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Assessment Factors In Human Health Risk Assessment

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ASSESSMENT FACTORS IN HUMAN HEALTH RISK ASSESSMENT

Contents

SUMMARY

This Technical Report reviews the background to the role of 'Assessment Factors' (AFs) in Human Health Risk Assessment. The use of these factors is described in the context of the overall Risk Assessment and risk management process. The disparity between AFs contained or implicit within the approaches to Risk Assessment which have developed separately for occupational and non-occupational situations is pointed out.

The Reports sets out to recommend a scientifically based approach to the use of Afs in Health Risk Assessment which will allow consistency across the entire spectrum of human exposure. The Task Force considered that any such approach should be capable of general applicability while enabling justifiable distinctions to be made between occupational and non-occupational situations. It should also draw clear distinctions between the scientific and non-scientific aspects of the Risk Assessment/risk management process. A number of criteria for acceptability are proposed.

Three existing approaches developed principally for non-occupational situations are reviewed in some detail, as is the generic approach to the setting of occupational exposure limits. The scientific basis for the factors used in these approaches is explored. None of these approaches is regarded as meeting the criteria for general acceptability and the Task Force decided to develop a new approach, utilising the best elements of those currently available.

The Report defines the scientific elements which are considered to be relevant to the Risk Assessment process and these are reviewed in some detail. The basis in the scientific literature for specific numerical ranges and default values for each of the component elements of the overall AF is explored.

An approach is recommended which provides a method of deriving the best scientific estimate of a human no adverse effect level which is referred to in this report as the Predicted No Adverse Effect Level (PNAEL). An important feature of this approach is the need to establish the route and duration of exposure to which the PNAEL refers before attempting to derive factors, since these may vary for different routes or exposure durations. For each element of the approach, ranges and/or default values for the numerical factors involved are recommended.

The approach permits justifiable distinctions to be made between occupational and non-occupational situations and, being solely based on scientific considerations, is properly the province of the risk assessor. The risk assessor will make an estimate of the degree of scientific uncertainty involved in the process and it is recommended that due allowance be made for this uncertainty by the risk

assessor and the risk manager together. Any further, non-scientific factors which the risk manager considers to be relevant may then be taken into account. The overall process should thus enable clear distinctions to be made between scientific and non-scientific elements.

1. INTRODUCTION

1.1 LEGISLATIVE BACKGROUND

The European Union has recently adopted legislation which formally requires that risk assessments be conducted to predict the impact of substances on human health and the environment. Council Directive 92/32/EEC, the Seventh Amendment of the Directive 67/548/EEC relating to the Classification, Packaging and Labelling of Dangerous Substances (EEC, 1992) and the Council Regulation 793/93 relating to the risks of Existing Substances (EEC, 1993a) address risk assessment of new and existing substances, respectively. The general principles of risk assessment are defined in Commission Directive 93/67/EEC for New Substances (EEC, 1993b) and Commission Regulation (EC) No. 1488/94 for Existing Substances (EEC, 1994). Both of these documents are supported by Technical Guidance Documents.

The relatively recent emergence of this risk assessment legislation should not imply that the process of risk assessment is new; scientists in industry and government have for decades been assessing the risks for human health and the environment resulting from exposure to substances. The objectives of the European Union in enacting this new legislation include the following:

- define and harmonise the risk assessment process to ensure that all Member States can reach similar conclusions about any one substance or preparation;

- make the assessment process "transparent" so that all interested parties can understand the basis on which the prediction of risk is determined;

- make the risk assessment an iterative process such that it can be refined if and when new and relevant information on effects or exposure becomes available.

While not specifically required, industry will also certainly make use of, and seek to contribute to, the developing an integrated risk assessment guidance document for new and existing substances in order to reach a greater harmonisation between assessments conducted by industry and regulatory authorities.

1.2 OVERVIEW OF RISK ASSESSMENT

Risk assessment is the process which provides a link between scientific knowledge and the action taken to protect man and the environment from unreasonable risk resulting from exposure. In human health terms, it covers the assembly and interpretation of all relevant information, which then enables the risk assessor and risk manager to define the risks and hence estimate an acceptable level of exposure to humans.

The four principle elements of risk assessment for human health are: hazard identification, dose-response assessment, exposure assessment and risk characterisation. The risk characterisation step involves the comparison of information on toxicology with information on exposure. For the majority of industrial chemicals to which man may be exposed, indirectly via the environment, as a consumer or in the workplace, only limited information from human experience exists. Therefore, the question of how to extrapolate the results of laboratory studies in animals to man in a meaningful way has become an important aspect of the risk characterisation step.

The general principle of extrapolation involves compiling dose-response data obtained from toxicology studies conducted in laboratory animals. Of necessity, these are performed at high doses, typically ranging from a dose which produces adverse effects (which may be a maximum tolerated dose, MTD) down to the dose below the No Observed Adverse Effect Level (NOAEL). The results from animal studies are then extrapolated to enable judgements to be made about the effects expected to occur in man.

Historically, the so-called "safety factor" approach was introduced in the United States in the mid-1950's in response to legislative guideline needs in the area of food additives (Lehman and Fitzhugh, 1954). This approach proposed that the Acceptable Daily Intake (ADI) for food additives or contaminants be derived from a chronic animal NOEL (in mg/kg of diet) divided by a 100-fold factor.

This 100-fold factor was understood to comprise a factor of 10 to reflect the hypothesised increased sensitivity of man relative to laboratory test animals and an additional factor of 10 to take into account the presumed range in biological sensitivity to be found in the human population. This fundamental approach has been adopted into guidelines and recommendations by several international agencies and governmental bodies.

The selection and justification of the applied factors have been reviewed for food additives and environmental exposures to industrial and agricultural chemicals (Dourson and Stara, 1983; Lu, 1979).

It is important to note that quite distinct processes have evolved for risk assessment of chemical exposures in occupational and non-occupational settings. While the classical ADI approach has been adopted in the non-occupational setting, the establishment of "Occupational Exposure Limits" (OELs) has not consciously involved the application of assessment factors to NOAELs. Recently, the use of "safety factors" in determining occupational exposure limits has been reviewed by Illing (1991) and Galer *et al* (1992) and, specifically for developmental toxicity endpoints, by Hart *et al* (1988). The "ADI" approach and the "occupational" approach have both developed over several decades and each has become well established in its own field. No significant attempt appears to have been made to ensure that both have a common scientific basis and that they lead to consistent conclusions. The different approaches used in developing exposure limits in occupational and non-occupational settings are described further in Section 2.

1.3 OBJECTIVES

The entire risk assessment process is beyond the scope of this report. Instead, the primary subject of this work is the risk characterisation step, and in particular the derivation of the assessment factors - the overall factors used for converting data on animal responses into a reasonable prediction of human response. The Terms of Reference for the task force producing this report are:

- review the basis for developing assessment factors used in the derivation of acceptable human exposure;

- review the assessment factors currently available for use in assessing the risk of occupational and non-occupational exposure to chemicals;

- recommend a scientifically-based approach for use in the derivation of acceptable human exposures. This approach will be based on assessment factors which provide consistency when evaluating different chemicals and different exposure settings.

