together to give an overall modifying (uncertainty) factor. In most cases an MF of between 10 and 1000 is considered sufficiently protective. Any situation that results in an MF greater than 10 000 is considered to be indicative of a high degree of imprecision in the analysis, and in such cases, depending on the extent of anticipated exposure, additional data may be urgently required.

If the TI is reasonably achievable this level of exposure is set as the allowable limit (AL). If the TI cannot be met due to technical constraints, or if the cost of meeting the TI is prohibitive and the lack of the device would have an adverse impact on public health, then a further adjustment factor, the benefit factor (BF), can be introduced. This is not an uncertainty factor, but one that allows excursions to the scientifically derived TI where necessary for practical reasons and where justified by the benefit arising from the use of the device. The method ensures that any exposure to leachable substances in excess of the TI is as low as reasonably practicable, since use of a BF is only permitted when indicated by a feasibility evaluation, and the magnitude of BF must be justified.

As well as developing a TI for systemic toxicity, ISO 10993-17 (ISO, 2002) provides guidance for the development of a tolerable contact limit (TCL) for local irritation that may be induced by a medical device. The TCL is derived by taking the non-irritating level (NIL; essentially the NOAEL) or the minimally irritating level (MIL; essentially the LOAEL) and dividing by the product of an MF and the body contact surface area. As for TIs, the MF is the product of the uncertainty factors covering the same areas of uncertainty as the standard uncertainty factors, and the TCL can, if necessary and justifiable, be adjusted upwards by a benefit factor to arrive at the AL.

5.10 Industrial chemicals

5.10.1 Substances covered

In principle, most substances, man-made or natural, could at some point be considered 'industrial chemicals' in that they are either manufactured or used within the industrial (occupational) environment. Normally, though, the term is used loosely to describe the large number of chemicals that are not covered in the sections above. For the purposes of this document it is useful to consider the risk assessment of industrial chemicals as being compartmentalised into two approaches: the establishment of occupational exposure limits (OELs), and the EU regulatory programmes. Under the current UK system, substances appearing in the national OEL list and possessing demonstrable threshold forms of toxicity can have (and in most cases do have) so-called health-based occupational exposure standards, OESs, set for them. An OES is a risk management measure used directly in the workplace by the occupational health professional (e.g. occupational hygienist) in order to help assess the adequacy of control of exposure to a chemical. In addition to OELs, there are the major EU-wide regulatory programmes for industrial chemicals of ESR and NONS. A new substance is defined as any substance not exempted from the scheme (e.g. pharmaceuticals) or which is not listed on EINECS (European Inventory of Existing Commercial Chemical Substances). An industrial chemical considered to be an existing substance is defined legally as one that is present on EINECS.

5.10.2 Processes and procedures: Establishment of OESs

OELs are important features of the COSHH regulations (Topping, 2001); they help to define adequate control of exposure by inhalation and provide consistent standards across industry. Currently COSHH uses two types of limit, the OES and the maximum exposure limit (MEL)[1]. Both are expressed as airborne concentrations averaged over a specified time period, either as a long-term exposure limit (8-hr time-weighted average; TWA) or a short-term one (15-min reference period; STEL). In effect, this procedure follows the route shown in Figure 2a.

OESs and MELs are set by the Health and Safety Commission (HSC) and therefore have tripartite consensus and endorsement: the HSC, its Advisory Committee on Toxic Substances (ACTS), and the scientific subcommittee of ACTS, WATCH (Working Group on the Assessment of Toxic Chemicals) are all involved in setting OELs. First WATCH considers a package of information on a chemical, which includes information on both hazard and exposure. If WATCH considers that the criteria for an OES are met it recommends a value to ACTS. If it does not, then WATCH refers the substance to ACTS for further consideration, often the setting of a MEL. ACTS considers proposals for OESs and, if the WATCH recommendations are agreed, they are then subject to public consultation. Finally, subject to the outcome of the consultation, the HSC is invited to formally endorse the proposals, which are then published in EH40 (HSE, 2002b).

5.10.3 Risk assessment and dealing with uncertainties: Establishment of OESs

OESs are set for substances for which it is considered possible to identify, with reasonable certainty, an exposure concentration at which there is no significant risk to health, and with which compliance by industry is reasonably practicable. In practice this applies to those substances where there is believed to be a threshold for the critical effect. MELs are reserved for those substances for which such a threshold cannot be identified or assumed (e.g. genotoxic carcinogens) or, where a threshold is considered to apply, industry cannot meet a desired level of exposure for health protection reassurance.

The starting point for an OES often has to be a NOAEL from an animal study, although in a significant number of cases there are some data available, albeit of very variable quality, from human experience (e.g. see Example 4). A frequent feature in the establishment of these workplace airborne standards is consideration of effects that may be induced at the site of contact (e.g. in the respiratory tract) through irritant properties, local metabolic activation or localised inflammatory reactions towards deposited particulates.

The process of establishing OES values in the UK by this system has not used a formalised framework incorporating specified default uncertainty factors, but reflects the traditional practice by which OELs have been established around the world over many years. This procedure for setting OESs has involved moving directly from the NOAEL (or LOAEL) to the derived standard, involving the expert judgement of WATCH who have data on both hazards and exposure available to them (see Example 12 for an illustration). However it should

[1] It should be noted that the UK OEL framework is currently under review, see http://www.hse.gov.uk/consult/disdocs/dde19.pdf

be noted that in establishing OESs WATCH has to accommodate other considerations, such as the reasonable practicability of controlling exposure to the standard and the ability to monitor exposure at the level of the standard (Fairhurst, 1995). These considerations, and socio-political traditions surrounding the accommodation of risk in the workplace relative to risk in other aspects of life, have meant that uncertainty has been dealt with rather differently in the occupational setting, with smaller margins between the toxicological reference point and the exposure deemed to be satisfactory.

5.10.4 Process and procedures: Notification of new substances

Chemicals meeting the definition of a 'new' substance are currently subject to an EU-wide notification scheme, the UK version of which is the Notification of New Substances (NONS) regulations. This scheme requires the submission of information and a risk assessment to be performed. A notification for a substance is usually made to a 'lead' EU member state, and once accepted as meeting the legislative requirements the substance is then available for supply to the whole of the EU without further detailed notification. The data requirements are related to supply levels (in metric tonnes) — requirements increase as levels of supply increase. At low levels of supply (e.g. 10 kg/year), basic acute toxicity data are required. A key trigger is when the supply rate reaches 1 tonne/year, at which point data on a range of toxicological endpoints are required, including information on repeated exposure, normally a 28-day study, most often conducted via oral dosing. There are usually no data available from human experience for the substance (the scheme operates at the pre-marketing stage of a substance's lifecycle) and estimates of exposure are often modelled. If the supply tonnage level increases further then additional data are required at trigger points of 10, 100 and 1000 tonnes/year. This procedure acts to steadily increase the amount of available hazard information, for example the amount of repeat-dose toxicity data and information on toxicokinetics and reproductive toxicity.

5.10.5 Risk assessment and dealing with uncertainty: Notification of new substances

The legislation requires that a risk assessment be conducted. For acute and repeated-dose (threshold) endpoints a comparison is made between a NOAEL or LOAEL and the exposure estimate (i.e. the route shown in Figure 2b). The ratio generated is called a margin of safety (MOS), and the regulations require that a risk management conclusion is drawn from such a risk assessment.

Example 12
Establishment of an OES for 1,2,4-trichlorobenzene[1]

1,2,4-trichlorobenzene is used in the manufacture of high performance insulation for use in wire and cable products, as a brightener solution in lead or tin plating baths and also in laboratory applications. There are no reliable human data on which to base an OES. Data from experimental animal studies indicate that the liver is the key target organ for toxicity, with the most sensitive marker being an elevation in the level of urinary prophyrins. The NOAEL and LOAEL for this effect, from repeat dose exposure inhalation studies in rats, were 3 and 10 ppm, respectively. An OES of 1 ppm (8-hour TWA) was considered appropriate to protect against health effects in humans. This value is a factor of 3 below the NOAEL in rats and 10 below the LOAEL, which were considered as adequate taking into account that the lead effect is a very sensitive biochemical marker for toxic change. The occupational hygiene assessment indicated that control of exposure to this OES is readily achievable across all user industries. A STEL (15 minutes) of 5 ppm was also considered necessary in order to limit peaks in exposure which could result in irritation.

[1] HSE, 2002a

Clearly with the information available at the 1 tonne/year level of supply there are many uncertainties involved in attempting to perform a risk assessment. Some EU member states use a series of default uncertainty factors (e.g. for inter- and intraspecies extrapolation, for lack of longer term dosing data, for gaps in the database) in order to help interpret the MOS generated from this relatively sparse data set (see, for example, the approached used by The Netherlands described in Section 4.2.3). However, in the UK it is considered that the uncertainties are too great to attempt any meaningful risk assessment using numerical data inputs. If the standard default approaches that have been used elsewhere were applied, then in the vast majority of cases the overall composite uncertainty factor would be 10 000, if not greater. As indicated in Section 4.2, other regulatory authorities would consider this margin to be too great to conduct a meaningful risk assessment. However, there remains a statutory requirement to conduct a 'risk assessment'. Thus the UK takes a more qualitative approach, whereby an MOS is calculated and then considered in light of the value that emerges, the potential toxicity of concern and the type of exposure that is being considered. So, for example, where the calculated MOS is large (e.g. greater than 100) and exposures are relatively infrequent (e.g.

occasional worker exposure) then this would generally be seen as providing reassurance of little risk to human health (see Example 13). Conversely, where the MOS is small (e.g. 10 or less) and human exposure is likely to be often and uncontrolled (e.g. potential consumer exposure) then this would be cause for concern and would require regulatory action. For those cases where the MOS is of an intermediate value then, on a case-by-case basis and taking all the factors into account, further information may be required either immediately or at some specified future date.

Example 13
NONS risk assessment using the MOS approach

A notified substance is manufactured and used in the EU as an intermediate in batch process chemical synthesis. The substance is respirable (18.3% of particles <10 μm) and has a potential to cause functional and histopathological changes in the liver by repeated exposure, with a LOAEL of 50 mg/kg/day in a 28-day oral dosing study.

Operators may be exposed to the substance in dedicated areas with ventilated hoods, equipped with double layer personal protective equipment (PPE), including independent air-fed suit, respirator and cuff-taped nitrile gloves. Static and personal air monitoring has been carried out at an analogous site where 8-hr exposure levels ranged from 0.002–0.02 mg/m^3.