As cited above, numerous documents have been published on risk assessment, the risk characterisation step, and the derivation of the assessment factor. The goal in developing the approach recommended in this document is to recognize and advance two important concepts:

- the same general process should be used to assess risk in the occupational and non-occupational environments; the approach should be consistent but sufficiently flexible to allow the possibility of different outcomes;

- risk assessment and risk management must be conducted as two related but independent processes, the former based on scientific principles exclusively, while the latter also takes into account issues such as socio-economics, technical feasibility, societal perceptions and governmental policy.

The following are thus proposed as criteria for an acceptable approach:

- applicability to both occupational and non-occupational exposure scenarios;
- clear distinction between scientific and non-scientific aspects;
- flexibility and ease of use;
- transparency;
- acceptability for general use.

1.4 OCCUPATIONAL AND NON-OCCUPATIONAL EXPOSURES

Distinctions are apparent in the magnitude of the assessment factor applied in occupational and non-occupational exposure settings (Zielhuis and van der Kreek, 1979; Illing 1991; Fairhurst, 1994).

Different limit values are often based on policy considerations and/or pragmatism, and therefore include risk management as well as risk assessment considerations. There are, however, scientifically-based differences that justify quantitative distinctions in assessment factor selection. This issue is discussed further in Section 5.

1.5 THE RELATIONSHIP BETWEEN RISK ASSESSMENT AND RISK MANAGEMENT

In the risk characterisation step of the risk assessment process, the incidence and severity of effects has to be estimated in humans who may be exposed to a specific substance. The goal should be to determine the best scientific estimate of human risk and the degree of uncertainty associated with this estimate, recognising that interindividual variation is likely and also that humans could be more susceptible than animals to some chemical substances. Once the risk has been characterised, the risk manager has the responsibility to adequately protect the potentially exposed population. This

responsibility will include socio-economic and political factors as well as consideration of societal concerns and public perception of risk particularly in relation to emotive issues. It is recommended that any additional factors applied by risk managers are identified and are transparent.

1.6 NON-THRESHOLD EFFECTS

For most toxicological endpoints it is generally agreed that there is a threshold below which no toxic effect occurs. Thus, applying an assessment factor to an appropriate NOAEL or Lowest Observed Adverse Effect Level, i.e. LOAEL, provides a method of estimating an acceptable level for humans.

This procedure, however, is not universally applicable. The assessment of risk for substances which are generally assumed to act through a mechanism where a threshold cannot be identified, e.g. germ cell mutagens and genotoxic carcinogens, poses specific scientific and societal challenges and is beyond the scope of this report.

For such substances, it is suggested that the risk assessor should characterise the extent of the human health risk at various exposure levels to the best of his ability. The risk manager should then consider the scientific uncertainty inherent in this process and, after taking into account relevant non-scientific factors, determine appropriate risk management actions.

2. REVIEW OF EXISTING APPROACHES

2.1 OCCUPATIONAL APPROACHES

In the late 1930s and early 1940s, two factors came together to provide the genesis of the concept of occupational exposure limits (OELs). These were the then relatively new discipline of industrial hygiene, seeking ways of applying the principle that "prevention is better than cure", and developments in analytical methodology and instrumentation, which made measurement of exposure in the workplace a practical proposition. These developments led to the need for quantitative criteria against which to judge the acceptability of measured exposure levels and the concept of Threshold Limit Values (TLVs) began to be developed under the auspices of the American Conference of Governmental Industrial Hygienists (ACGIH).

Over the following decades the concept of OELs developed steadily and is now enshrined in the occupational health legislation of most developed countries. Apart from the ACGIH TLV system, a number of other approaches to OEL setting have been developed in industrialised countries. These have been extensively reviewed (Alexiadis, 1990). The approaches of principal interest are:

- the United States National Institute for Occupational Safety and Health (NIOSH)/Occupational Safety and Health Administration (OSHA) system;
- the German system of "Maximale Arbeitsplatzkonzentrationen" (MAK, Maximum Concentration Values in the Workplace) and "Technische Richtkonzentrationen" (TRK, Technical Exposure Limits);
- the Netherlands "Nationale MAC-lijst" (Maximale Aanvaarde Concentratie);
- the United Kingdom system of "Occupational Exposure Standards" (OES) and "Maximum Exposure Limits" (MEL);
- the EU system of developing "Occupational Exposure Limits" (OEL).

The ACGIH published its first full list of TLVs in 1946, with the intention that it be revised annually (see, for instance, ACGIH, 1991). The ACGIH operates through its TLV Committee, which comprises four sub-committees. TLVs are based solely on health considerations and have the status of recommended limits (i.e. they are not legally binding unless adopted by a regulatory agency). Lists and a "Notice of

Intended Changes" (allowing a two year period for comment) are produced annually. Documentation (describing the basis for the limit) is also published.

In 1970, OSHA was created in the United States with the responsibility to promulgate and enforce federal exposure limits known as Permissible Exposure Limits (PELs). OSHA initially adopted the 1968 ACGIH TLV list, although it also has the option to develop its own standards, using those recommended by NIOSH or other agencies. Standards are set through a "rule making" process which allows for public comment on proposed standards. NIOSH is directed to provide OSHA with health-based recommended exposure limits. These are based on and contained within published criteria documents.

In Germany the MAK Committee of the Deutsche Forschungsgemeinschaft (DFG) has been publishing its recommendations for MAKs since 1968. These are scientifically based eight hour time weighted averages. A tripartite group (the Committee for Hazardous Working Materials) advises the Ministry of Labour on the formal adoption of the proposed MAK values. For certain substances (e.g. genotoxic carcinogens) the MAK Committee may decide that a health based MAK can not be set, in which situations the tripartite group may develop a TRK, based on technical feasibility and medical experiences. Documentations are published on each substance, for which the MAK Committee has set a MAK or for which a classification has been decided on. MAKs and TRKs are legally binding.

In The Netherlands a three stage standard setting process is operated, with involvement from government, industry and trade unions at all three stages. In the first stage a Working Group compiles a strictly health based criteria document with a recommendation for a limit. Socio-economic and compliance factors are considered in a separate document produced by the relevant government department. At the next stage the proposals are considered by the tripartite Commission on Exposure Limits for Hazardous Chemical Substances, which will consult with industry about feasibility. In the final stage an administrative OEL is determined (after an appropriate period for comment) by the relevant Ministry. The limits so produced are not legally binding and may either be health based or based on the practicability of compliance. The system is very open and full documentation is published.

In the United Kingdom (UK-HSE, 1992), OELs are set by the Health and Safety Commission (HSC) advised by its Advisory Committee on Toxic Substances (ACTS) and the latter's sub-committee WATCH (Working Group for the Assessment of Toxic Chemicals). All three bodies are tripartite and the process of standard setting commences with the relevant government department (Health and Safety Executive (HSE)) preparing and submitting a criteria document to WATCH. WATCH may decide that a health

based standard can be set and complied with (in which case it recommends to ACTS an Occupational Exposure Standard (OES)). Alternatively (e.g. with genotoxic carcinogens) WATCH may decide that this is not possible and that ACTS should set a Maximum Exposure Limit (MEL), which will take into account the practicability of compliance. Indicative Criteria for the establishment of both types of limit are published. Both OESs and MELs have legal status, although the compliance requirements differ. Documentation is published in the form of Criteria Documents and Criteria Document Summaries and there is opportunity for public comment.