There is no immediate concern regarding the identified health hazards for workers. A worst-case daily intake, based on the highest available exposure monitoring data and assuming no PPE, yields an intake of 0.003 mg/kg/day for a 70 kg person breathing 10 m^3 over an 8-hour working day. This is still more than four orders of magnitude below the LOAEL of 50 mg/kg/day seen in the 28-day study. This MOS (~16 000) is considered sufficient to take into account the uncertainty in extrapolating between species, the uncertainty in human variability in the potentially exposed population, any differences between the routes of exposure in the experimental (oral) and human exposure (inhalation) situations and the fact that only a LOAEL was available. Furthermore, the exposure in the 28-day study was judged to reflect the intermittent nature of the human exposure. In addition, the PPE used offered further reassurance.

As the supply tonnages rise for new substances then the increasing amounts of data that become available ensure that some of the uncertainties are addressed and reduced. At each stage, as further data become available, the risk assessments for each exposure scenario can be reassessed and with increasing information the interpretation of the MOS becomes less speculative. Once enough information becomes available to give an adequate database for risk assessment when compared with the norm in other areas of chemical risk assessment then the standard 10-fold defaults for inter- and intraspecies extrapolation are applied for consumers and indirect exposure via the environment. With respect to occupational exposure, the experience developed through the setting of health-based OELs has been drawn on, and the acceptability of the MOS judged accordingly.

5.10.6 Processes and procedures: Existing substances

The assessment of existing substances has been conducted under the Existing Substances Regulation (ESR). Periodically, priority lists of substances (four to date) have been drawn up by the EC, and individual EU member states act as rapporteurs for specific substances. Data supplied by industry or available in the scientific literature are reviewed by the rapporteur member state and a draft risk assessment prepared. In the UK, the draft human health hazard and occupational risk assessment is peer-reviewed by WATCH in order to obtain a tripartite UK view on the assessment. The draft review is submitted to the EU, where it is considered in a technical meeting by all member states. Once a final EU position on the risk assessment is agreed (which may in fact reflect a range of views rather than a single consensus view) then the outcome of the risk assessment is formally adopted through a voting procedure. The outcome of the assessment can be a decision to take no further action, a request for more information, or a requirement that risk reduction takes place.

5.10.7 Risk assessment and dealing with uncertainty: Existing substances

In contrast to the situation with new substances, the existing substances so far considered under this scheme in the EU (around 140) have variable but generally stronger databases, including information from human studies. There is a requirement that all key endpoints are addressed prior to the conduct of the risk assessment, so there are generally few data gaps. Risk assessments are conducted by the rapporteur, using the MOS approach described above for NONS. The UK approach to interpretation of the MOSs generated for consumers and indirect exposure from the environment is to use the 100-fold default if no data are available to quantitatively compare experimental animals with humans, or on human

variability. Extra factors may be employed where there are limitations in the database (e.g. use of LOAEL or short-term dosing), although these are considered on a case-by-case basis and take into account all the available information. For example, the value of a factor applied in allowing for the use of a LOAEL depends on the severity and incidence of the effect at the LOAEL. Expert judgement is used to determine how close a prospective NOAEL is likely to have been to the observed LOAEL and the factor suitable to allow for this. The approach used by the UK for the workplace has been to apply the experience gained through the setting of OESs in judging the acceptability of the calculated MOS. Human data are the most useful for the workplace situation and are used where available. In such cases a low MOS (1–2) has been deemed acceptable, particularly if the effect in question is relatively minor (e.g. sensory irritation). Where more significant effects are observed in humans, for example on respiratory function, then a larger MOS (up to the 10-fold default for intraspecies variation) may be preferred, since the data are often generated on relatively small numbers of individuals and little may be known of variability in human response across the entire working population potentially exposed. Example 14 provides an illustration of part of a risk assessment conducted under ESR.

Overall, therefore, in the general assessment of industrial chemicals where exposure is to consumers or indirectly from the environment, a standard 100-fold default is used as a required MOS where the starting point is an experimentally determined NOAEL, with the inclusion of extra factors for limitations in the database. Where the database is particularly weak (i.e. a basic NONS data set) then a more qualitative expert judgement is used. For worker exposure, the experience gained from 'health-based' occupational standard setting has been employed in the interpretation of the MOS. It should be noted that the legislation underpinning the new and existing substances schemes is under review in the EU[1]. A new strategy for the assessment and control of industrial chemicals is currently under development. This will present the opportunity to review current practices in the use of uncertainty factors in this area.

Example 14
Risk assessment of DEGBE under ESR[1]

DEGBE (2-(2-butoxyethoxy)ethanol) is used as a solvent in a wide range of applications, including paints, dyes, inks, detergents and cleaners. Humans may be exposed at work, through the use of consumer products or from the environment. A repeat exposure NOAEL of 94 mg/m^3, the highest concentration used, was obtained in a 90-day inhalation study; effects on the liver were seen at 117 mg/m^3 in a 28-day inhalation study.

Most workplace exposures were such that MOS values were calculated to be ~30 or higher. These MOSs were considered sufficient in allowing for the uncertainties in extrapolation between and within species and for the use of a NOAEL from a 90-day study, thus providing reassurance that no further risk reduction measures were required. However, for workers manually applying products containing DEGBE a MOS of 9 was calculated; this was considered too small to allow for these uncertainties and the need for risk reduction measures was identified.

For consumers using DEGBE-containing hard surface cleaners, a MOS for inhalatory exposure of >1300 was calculated, which was considered sufficient to allow for the uncertainties, and reassuring to consumers in this use pattern. Comparison of the NOAEL with ambient air environmental exposures produced MOS values of 460 or much greater. This was again considered sufficient to allow for the uncertainties and provided reassurance that DEGBE in ambient air is of no concern for the public at large.

[1] EC, 2000

[1] http://www.defra.gov.uk/environment/chemicals/eufuture.htm

6 Future directions

The use of uncertainty factors is well established in the risk assessment of chemicals for harm to human health. However, we must always bear in mind that uncertainty factors are only a means of dealing with lack of knowledge. In some cases, the position initially arrived at when the usual 'default' uncertainty factors are used may be sufficient to deal with the issue in question when, for example, it can be shown that large margins already exist between hazard and exposure. In such cases there is little need to refine the assessment further since nothing would be gained by doing so. However, in cases where the margins appear smaller, it is likely that further exploration, involving more detailed analysis and perhaps the pursuit of additional data, will be of benefit in ensuring that appropriate risk management decisions are made.

Recent years have seen a considerable move forwards in the thinking, development of technologies and the generation of data that may help to significantly improve our knowledge and our approaches to dealing with toxicological uncertainties. It is important that these avenues are followed in order to improve chemical risk assessment. Although not intended to give a comprehensive coverage of all these areas, this chapter explores some factors that are potentially the most valuable and most likely to be productive in taking forward the science used in risk assessment.

The International Programme on Chemical Safety (IPCS) activity on chemical-specific adjustment factors (CSAFs; see Section 4.2.4), which builds on previous developments in this field, provides a significant framework through which refinements can be incorporated into addressing uncertainty in risk assessment. This framework offers a route to improved risk assessment with the introduction of more science into the typical extrapolation issues faced. Its use is encouraged in UK risk assessments wherever possible, so that default positions can be replaced, when appropriate, by scientifically derived factors. In this way, those responsible for generating the data will also be able to see what data would be required to bring more science into the process, and the value of providing appropriate information in developing more robust positions on specific risk assessments. One aspect that must be considered here is the possibility that improved data could lead to a value for a CSAF larger than the standard default. It is hoped that this possibility does not trigger resistance to the pursuit of better data and the use of CSAFs; to some extent this issue should be addressed through the regulatory systems. It should then be possible to request the generation of more informative data, irrespective and independent of the possible outcome. Critically, what the IPCS activity on CSAF also provides is a valuable framework for systematic consideration of the uncertainties in the available databases so that these can be addressed more transparently.

The data generated and used in relation to the IPCS CSAF framework may also be useful in more advanced approaches, such as physiologically-based pharmacokinetic (PBPK) and physiologically-based pharmacodynamic (PBPD) modelling. PBPK can be used to predict the tissue concentrations of chemicals in different species under various conditions, based on independent anatomical, physiological and biochemical parameters (Andersen, 1995; Risk Assessment and Toxicology Steering Committee, 1999d). Predicted concentrations are based on knowledge of the anatomy of the organism in question and rules determining movement of a substance between tissues based on accepted physiological and physicochemical processes. Recently PBPD modelling has been under development using similar principles for the prediction of toxicological or biological effects in cells and tissues. PBPK and PBPD modelling may provide a useful means for

more accurate extrapolation between species, between routes of exposure, and from high to low doses, reducing the need for uncertainty factors at least in some aspects of risk assessment. However, because of the need for (but frequent absence of) detailed substance-specific information, the routine use of PBPK and PBPD modelling in the regulatory setting is unlikely in the near future. For example, it is unlikely that the specific data required for pesticides will be routinely generated. Nevertheless, there has been increasing use of PBPK modelling elsewhere (e.g. in the USA: OSHA, 1997; EPA, 2000 and Canada: Health Canada, 1993), where it is beginning to be used in a regulatory context), and so, where models are validated, their appropriate use is to be encouraged in order to provide more accurate predictions of the likelihood of adverse effects in humans from chemical exposure. Furthermore, with sufficient knowledge and the use of appropriate mathematical techniques (e.g. Delic *et al.,* 2000), it is possible to model variability in populations in order to try to reduce the uncertainty in these aspects of risk assessment. Similarly, where human data do exist, techniques which have largely been used in the pharmacological arena can enhance the value of what are often 'sparse' data sets (Aarons *et al.,* 1997). Such approaches could usefully be employed in other fields where human data are available in order to address the problems of the uncertainties in human variability. It will, however, be necessary to develop a clear framework of guidance for the use of PBPK and PBPD and population modelling in the regulatory setting.

The use of probabilistic approaches in risk assessment is also likely to have a significant impact in the foreseeable future. This impact may take a number of forms depending upon the information available. For example, using the current risk assessment paradigm, the usual approach where a number of uncertainty factors are required within the risk assessment process is simply to multiply them together in order to generate an overall composite numerical factor. An alternative is to combine estimates of the ranges that these factors may encompass through a probabilistic assessment (Slob & Pieters, 1998; Vermeire *et al.,* 2001). This is essentially a variation on the standard paradigm. However, in addition, probabilistic approaches are being proposed that differ from the traditional risk assessment paradigm and use alternative mathematical and philosophical approaches to give an estimate of risk and the uncertainty in its estimate (FORA, 2000). It is likely that UK Government departments, agencies and their advisory committees will give further consideration to such approaches over the coming years.