In the EU, the development of occupational exposure limits was given a boost in 1988 by the adoption of the Council Directive 88/642/EEC (OJ L 356, 24.12.88) amending the Council Directive 80/1107/EEC (OJ L 327, 3.12.80) on the protection of workers from the risks related to exposure to chemical, physical and biological agents at work. An ad-hoc scientific expert group (SEG) has been set up to provide the Commission scientific advice on the latest scientific data.

All the above systems publish documentation which permits the identification, with varying degrees of precision, of the critical effect[1], the pivotal study[1] and the rationale for establishing an OEL at a particular level for a given substance. However, for none of them is there available a detailed generic methodology which enables an outsider to track the scientific processes involved in moving from a database review to a health based OEL. The systems are, however, understood to be similar in that they rely on the judgement of groups of scientific experts to review the available data and establish appropriate OELs for substances on an individual, case by case basis.

Although detailed practices and the degree of 'transparency' vary from one system to another, they are all thought to comprise the following steps:

1. preparation of a criteria document containing all available relevant data;

2. review of this document by an expert group to establish the critical effect (or effects) and to establish a NOAEL or a LOAEL for this effect. This may be on the basis of human or animal data or both;

3. in depth review of the key publications and reports relating to 2) above and establishment of an OEL at a level which takes into account all the many factors which may be relevant (including quality of key studies, human or animal database, severity of critical effect, local or

[1] These terms are generally used in this report as defined in Appendix A. Where other authors/organisations use differing definitions, this is indicated in the text.

systemic, well understood or rare, concordance in database, NOAEL or LOAEL, slope of dose response curve, species differences (kinetic or dynamic), role of metabolism, precedents from similar substances/effects, etc.).

As previously stated, documentation outlining the basis for each OEL decision is available for all these systems. Although there is considerable variation in the quality and degree of detail contained within this documentation, there is a steady trend towards more 'transparency', permitting easier identification of the logic path followed in each case.

The procedure followed for setting exposure limits in the occupational situation generally involves moving directly from the database (NOAEL or LOAEL) to an OEL without the intermediate definition of a specific 'assessment factor'. In this respect it differs from the procedures adopted for the establishment of ADIs. It is nevertheless possible, where the documentation is sufficiently 'transparent', to infer what 'assessment factors' have effectively been involved by comparison of the values of established OELs with the values of the relevant NOAEL/LOAELs. HSE have carried out such a retrospective analysis of OESs established for 24 substances in the UK since 1990 (Fairhurst, 1994).

This has indicated effective 'assessment factors' in the range of 1-10 for most substances where the database is from animal studies (higher factors applied in a few cases where the nature of the critical effect called for more caution). Factors of 1-2 were effectively applied where the database was derived from human evidence.

2.2 NON-OCCUPATIONAL APPROACHES

2.2.1 Introduction

In the case of non-occupational approaches to risk assessment a number of more structured schemes have been developed, most involving the application of uncertainty factors to the lowest (appropriate) animal NOAEL to derive a human TDI (Tolerable Daily Intake). Three of the varying approaches are described below.

2.2.2 Approach Described by the US EPA

The US EPA developed an approach for assessing risk for health effects (other than cancer and gene mutation) from chronic chemical exposure (EPA, 1987). Systemic effects have mostly been evaluated using the terms "acceptable daily intake" (ADI), "safety factor" (SF) and "margin of safety" (MOS). In

its approach, the EPA has established the terminology "reference dose" (RfD), "uncertainty factor" (UF), "margin of exposure" (MOE) and "regulatory dose" (RgD) to make a clear distinction between aspects of risk assessment and risk management.

Hazard Identification

The results from all available studies should be considered, although the critical effect which is defined by the EPA as "typically" exhibiting the lowest NOAEL (EPA, 1993) should receive primary attention. Studies that contribute most significantly to the qualitative assessment of whether or not a particular chemical is potentially a systemic toxicant are called "principal studies". Human studies are given the first priority, with animal toxicity studies serving to complement them. The principal studies however are normally experiments carried out with non-human mammals. Toxicokinetic studies, in vitro studies and SAR considerations can give additional information and are called "supporting studies". Because in most cases, the available data for a chemical substance does not include studies for all possible exposure routes, the US EPA assumes that the toxic effects which may appear during testing via one route are relevant for any other exposure route, unless convincing data exist to the contrary. Results from all animal studies performed with the chemical should be used including those using different dosing frequencies and different exposure durations.

Selection of Most Appropriate Study

Since there are usually insufficient human data for quantitative risk assessment, animal studies are often selected to provide the information most relevant to man. This selection (of critical data) might be based for instance on similarities in toxicokinetics. If it is not possible to define the most relevant species, the risk assessor uses the most sensitive species, since humans may be as sensitive as the most sensitive animal species tested. Next, the "critical study" is then chosen from all the studies conducted on the most relevant species. If a chemical leads to more than one toxic effect, the effect exhibiting the lowest NOAEL should be used as the critical endpoint in the dose-response assessment. The NOAEL derived from the critical study is the primary basis for the evaluation of human risk.

Reference Dose (RfD)

In order to develop a Reference Dose (RfD), all available data on the chemical of interest should be used. The RfD is a dose derived from the NOAEL by application of uncertainty factors (UF) that reflect the overall confidence in the various types of data sets. Modifying factors (MF), based on scientific judgement are sometimes additionally used. These factors are presented in Text Box 1. Default values

are 10 for intraspecies extrapolation and 10 for interspecies extrapolation. Additional 10-fold factors are used when extrapolating from less than chronic NOAELs to chronic NOAELs and also when deriving a RfD from a LOAEL instead of a NOAEL. No scientific reasons are given for the magnitude of these factors.

According to the EPA, "..the RfD, which is indicated in mg/kg bw/day, is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure of a human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime". In spite of this, the EPA states that not all doses below the RfD are "acceptable" or will be risk-free but, that all doses in excess of the RfD are "unacceptable" or will result in adverse effects.

Importantly, the evaluators provide a statement of the confidence (high, medium or low) which they have in the stability of the RfD. High confidence indicates that the RfD is unlikely to change in the future because there is consistency among the toxic responses observed in different species or study designs. A statement of high confidence is often given to RfD's that are based on human data. Low confidence indicates that the database is of limited quality and/or quantity.

Risk Characterisation

In this process, the RfD is compared with the "estimated exposure dose" (EED). If the EED is less than the RfD, then there is usually little need for regulatory concern. Another measure used by the EPA is the "margin of exposure" (MOE) which is "the magnitude by which the NOAEL of the critical toxic effect exceeds the estimated exposure dose".

Application in Risk Management

If the hazard identification and the risk characterisation step including exposure assessment is complete, then the next step is risk management. Risk management decisions are made on a case-by-case basis. The different risk and non-risk factors, regulatory options and statutory mandates in a given case must be evaluated with care. The risk manager has to choose the appropriate statutory alternative for calculating an "adequate" margin of exposure. This procedure establishes the regulatory dose (RgD).

2.2.3 Approach Described by Renwick

The approach proposed by Renwick (1991, 1993), attempts to give a scientific basis to the default values of 10 which have been traditionally used to account for the interspecies and interindividual differences. A major advantage of this approach is that scientific data relevant to the safety evaluation of a chemical substance can contribute quantitatively to the Tolerable Intake (TI) calculation. According to Renwick, each of the two elements in the extrapolation of animal data to man (species differences and human heterogeneity) can be subdivided into:

1. delivery of the substance to the site of toxicity (toxicokinetics);

2. activity or potency of the substance at the site of toxicity (toxicodynamics).

Although this approach retains the two 10-fold factors for interspecies and interindividual variation as the cornerstone for extrapolating from animals to man, it allows the modification of these default values to incorporate appropriate data on toxicokinetics and toxicodynamics where these exist. Thus, where appropriate data are available, the method replaces the 10-fold factor with a "Correction Factor" which, based on the quality of the data, can be considerably lower (or in some cases, higher) than the initial default values. Examples of potentially useful data for the toxicokinetic component are information on substance bioavailability, total clearance from the body, bio-accumulation within an organism etc. Data which are useful for the toxicodynamic component include *in vitro* sensitivity information, concentration-effect data etc. Clearly, the same chemical entity should be considered in each case i.e. the parent compound should not be confused with a metabolite or intermediate when evaluating toxicokinetic and toxicodynamic data. Thus, different correction factors would need to be applied when considering the various chemical forms.

Text Box 1: EPA (USA)-Guidelines for the Use of Uncertainty Factors in Deriving Reference Doses and Modifying Factors*

Standard Uncertainty Factors (UFs):

Use a ten-fold factor when extrapolating from valid results in studies of average healthy humans exposed over prolonged periods. This factor is intended to account for the variation in sensitivity among the members of the human population and is referenced as "10H".

Use an additional ten-fold factor when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty involved in extrapolating from animal data to humans and is referenced as "10A".

Use an additional ten-fold factor when extrapolating from less than chronic results on experimental animals when there are no useful long-term human data. This factor is intended to account for the uncertainty involved in extrapolating from less than chronic NOAELs to chronic NOAELs and is referenced as "10S".

Use an additional ten-fold factor when deriving an RfD from a LOAEL, instead of an NOAEL. This factor is intended to account for the uncertainty involved in extrapolating from LOAELs to NOAELs and is referenced as "10L".

Modifying Factor (MF):

Use professional judgement to determine the MF, which is an additional uncertainty factor that is greater than zero and less than or equal to ten. The magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study and database not explicitly treated above; e.g. the completeness of the overall database and the number of species tested. The default value for the MF is one.

* Source: adapted from Dourson and Stara, 1983

A decision critical to the successful use of the approach is the importance or weighting each component value of the Correction Factor should receive. Since research indicated that there was a greater potential for differences between common laboratory animals and man in kinetics than in dynamics, an equal split of the 10-fold factor was not appropriate. Instead, a default value of 4 was suggested for differences in kinetics and a default of 2.5 was assigned for differences in dynamics. While this subdivision is a value judgement, it is based on currently available data on several compounds from the literature and is less arbitrary than the original choice of a 10-fold factor.

In the case of interindividual variation, the differences in kinetics may vary widely and those individuals

with values for a kinetic parameter higher than the mean must be taken into account. Although the dataset is not as comprehensive as that for the interspecies variation, comparison of the variability in kinetics and dynamics within healthy populations suggests that there may again be slightly greater variability. In consequence, Renwick proposed that the human interindividual factor of 10 should be divided into 4 for kinetic differences and 2.5 for differences in dynamics.

A review of the Renwick approach has been undertaken by IPCS (1994) and a recommendation was made that the interindividual toxicokinetic and toxicodynamic default values should be 3.2 and 3.2, reflecting the inability to distinguish the relative importance of the two components.

Further, both Renwick and IPCS propose the inclusion of additional factors to account for the "nature of the toxicity" and the "adequacy of the database". These values may be selected from a continuous scale (1 ⇒ 100) and even factors less than 1 are possible if, for example, the specific toxicity is not relevant for humans.

2.2.4 Approach Described by Lewis/Lynch/Nikiforov

Lewis and his colleagues undertook revision of the long-established practices, with the goal of introducing flexibility such that both new information and expert judgment could be readily incorporated. The approach has been developed in the USA in 1990 (Lewis *et al*, 1990) and subsequently been modified by the Houston Regional Monitoring Corporation (HRMC, 1992).

Two additional features distinguished the Lewis/Lynch/Nikiforov (LLN) method from the previous status quo. First, LLN had been specifically designed to separate scientific conclusions or inferences from non-scientific judgments (i.e., those based on social, cultural, or political values). Second, the approach asked the data evaluator to estimate most-likely values for each adjustment, and to estimate separately the degree of uncertainty in each factor.

The original LLN method, and its refinements, are extensions of established principles and procedures. LLN guides the data evaluator to adjust experimentally determined "no-effect" (or "minimum effect") levels from laboratory animal studies, while taking account of:

- differences between laboratory animals and humans;
- differences between experimental conditions and actual or anticipated human exposures;

- the sensitivity of the exposed human populations;
- weight of evidence indicating an actual human health hazard;
- quality of the experimental information base;
- uncertainties in extrapolating from animals to humans;
- potency of the toxic agent.

The No-Adverse-Effect-Level (for humans) is estimated from laboratory research results, using the following algorithm:

$$NAEL_{human} = \frac{NOAEL_{animal} \cdot S}{R \cdot H \cdot Q1 \cdot Q2 \cdot U \cdot (C)} \quad (1)$$

with

S = Scaling Factor
R = Interspecies Adjustment Factor
H = Heterogeneity Factor
Q1 = Critical Human Health Factor
Q2 = Study Duration Factor
Q3 = LOAEL-to-NOAEL Factor
U = Uncertainty Factor
(C) = Severity Factor

The definitions/descriptions of the terms, their default values and their ranges, are documented in the report "A Consensus Method for Setting Community Exposure Guidelines" from the Houston Regional Monitoring Corporation Toxicology Panel. A summary is given in Appendix B. The computational algorithm above differs in only one detail from the Consensus Method in that report. The final denominator term (i.e., adjustment factor for "severity of effect") has been removed from this algorithm as a result of the authors' recommendation that this factor should be treated as non-scientific.

The authors state that the LLN approach is applicable to deriving either ambient or occupational exposure guidelines. Workplace exposure guidelines usually allow smaller adjustment factors, reflecting the "healthy worker phenomenon", intermittent exposures, and a greater range of risk management options (i.e., workers are under direct supervisory control, whereas members of the public are not).

The approach takes the above factors into account on a case-by-case basis and recommends ranges and default values on the basis of best available scientific evidence. The approach suggests that adjustment factors of 10 are often unjustified.

For example, Weil and McCollister (1963) found that nearly all LOAEL-to-NOAEL ratios from well-conducted studies were 5 or less. The average ratio for chronic studies was about 3.5. McNamara (1976) found that the NOAEL subchronic to NOAEL chronic ratios of all 41 different chemical agents under investigation were less than or equal to 3. Thus, updating of all data of both investigations LLN revealed by either treatment that adjustment by a factor 3 or less is sufficient for subchronic to chronic extrapolation.