The consequence of increasing the requirements for data derived from experiments in non-human species may be to increase (at least transiently) the use of animals in research, although the overall and ultimate aim is to minimise their use through improvements in the efficiency surrounding data generation and use. In some instances the only way of gathering extra useful information may be to undertake further studies in animals. This should be done in such a way that the data generated can be used in the application of the techniques outlined above in order to reduce the subsequent need for further research or 'routine' testing. The development and use of alternatives to the use of animals is also critical in this respect. Despite limitations still to be overcome, the use of *in vitro* systems derived from both animal and human tissues is beginning to be useful in some aspects of hazard and risk assessment (Eisenbrand *et al.,* 2002). From the perspective of dealing with uncertainties in risk assessment, these alternatives may provide useful information, for example in determining the variability in cellular metabolism of a chemical between species and individuals. Such information can aid in mechanistic understanding of toxicity and help inform the replacement of default uncertainty factors with experimentally derived values. Furthermore, the information generated can be used directly in techniques such as PBPK modelling. The continued development of such *in vitro* systems is therefore essential in order to reduce the need for studies in animals and to secure their longer-term role in contributing to risk assessment.

While animal studies continue to be used to provide the basis for risk assessment, it is important to reduce uncertainties by more thorough use of the data generated. As described elsewhere in the document, the NOAEL or LOAEL is often used as the starting point in risk assessment. This value, as a surrogate for the 'true' threshold dose for inducing an adverse effect in the species in question, is itself uncertain as it is often based on relatively few animals. The benchmark dose (BMD) has been developed and used, particularly in the USA, as an alternative starting point to the NOAEL in risk assessment. The BMD potentially provides a statistically more robust value than the NOAEL and thus reduces the uncertainty in the starting point for a risk assessment. Although the BMD has been used elsewhere, it has generally not been adopted in the UK regulatory setting. Therefore consideration of its use as an alternative to the NOAEL/LOAEL is encouraged. However, it is important that adoption of the BMD should not result in any increase in the use of animals in specific studies (in order to boost the number of dose levels used); rather, its use should be pursued

through improved study design. It is also noted that training in the use of the BMD will probably be required.

One relatively novel area of research that is currently developing rapidly is that of genomics and proteomics. The effects of a toxic chemical will, in most cases, be reflected at the cellular level in changes in gene expression. These changes can, in principle, be detected by alterations in the extent to which a gene is transcribed and subsequently translated into a protein. 'Genomics' strictly refers to the techniques available to identify the DNA sequence of the genome, but in this context the term is also used to encompass the techniques available to identify the mRNA (i.e. the gene transcript) from actively transcribed genes ('transcriptomics' is another term used for the latter). Similarly, the term 'proteomics' refers to the techniques available to identify the proteins in a biological sample. These techniques may provide powerful tools in helping to determine how chemicals can induce toxic effects, and how the expression of these toxicities may be found to vary between species and individuals, thus providing information to help reduce the uncertainties in risk assessment. The use of genomics and proteomics in toxicology and risk assessment was the subject of a recent joint symposium held by the UK committees on toxicity, mutagenicity and carcinogenicity (FSA, 2002[1]). The potential value of these techniques in future toxicological risk assessment was recognised by these committees, as well as the fact that they may serve as useful adjuncts to conventional toxicology studies, particularly where proteins under investigation are known to be causally related to toxicity. However, the committees considered that further research and validation is needed before these techniques can be considered for routine use in regulatory toxicological risk assessment. In particular, the committees noted the need for more research leading to the development of genomic and proteomic databases, development of methods of bioinformatic and statistical analysis of data and pattern recognition, and for information on the normal range of gene expression.

This latter aspect is of particular importance since, as described in this document, the basis for risk assessment is the identification of a 'critical effect'. In conventional toxicological studies, the critical effect is the relevant adverse effect(s) in animals observed through standardised means, for example pathological or biochemical investigations. Changes observed using these measures are judged against a background of a well-developed and extensive historical knowledge and experience, from which expert judgement can draw in order to distinguish real toxicological changes from normal variation that is known about and codified. The data from studies using genomics and proteomics will need to be set against knowledge of the range of normal gene expression in order to discriminate between chemical-induced changes and natural variation. Also, once a chemical-related change in gene or protein expression has been identified, it is still necessary to determine whether or not this is related to any expression of toxicity, or whether the change in gene expression just represents natural variation and is unrelated to any known toxicity, or not sufficiently large to have any particular biological or toxicological consequence. This may prove to be a particular challenge since it is possible that chemical-induced changes in gene expression may be detected at levels of tissue exposure or applied dose considerably lower than those associated with expression of pathological change. Clearly there is much work to be undertaken in order to apply these novel techniques to toxicological risk assessment. Nevertheless, their potential in contributing to reducing uncertainty is apparent and their application to this is to be encouraged.