The LLN approach relies on expert consensus as the most trustworthy basis for safety assessment. Even failing to reach a single consensus, a narrow range of values can usually be agreed.

2.2.5 Comparison of the EPA, LLN and Renwick Approaches

Table 1 gives an overview on the elements of the three approaches.

Table 1: Comparison of various assessment methods

	LLN		RENWICK		EPA	
	Range	**Default**	**Range**	**Default**	**Range**	**Default**
Interspecies						
Kinetic	(S) >0	1	>0 - 4	4		10
Dynamic	(R) 0.3 - 3	1	>0 - 2.5	2.5		
Intraspecies						
Kinetic	(H) 1 - 5	3	>0 - 4	3.2		10
Dynamic			>0 - 2.5	3.2		
Human relevance	(Q1) 0.1 - 1	1				
Study duration	(Q2) 1 - 5	3				10
LOAEL-NOAEL	(Q3) 1 - 5	3				10
Adequacy database			1 - 10	-	>1 - 10	10
Uncertainty	(U) 1 - 10	1				1 - 10
Secerity	(C) (1 - 10)		1 - 10	-	1 - 10	-

The EPA approach uses the traditional factors of 10 x 10 x 10 to derive the Reference Dose. The main difference between this and the two more recent approaches is the latters' flexibility. At first glance the Renwick and the LLN approach appear to differ in their innovation strategy.

The Renwick method starts from the traditional factors of ten by ten and then modifies them by introducing subdivisions of the 10-fold factors and additional safety factors. The LLN method completely abandons these commonly applied factors and develops a new approach from first principles.

A closer comparison of both approaches reveals that, although in principle the procedures and basic elements of analysis for both methods are quite similar, there are major differences particularly in the definition and the range and default values to be assigned to the individual parameters. Basically, both methods consist first in a review of the database to identify the critical toxicological effect and the pivotal study which yields the lowest NOAEL. If there are other significant toxicological endpoints, the evaluations should be repeated considering all relevant NOAELs. The most conservative result should then be adopted.

Once the relevant effect and the related study have been identified, adjustment or uncertainty factors (which consider several parameters such as adequacy of database, toxicokinetics, etc.) have to be determined to extrapolate the NOAEL to be used for human exposures (see below).

The next step in both procedures is the review of all available data to determine whether the selected critical effect, its NOAEL and the uncertainty factors are appropriate. However, the Renwick and LLN approaches differ in this step by the extent of the review. While the LLN approach strongly recommends a "consensus review" which involves a group of scientists, Renwick does not state this as a requirement.

The adjustment of the critical NOAEL by uncertainty factors and particularly the magnitude of these factors are the main source of discrepancies between the methods. The Renwick approach considers the nature of toxicity, and for this a range from 1 to 10 is suggested.

The LLN approach is equivocal with respect to how this parameter should be treated. The adequacy of the database is reflected using a range from 1 to 10 by Renwick while it is analysed in more details in the LLN approach (Q2, Q3). The study duration and the absence of a NOAEL are considered separately by both approaches in a range from 1 to 5, with default values of 3. Thus, a maximum value of 25 is possible with the LLN method, but since the default values will probably be employed in most

of the cases, i.e. 3 x 3, there is no significant difference in comparison with the maximum value of 10 derived from the Renwick method. There are significant differences in the treatment of the inter- and intraspecies toxicokinetic and toxicodynamic parameters, where the default values in the LLN approach (S, R and H) lead to a maximum value of 3, whereas the default values in the Renwick approach lead to a value of 100. Finally, in the LLN approach there are two further parameters which are considered separately, i.e. the relevance of the toxicological effect to humans (Q1) with a default value of 1, which in the Renwick method is included in the analysis of the toxicokinetic and toxicodynamic parameters and the overall uncertainty factor (U) with a default value of 1, which in the Renwick method will also be generally included in the evaluation of all other parameters.

In conclusion, there are two important differences between the LLN and Renwick approaches. The first one is that the LLN approach is equivocal in its treatment of the nature/severity of toxicity (C), while a factor of 1-10 is suggested by Renwick. The second main difference is represented by the evaluation of the kinetic and dynamic properties of a compound.

2.3 REVIEW OF THE APPLICABILITY OF THE APPROACHES

The LLN, Renwick, EPA (Section 2.2) and "occupational" (Section 2.1) approaches may be compared against the criteria for an acceptable approach defined in Chapter 1.3. The position is summarised in Table 2.

Table 2: Purpose and Scope of Various Approaches

	EPA	Renwick	LLN	"Occupational"
Covers occupational exposure ?	-	-	+ ?	+
Covers non-occupational exposure ?	+	+	+	-
Science/safety distinction ?	-	-	+	-
Flexibility ?	-	+	+	+
Ease of use ? *	+	+	-	+
Universally accepted ?	- (+: USA)	- (+: IPCS)	-	+
Transparency ?	?	+	+	-

* All these approaches are likely to require varying degrees of consensus agreement.

It is evident from Table 2 that the approach satisfying most of the criteria is the LLN method. In particular, this approach goes furthest to addressing the two principal concepts defined in Chapter 1.3,

namely distinction between scientific and non-scientific factors and applicability to both occupational and non-occupational situations (although there are some reservations about the latter). However, this approach is not particularly easy to use (requiring a consensus of experts), and is thus unlikely to gain wide acceptance. The Task Force thus came to the decision to take the best from the available methods and develop this into a suitable approach.

3. RECOMMENDED APPROACH - REVIEW OF RELEVANT ELEMENTS

3.1 REVIEW OF DATA

3.1.1 Introduction

Most current approaches to the problem of risk assessment for humans involve comparing an experimentally derived or observed NOAEL or LOAEL (in animals or humans) with a measured or estimated exposure level. The extent to which the former exceeds the latter (the 'margin of safety') is then used to judge whether the situation is satisfactory or whether risk management measures are justified. In consumer situations it is common practice to apply a safety factor of 100 or 1000 (modified in some instances) to the NOAEL/LOAEL as an aid to this judgment. This method does not distinguish between scientific extrapolation, allowance for scientific uncertainty and the application of additional 'safety' factors which have no scientific foundation.

The scheme recommended by the Task Force and described in the following pages comprises three stages:

1. derivation from the available data of a human Predicted No Adverse Effect Level (PNAEL). This is the scientifically most likely estimate of the dose or exposure which will have no adverse effect in humans. This exercise is conducted by the Risk Assessor and involves the application of a scientifically derived 'adjustment factor' to the NOAEL/LOAEL of the critical effect;

2. by the Risk Assessor and the Risk Manager together of an 'uncertainty factor' to the PNAEL to take into account the degree of scientific uncertainly involved in derivation of the PNAEL;

3. further if considered necessary by the Risk Manager) of a 'safety factor' to the resulting figure to take into account political, socio-economic or risk perception factors. The product of these three factors ('adjustment', 'uncertainty', and 'safety') is described in this report as the 'assessment factor'.