The issue of the normal range of gene expression is one of potentially broader significance in risk assessment. A number of factors are important when considering how a population varies in response to a chemical exposure. One of these is the genetic variation within the population and the normal expression of genes within that population (Boobis, 2002). Since one of the major uncertainties faced in risk assessment is variation in the human population, knowledge of normal genetic variation and how this translates into differential gene expression in the population affected and in individual sensitivity is potentially of great value. With the advent of the Human Genome Project (IHGSC, 2001) information is becoming available on genetic variation in the human genome. It is becoming increasingly clear that most human genes show variation (i.e. are polymorphic). The significance of this variation, in terms of contributing to our understanding of variation in response to chemical exposure, very much depends upon where in the gene the variation lies. Potentially, though, this further knowledge and understanding of the genetic variation in the human population may contribute significantly to

[1] FSA (2002) *Use of Genomics and Proteomics in Toxicology* (Joint Statement by the Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment on a Symposium held by the three Committees), London, UK, Food Standards Agency, Available [February 2003] at http://www.food.gov.uk/multimedia/pdfs/JointCOT-COM-COCStatement.PDF

reducing the uncertainties in risk assessment through the identification of genes critical to the expression of toxicity and quantitation of their variation within the population.

The discussion above has focused essentially on approaches, techniques and methodologies for reducing uncertainty and ultimately the replacement of uncertainty factors in risk assessment of chemicals. While some of these could be applied relatively rapidly and others require further development, there are other aspects of the use of uncertainty factors in UK chemical regulatory risk assessment that can be addressed more immediately.

As indicated previously in this document, the handling of toxicological uncertainty in the occupational setting, both in terms of risk assessment and the establishment of exposure standards, has evolved independently to that in other fora. A feature of this has been that a formalised framework incorporating specified default uncertainty factors has not been used, although the process has included a consideration of these issues. The current IGHRC activity leading to the production of this document has acted as a stimulus for the Working Group on the Assessment of Toxic Chemicals (WATCH) to consider the issue of handling toxicological uncertainty, and particularly to reflect on the approaches used in other fora. The committee considers that its approach of using expert judgement to address toxicological uncertainty on a case-by-case basis remains important to the setting in which it operates. However, the committee recommended that, for occupational regulation in the UK, there should be more transparency in how uncertainty factors are used to address each of the areas of uncertainty that may occur within any particular risk assessment, or for standard setting for specific chemicals. As a consequence the thinking underlying expert judgement would be more transparent. This should lead to a clearer portrayal of the similarities and differences between the occupational and other arenas in terms of any conclusions reached about accommodating uncertainty. It is also a move directed towards securing a common framework of thinking about scientific issues involved in uncertainties across all regulatory areas.

As described in detail in this document, the use of uncertainty factors is established practice in chemical risk assessment. However, in order to help increase transparency and understanding in how uncertainty factors are used, it would be of value for published regulatory risk assessments to address, in greater detail and with greater clarity than has been the case to date, the adequacy of the data available, the areas of uncertainty that are met and the uncertainty factors that are used, with the associated rationale, in the risk assessment process.

Uncertainty is inherent in toxicological risk assessment, and the use of uncertainty factors to address this problem is part and parcel of the conventional approach that has developed over the years. Our ability to examine and understand how chemicals can induce toxicity and then to analyse this information is on the threshold of major advances that may ultimately change the way we assess risks. However, it will take some time before these advances are ready for routine use in regulatory risk assessment work aimed at securing reassurance of protection of human health.

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Glossary of terms and abbreviations

ACGIH - American Conference of Government and Industrial Hygienists

ACP - Advisory Committee on Pesticides

ACTS - Advisory Committee on Toxic Substances

Acute: Short term, in relation to exposure or development of toxic effect

Acute toxicity: Effects that occur over a short period of time (e.g. up to 14 days) immediately following exposure to a toxic substance

ADI - Acceptable daily intake: Estimate of the amount of a substance in food or drink, expressed on a body weight basis, that can be ingested daily over a lifetime by humans without appreciable health risk

Adverse effect: Change in morphology, physiology, growth, development 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

Allergen: A substance capable of inducing a sensitised state in an individual through stimulation of the immune system

Allergy: Symptoms or signs occurring in sensitised individuals following exposure to a previously encountered substance (allergen), which would otherwise not cause such symptoms or signs in non-sensitised individuals

Aneugenic: Inducing aneuploidy (qv)

Aneuploidy: The circumstances in which the total number of chromosomes within a cell is not an exact multiple of the normal haploid (see 'polyploidy') number. Chromosomes may be lost or gained during cell division.

AOEL - Acceptable operator exposure level

AQS - Air quality standard: The concentration of a pollutant in the atmosphere, determined by an assessment of health effects, which can be broadly taken to achieve a certain level of environmental quality

ArfD - Acute reference dose

Assay: A procedure for measurement or identification

Bioavailability: The proportion of a substance that reaches the systemic circulation after a particular route of administration

Biomarker: Observable change (not necessarily pathological) in an organism, related to a specific exposure or effect

Body burden: Total amount of a chemical present in an organism at a given time

BMD - Benchmark dose: A mathematically derived alternative to the NOAEL/LOAEL, using the data from a dose–response relationship as a toxicological reference point for use in risk assessment

Carcinogens: The causal agents which induce tumours. Chemical carcinogens are structurally diverse and include naturally-occurring substances as well as synthetic compounds.

Case–control study: A study that starts with the identification of persons with the disease of interest and a suitable control group of persons without the disease. The relationship of some attribute to the disease (such as exposure to a carcinogen) is examined by comparing the disease and non-disease groups with regard to how frequently the attribute is implicated in each of the groups.

Chromosome: The DNA in a cell is divided into structures called chromosomes, which are large enough to be seen under a microscope. Normally a cell from a species contains an even number of chromosomes which are in pairs, one derived from the male parent and the other from the female.

Chronic effect: Toxic effect or consequence which develops slowly and has a long-lasting time course

Chronic exposure: Exposure to a chemical which occurs over an extended period of time or a significant fraction of the lifetime. Such exposures can be continuous (all the time) or repeated daily for many months or years.

Clastogen: An agent that produces chromosome breaks and other structural aberrations. Clastogenic events may play an important part in the development of some tumours.

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

COSHH - Control of Substances Hazardous to Health

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

Critical effect: The adverse effect judged to be the most important for setting an acceptable human intake or exposure, or for use as a starting point in risk assessment. It is usually the most sensitive adverse effect (i.e. that with the lowest effect level), or sometimes a more severe effect, not necessarily having the lowest effect level.

CSAF - Chemical specific adjustment factor: A factor derived from data for a specific chemical, which can be used to replace a default uncertainty factor in a risk assessment

CSM - Committee on the Safety of Medicines

CVMP - Committee for Veterinary Medicinal Products

Cytogenetic: Concerning chromosomes, their origin, structure and function

Developmental toxicity: The ability to produce an adverse effect in embryo, fetus or immature organism, which is induced or manifest either prenatally or postnatally before sexual maturity

DNA - Deoxyribonucleic acid: The molecule that encodes genetic information

Dose: Total amount of a substance administered to, taken or absorbed by an organism

Dose–response assessment: Determination of the relationship between the magnitude of the dose or level of exposure to a chemical and the incidence or severity of the associated adverse effect

EFSA - European Food Safety Authority

EINECS - European Inventory of Existing Commercial Chemical Substances

EMEA - European Medicines Evaluation Agency

EPAQS - Expert Group on Air Quality Standards

Epidemiology: Study of the distribution and, in some instances, the causal factors of disease in communities and populations

ESR - Existing Substance Regulation

Exposure assessment: The measured, estimated or predicted intake of or exposure to a chemical, in terms of its magnitude, duration and frequency for the general population, for different subgroups of the population or for individuals

FAO - Food and Agriculture Organization

Gavage: Administration of a liquid by a stomach tube; commonly used as a dosing method in toxicity studies

Gene: A length of DNA that codes for a particular protein, or, in certain cases, for a functional or structural RNA molecule

Genetic polymorphism: A difference in DNA sequence among individuals, groups or populations giving rise to differences between individuals (e.g. a genetic polymorphism might give rise to blue eyes or brown eyes, or the presence or absence of a particularly key enzyme)

Genome: All the genetic material in the chromosomes of a particular organism; its size is generally given as its total number of base pairs

Genomics: The study of genes and their function

Genotoxic: The ability of a substance to cause DNA damage, either directly or after metabolic activation

Genotype: The particular genetic pattern seen in the DNA of an individual

Hazard: The inherent properties of a substance, or mixture of substances, that make it capable of causing adverse effects in organisms

Hazard characterisation: The quantitative (potency) evaluation of any adverse effects observed, usually by dose–response assessment, and the identification of mechanisms of action and of species differences in response

Hazard identification: The identification, from animal studies, *in vitro* studies and structure–activity relationships, of adverse health effects associated with exposure to a chemical

Hepatic: Pertaining to the liver

Hepatotoxic: Causing liver toxicity

HSC - Health and Safety Commission

Human Genome Project: An international research effort aimed at discovering the full sequence of bases in the human genome

IGHRC - Interdepartmental Group on Health Risks from Chemicals

ILO - International Labour Organization

In vitro: A Latin term used to describe effects or studies conducted in biological materials outside the living body

In vivo: A Latin term used to describe effects or studies in living animals

IPCS - International Programme on Chemical Safety of the World Health Organization

JECFA - Joint FAO/WHO Expert Committee on Food Additives

JMPR Joint (FAO/WHO) Meetings on Pesticides Residues

Leachable substance: A chemical removed from a medical device by the action of water or other liquids related to the use of the device

LOAEL - Lowest observed adverse effect level: The lowest dose level in a study at which adverse effect(s) are observed

MEL - Maximum exposure limit: A maximum airborne concentration for the workplace, averaged over a reference period, which may be set for chemicals that cause serious health effects, and which should not be exceeded

Metabolic activation: The process by which relatively stable substrates are converted to highly reactive, generally electrophilic products with the capability of producing damage to critical cellular macromolecules. The term is occasionally used to refer to the metabolism of therapeutically inactive pro-drugs to the active form of the drug.

Metabolism: Changes made to a substance by biological systems to modify its properties

Metabolite: Product formed from the original compound by enzymic/hydrolytic reactions in the body or cell

MIL - Minimally irritating level: The amount of a leachable substance that is minimally irritating to the patient

MOS - Margin of safety: The ratio of a toxicological reference point (e.g. NOAEL or LOAEL) to an estimate of exposure. Also known as the TER (toxicity exposure ratio)

MRL - Maximum residue limit: For agricultural pesticides, MRLs are defined as the maximum concentration of pesticide residue (expressed as milligrams of residue per kilogram of commodity) likely to occur in or on food commodities and in cereals and products of animal origin, after the use of pesticides according to good agricultural practice (GAP). MRLs for agricultural pesticides are intended primarily as a check that GAP is being followed, and to assist international trade in produce treated with pesticides. They are not safety limits, and exposure to residues in excess of an MRL does not automatically imply a hazard to health. It is the maximum concentration of a pesticide residue permitted to be present in food commodities or in animal feeds.