The final figure obtained by applying the 'assessment factor' derived by this scheme to the NOAEL/LOAEL may then be directly compared with the exposure to determine whether risk management measures are necessary. The scheme is outlined in Figure 1, where its relationship to

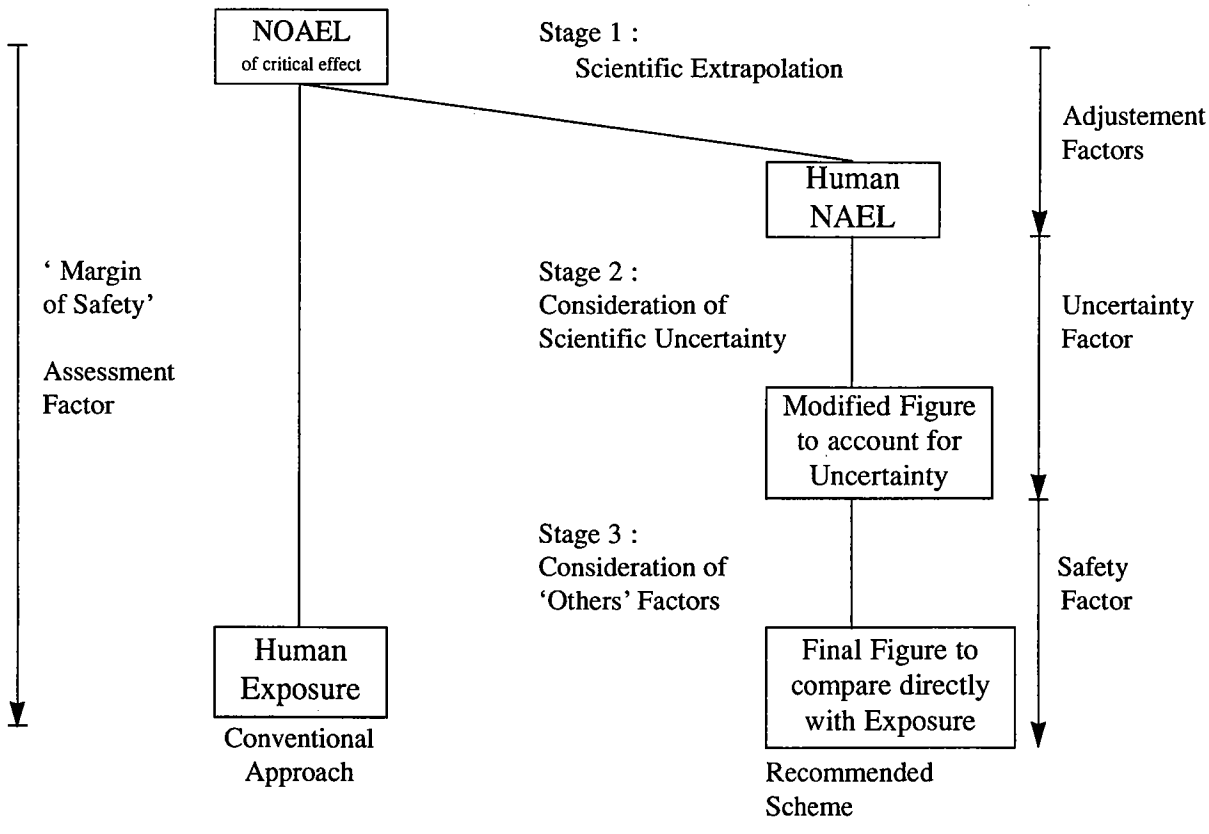
the conventional approach may be seen.

This Chapter describes the process recommended for the derivation of human PNAELs. The first stage in this is to review the adequate of the database containing information on human exposure and toxic hazards to health. If the database is inadequate then human PNAELs can not be derived scientifically and the recommended scheme can not be developed further.

In this situation it is the responsibility of the Risk Manager to take such measures as are appropriate within the relevant regulatory framework.

Where the database is adequate, the recommended scheme comprises a number of stages, in each of which an estimate is made of the most likely value of the factor described by that stage. At the end of the process these factors are multiplied together and the resultant number used to derive the human PNAEL.

FIGURE 1: Comparison of Recommended Scheme with Conventional Approach



3.1.2 Review of Exposure for Identification of Required Human PNAELs

A review of the data base should start with the information available on uses of, and human exposure to, the chemical of interest so that it can be decided which human PNAELs are required. The extent of data available under this heading will vary considerably. A well established high tonnage existing chemical, for example, could have extensive data on human exposure in the various applications in which it is used. Alternatively, a new chemical being notified for the first time will by definition have no actual exposure data, and the likely pattern of human exposure will have to be inferred.

The purpose of the review of exposure data is to establish the principal human exposure situations. This will involve identifying the following:

- exposed populations (occupational, consumer, general public);
- route of exposure (oral, inhalation, dermal);
- pattern of exposure;
- single or occasional (acute) exposures;
- long-term repeated exposure;
- long-term continuous exposure.

Information on tonnage, physical properties (particle size, volatility, solubility) and type of use will be relevant to the above analysis.

In the consumer situation, some knowledge of any likely or actual consumer uses of the substance is essential in order to assess whether there will be significant consumer exposure.
It is the responsibility of suppliers of products for consumer use to have or to obtain such information in order to establish that they will be without undue risk to consumers if used as recommended. On the basis of such information it should be possible to determine whether consumer exposure is likely to be occasional or continuous. The information should also be adequate to indicate the likely pattern and route of exposure.

A knowledge of the pattern of uses, together with the physical properties (and in some instances

specific measurements) will enable a judgement to be made about the extent of any exposure of the general public via environmental air, food, soil or water. If there is such exposure, it must be considered to be long-term and the route of exposure will be self evident.

Having conducted the exposure review described above, it should now be possible to define which human PNAELs are required (ie for single, long-term repeated or continuous exposure and by what route). It is anticipated that in practice the number required for each substance will be no more than two or three.

3.1.3 Review of Hazard Database

The next stage in the process is to assess the extent and quality of health hazard data available, in order to decide whether an adequate starting point exists for the derivation of the required human PNAEL(s).

In practice, a common starting position will be the database obtained in the case of notified New Substances (the 'Base Set'- 6th Amendment of Directive 67/548/EEC), where the health hazard data available will be no less than the following minimum data set:

- acute data (oral plus one other route);
- skin and eye irritation data;
- skin sensitisation data;
- repeated dose toxicity data (28 days);
- mutagenicity data;
- (reproductive toxicity screen data)[2].

The above data set also represents the minimum requirement for an existing 'High Production Volume' substance appearing on a 'Priority List' under the Existing Substances Regulation.

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[2] The Minimum Data Set contains a requirement for a Reproductive Toxicity Screen 'for the record'. This means that although such a screening test does not exist at present, if and when it does it will become part of the required minimum data.

Each case will be different and must be judged on its own merits. However, it is considered that, in general, a hazard database comprising the minimum data set outlined above should provide an adequate starting point for the generation of any of the human PNAELs. This depends, of course, on the database being acceptable not only in terms of quality of studies, but also on the relevance of the chosen routes of administration.