An MRL for a veterinary medicine is the maximum concentration permitted to be present in the tissues (e.g. muscle, liver, skin or fat) or products (e.g. milk, eggs, honey) of food-producing animals. Based on a 'standard' food basket, MRLs for VMPs can be allocated to the different food items in appropriate proportions, such that residue intake of a 60 kg adult based on them should not exceed the ADI.

mRNA - Messenger RNA: The DNA of a gene is transcribed into mRNA molecules, which then serve as a template for the synthesis of proteins

NIL - Non-irritating level: The largest amount of a leachable substance that is not irritating to the patient

NOAEC - No observed adverse effect concentration: The highest administered concentration at which no adverse effect is observed

NOAEL - No observed adverse effect level: The highest administered dose at which no adverse effect is observed

NOEC - No observed effect concentration

NOEL - No observed effect level

Non-genotoxic carcinogen: A substance which induces tumours via a mechanism which does not involve direct damage to DNA

NONS - Notification of New Substances

OECD - Organisation for Economic Co-operation and Development

OEL - Occupational exposure limit: Regulatory standard for airborne concentrations of substance in the workplace

OES - Occupational exposure standard: An airborne concentration for the workplace, averaged over a reference period, set at a level at which it is believed that there will be no injury to health of workers if exposed over a working lifetime

PBPD - Physiologically-based pharmacodynamic modelling

PBPK - Physiologically-based pharmacokinetic modelling: Modelling the dose or degree of exposure to a chemical at a target tissue, cell or receptor through a mathematical description of the anatomical, physiological and biochemical properties of the body and the chemical of interest

PPE - Personal protective equipment

PTWI - Provisional tolerable weekly intake

Proteomics: Study of protein properties on a large scale in order to obtain a global integrated view of cellular processes including gene expression levels, post translational modifications, interactions and location

Reproductive toxicity: The ability to produce an adverse effect on an aspect of reproductive capacity, function or outcome. It includes effects on the embryo, fetus, neonate and prepubertal organism and on adult reproductive and neuroendocrine systems.

Regulatory standard: A standard, usually quantitative, developed by a regulatory authority in order to control human exposure to a chemical

Renal: Relating to the kidney

Risk: Probability that a harmful event (e.g. death, injury or loss) arising from exposure to a substance may occur under specific conditions

Risk assessment: The evaluation of the potential for adverse health effects in humans from exposure to toxic chemicals

Risk Assessment and Toxicology Steering Committee: Forerunner of the IGHRC

Risk characterisation: The integration of hazard identification, hazard characterisation and human intake or exposure assessment in order to assess the probability of occurrence and severity of a risk to human health

SCCNFCP - Scientific Committee on Cosmetics and Non-Food Consumer Products

SCF - Scientific Committee on Food of the European Commission

Sensory irritation: Stimulation of sensory nerves leading to subjective feelings of irritation (e.g. stinging of the eyes)

Structure–activity relationship: The qualitative association between the molecular structure or the physicochemical properties of a chemical and its biological properties, including toxicity

TCL - Tolerable contact level: The tolerable contact exposure to a leachable substance resulting from contact with a medical device

TDI - Tolerable daily intake: An estimate of the amount of contaminant, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk

TER - Toxicity exposure ratio: see MOS

Threshold: Dose or exposure concentration below which an effect is not expected to occur

TI - Tolerable intake: An estimate of the average daily intake of a substance over a specified time period, expressed on a body weight basis, that is considered to be without appreciable harm to health. It is derived as a part of the overall establishment of allowable limits for a leachable substance in a medical device.

TLV - Threshold limit value

Toxicodynamics: The description of the adverse effects that toxic chemicals exert on the body

Toxicogenomics: A new scientific subdiscipline that combines the emerging technologies of genomics and bioinformatics to identify and characterise mechanisms of action of known and suspected toxicants

Toxicokinetics: The description of the fate of chemicals in the body, including a mathematical account of their absorption, distribution, metabolism and excretion

Transcriptomics: Techniques available to identify mRNA from actively transcribed genes

Uncertainties: Those elements in the risk assessment process about which knowledge is absent or imprecise

Uncertainty factor: A numerical factor applied to a toxicological reference point to allow for uncertainties in risk assessment. These factors may be default values used in the absence of specific information on a chemical and may be modified in the light of specific information.

USEPA - United States Environmental Protection Agency

USFDA - United States Food and Drug Administration

WATCH - Working Group on the Assessment of Toxic Chemicals

WHO - World Health Organization

Xenobiotic: A chemical foreign to the biological system, not normally found in the body

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Risk Assessment and Toxicology Steering Committee publications

cr 1 Developing New Approaches to Assessing Risk to Human Health from Chemicals

cr 2 Risk Assessment Approaches used by UK Government for Evaluating Human Health Effects of Chemicals

cr 3 Risk Assessment Strategies in Relation to Population Subgroups

cr 4 Physiologically-Based Pharmacokinetic Modelling: A Potential Tool for Use in Risk Assessment

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cr 7 The Interdepartmental Group on Health Risks from Chemicals: First Report and Forward Plan to 2002

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