3.2 IDENTIFICATION OF CRITICAL EFFECT AND PIVOTAL STUDY

The first step in identifying the critical effect is to consider the type of human PNAEL required. This is necessary as the toxicity and hence critical effect may vary depending on the extent, duration and route of exposure. The primary concern may be for acute toxicity of a chemical if sporadic exposures to a high dose are likely, whereas if the concern derives from daily extended exposures to a lower dose, the information required may be from repeated dose toxicity. The same chemical may be present in the environment (food, water, air, soil) at very low levels and the concern may be from chronic low level exposure to the general population, in which case it may be more appropriate to use the critical effect seen in studies of longer duration.

A substance may induce several different adverse effects. It is desirable to distinguish between less severe (e.g. inflammation) and very severe effects (e.g. frank necrosis) and reversible (e.g. adaptive response like organ hypertrophy) and non-reversible effects (e.g. teratogenic effect). Furthermore, in deciding which is the appropriate critical effect, information from substances of the same chemical class should be taken into consideration, if available. Knowledge of SAR may provide alerts of a potential hazard that is, as yet, not identified.

Having decided which is the critical effect for the human PNAEL required, data from more than one animal study or other supporting information could be available. In view of the recognition that different exposure scenarios are possible, it is possible that more than one critical effect (and therefore more than one NOAEL) should be considered in the risk assessment. For example, local effects may be critical in certain exposure scenarios whereas in others systemic effects may dominate. In practice, test data with information on effects with a dose response relationship would normally be considered more appropriate than data with effects only at the highest dose level or where the dose response curve was flat. Hence, the risk assessor needs to decide, on the basis of scientific judgement, which studies provide the most relevant information with respect to human exposure.

For this reason the NOAEL chosen from the pivotal study may not necessarily be the lowest value, but

it should be the most pertinent and relevant.

3.3 SHORT-TERM REPEATED/SUBCHRONIC/CHRONIC EXTRAPOLATION

One important aspect of the data required to set the human PNAEL is the duration of exposure. If the only animal studies available are of a shorter duration than that required by the PNAEL, extrapolation may need to be considered.

The data base available for review on this topic appears to be very limited. Kokoski (1976) proposed an arbitrary factor of 10 when extrapolating from subchronic to chronic. However, the overconservative nature of this suggestion can be appreciated by examining the reports of Weil and McCollister (1963) and McNamara (1976).

Weil and McCollister found that 97% of the ratios comparing NOAEL (short-term) with NOAEL (long-term) were less than 10. They used NOAEL data from rat and dog studies for 33 different substances (agricultural chemicals, stabilisers, additives, antimycotics, water treatment chemicals and food packaging materials). The duration of the short-term studies was between 29 and 210 days and the long-term studies were all of 2 years duration. The ratios were 2 or less for about 50% of all cases. They were larger than 3 in 21% (6/28) of the cases where the duration of the short-term test was 130 days or less. For the other five cases the duration of the 'short-term' test was between 130 and 210 days. Surprisingly, in four of these cases the ratio was greater than 3. It is suggested that this apparently anomalous finding may have resulted from differences in study design (i.e. dose ranges) between tests of shorter and those of longer duration.

McNamara (1976) examined the ratio NOAEL (short-term) to NOAEL (long-term) of 41 other chemicals (pesticides, food additives, pharmaceuticals etc.), which were reported in various literature sources. Data were mostly derived from rat and dog studies, but performed by numerous investigators using diverse study durations and techniques. It can be assumed that due to study design in a number of cases the no-effect doses were much lower than the LOAELs. The body weights of the animals were not known for all of the studies. Consequently, estimates of daily food and substance intakes are crude approximations.

Despite these differences the data agree well with those of Weil and McCollister. Ratios of less than 3 were reported for all cases.

The size of this factor (sub-chronic to chronic) depends on the particular substance involved and may be as low as 1 for chemicals that neither produce cumulative effects nor accumulate in the body. A higher "duration" factor, however, may be applied in cases of cumulating effects or accumulating compounds, but double correction of this fact (e.g. as an interspecies kinetic factor) should be avoided.

An additional extrapolation may be needed if the short-term tests have a duration of (typically) 14-28 days, because it is generally accepted that NOAELs of subacute studies cannot simply replace NOAELs of subchronic studies. Woutersen *et al* (1984) compared the NOAELs of 82 chemicals, which were tested in short-term repeated and subchronic studies under similar conditions. They found that the ratios were equal or less than 10 in almost all cases, but identical (factor 1) for 56% of the compounds. A factor of 4 covered 80% of all cases.

A further factor may be needed where the route of concern is inhalation, the human PNAEL required is for continuous (24h/day, 7 days/week) exposure and the animal studies involve 6 to 8 h/day, 5 days/week exposure. The simplest way of accommodating this situation is to use a further factor of 4 to allow arithmetically for the difference in total hours of exposure. This factor may be justifiable for substances for which toxicokinetic data are available. Those with a short (e.g. <1 h) half-life will reach equilibrium in the body well within 6/8 h and the total body burden will not be increased by extending exposure over the full 24 h. Those with long (e.g. > 1 week) half-lives will accumulate in the body over a long period and it will be the total, integrated exposure which will determine the equilibrium level in the body. Where half-lives are between these two extremes (and substances are substantially cleared from the body between successive 6/8 h exposures), a further factor in addition to the above factor of 4 may be required. In the absence of such information on half-lives it is recommended that a factor of 4 be used and the increased uncertainty involved in the extrapolation allowed for by the risk assessor in his overall review.

It must be recognised that the scientific basis for establishing meaningful extrapolation factors in this area is still very weak. Nevertheless, a provisional default value of 2 - 3 when extrapolating from subchronic to chronic appears consistent with the available scientific data.

For extrapolating from short-term repeated to subchronic, a factor of 3 is recommended by the Commission of the European Communities (EEC, 1993b, Annex VI p.55). This appears consistent with the limited scientific data available and is therefore recommended as a provisional default value. The uncertainties inherent in these extrapolations must be taken into account by the risk assessor.

The data base for such extrapolations may be extended and improved by examination of the relevant HEDSET and SIDS data via the Existing Chemicals programmes operated by the EU and the OECD (1993), respectively.

3.4 LOAEL/NOAEL EXTRAPOLATION

A preferred starting point for the derivation of an exposure limit is the NOAEL. However, there may be cases where the NOAEL for the critical effect has not been determined and also cases where it may be wiser to use an "effect" level instead of a NOAEL. For these cases (where a LOAEL has to be used instead of a NOAEL) additional assessment factors have been proposed. A survey of the literature shows that the magnitude of these factors can vary between 1 and 10. Most of the experimentally derived arguments for the size of this factor rely on data adapted from results published by Weil and McCollister (1963). These data allow the extrapolation of ratios of LOAEL to NOAEL from either subchronic (27 examples) or chronic (25 examples) studies (Dourson and Stara, 1983). Comparison of the data for subchronic exposure reveals that the NOAEL values are maximally 5-fold (one case) less than the corresponding LOAEL value, the majority of the values ranging from 2 to 3. The mean value is 3.02. For chronic exposures a maximum value of 10 is calculated in two of the 25 examples.

The other values are also maximally 5-fold less than the corresponding LOAEL value, the majority varying from 2 to 4. The mean value is 3.8.

A more recent source of data for LOAEL to NOAEL comparison can be extrapolated from the examples contained in Fairhurst (1994), where the judgments of an expert committee for setting-up occupational exposure levels (WATCH) were studied retrospectively. For a very limited number of compounds it is possible to relate the recommended occupational exposure levels both to NOAELs and to LOAELs. This enables LOAEL/NOAEL ratios to be derived, and these range from 2 to 5.

Other approaches have proposed lower factors, e.g. for the evaluation of developmental toxicity data a doubling of the safety factor is suggested with the explanation that the lowest LOAEL in animal studies is often within a factor of 2 of the NOAEL, but this only applies in cases where the effects observed are minimal and indicate that the NOAEL is being approached (Hart *et al*, 1988).

The magnitude of the NOAEL/LOAEL ratio in any individual case will depend on the slope of the dose-response curve, the group size and the interval between doses. Thus the design of the study may

affect not only this ration but may, where large dose intervals have been used, result in an observed NOAEL being considerably lower that the 'real' NOAEL. It is possible to calculate NOAELs by extrapolation from appropriate dose-response data.

If the interval between doses is large (e.g. 10) and if the effects seen at the LOAEL are minimal (indicating that the NOAEL is close to the LOAEL), it may be more appropriate to base extrapolation on the LOAEL (with a default factor of 3) rather than on the observed NOAEL.

In spite of the limited data base, a provisional factor of 2-3 appears consistent with the available evidence. A value of 2 could be used in those cases where the extent of the relevant effect is of minor importance, e.g. a minor fatty infiltration of the liver, and the slope of the dose-response curve reasonably justifies the assumption that a halving of the LOAEL would be likely to arrive at the No Effect Dose. A factor of 3 is recommended as a default value, which would be used in the majority of cases. Extent and severity of the effect at the LOAEL, e.g. a pronounced liver cell necrosis, and/or a very flat dose-response relationship, may justify the use of a higher factor.

3.5 ROUTE-TO-ROUTE EXTRAPOLATION

It is often the case that toxicology data are not available for the most appropriate route of administration with respect to human exposure. Under such circumstances extrapolation from one route to another may have to be considered. It is important, however, to take into account the physical and chemical properties of the compound and to consider the relevance of SAR. In addition, it is clear that the absorption of a compound depends not only on the route of exposure but also on its physical state, e.g. liquid, solid or gaseous form.

Furthermore, the particle size and/or hydrophilic or lipophilic properties can influence rat of absorption by inhalation, dermal and oral dose routes.

3.5.1 Route to Route Extrapolation using Acute Study Data

In a study of 49 substances in which the LD_{50} was compared with the LC_{50} (after converting the inhalation concentration to a dose per unit body weight), the ratio oral dose/inhalation dose varied from 0.1-55 (Pepelko and Withey, 1985). In a comparison of LD_{50} versus LC_{50} for 265 substances, the observed variation was related to the magnitude of the LD_{50} (Klimisch *et al*, 1987). When the LD_{50} was approximately 100 mg/kg the LC_{50} varied 57 fold (0.07 - 4 mg/l) and when the LD_{50} was around

1000 mg/kg the LC_{50} varied 133 fold (0.3-40 mg/l).

This wide variation suggests that extrapolation from the oral route to the inhalation route using acute study data is extremely difficult and should not be undertaken.

In most cases it can be assumed that the dermal route leads to less absorption of a compound than the oral route, because of the skin barrier. This should be assessed on a case-by-case basis and in most situations an assumption of dermal absorption between 10 and 50% might be reasonable.

3.5.2 Route to Route Extrapolation using Chronic Study Data

Literature references to validated examples of route to route extrapolation are rare. A particularly important factor for long-term studies is the rate and extent of absorption of the test substance. Cells lining the intestinal tract may show differing permeability than those in the lung. For sparingly soluble particles, long residence time in the lung may allow considerable absorption to occur, whereas relatively little uptake across the GI tract may occur due to rapid passage across this membrane.

An approach to this problem was first proposed in 1959 by Stockinger and Woodward (cited in Pepelko and Withey, 1985), who described a method to establish drinking water standards in the absence of oral data by using TLVs intended to provide protection of humans in the workplace. In the absence of absorption data by inhalation 50% absorption by that route was assumed, whereas total absorption (100%) was assumed for oral intake. This approach has limitations particularly as absorption for inhalation and oral uptake were reported by Stockinger and Woodward to vary 33-fold.

When comparing cancer potency following different routes of administration the Risk Reference Dose (RRD_{25}, i.e. the calculated dose which increases the risk of cancer by 25% over background values) was estimated for inhalation and oral routes and compared for 14 substances tested on rats and 9 substances tested on mice (Pepelko, 1991). In rats, 8/14 (57%) substances and in mice 7/9 (78%) substances were more potent by the oral route, although the differences were occasionally very slight. Overall the variation between the two exposure routes was <10 fold.

Whilst it may be possible to undertake route to route extrapolation when making a risk assessment, caution is advised when so doing. Default values are therefore not recommended and conversion factors must be calculated for each individual situation, making appropriate assumptions about body weight, minute volume and percentage absorption.

3.6 INTER AND INTRASPECIES EXTRAPOLATION

Extrapolation from one species to another is a complex process and simple and accurate methods for predicting responses across species are not yet generally accepted. The extrapolation involves a consideration of the "interspecies variability" which refers to the differences between man and the experimental animal and the "intraspecies variability" which describes the heterogeneity within a given human population. Both of these elements are considered to reflect differences in toxicokinetics (substance disposition over time) and toxicodynamics (organ responsiveness) between and within species. While it is generally accepted that variability in toxicokinetics may be described both qualitatively and quantitatively, a meaningful analysis of toxicodynamic variability is more difficult to describe quantitatively. However, as the science of molecular toxicology develops, this quantification of the sensitivity of response to toxic insult may be possible and the term "toxicodynamics" may need to be redefined to describe the kinetics of the interaction between the toxin and the target tissue at a molecular level.

The scientific basis for the traditional 100-fold extrapolation factor (10-fold for interspecies and 10-fold for intraspecies differences), used today by some regulatory authorities and originally proposed by Lehman and Fitzhugh (1954), is unclear. It is uncertain whether the proposal was based on an analysis of data at all, or if so, just what fraction of the population was expected to be protected.

3.6.1 Interspecies Variability

Toxicokinetics

Toxicokinetics describes the uptake, biotransformation and delivery of a toxin to a site of action (see Appendix A) and wide variability in the relevant physiological processes (absorption, distribution, metabolism, excretion and retention) between animals and man can be expected. This variability depends on factors such as the laboratory species concerned, the biotransformation processes involved, the applied dose and the chemical substance of interest. There are rarely sufficient data on the metabolism of a substance to allow the use of complex models to extrapolate results accurately between species using physiologically-based pharmacokinetic models (PB-PK modelling). However, such data are becoming more plentiful and their usefulness in the risk assessment process is acknowledged (Frantz *et al*, 1994).

Considerations of interspecies variability will differ depending on the route of exposure involved.

Oral route

When considering exposure by the oral route, extrapolation of animal data to man based on adjustments for body size (termed scaling or allometry) is justified on the basis of similarities in anatomical characteristics, physiological function and biochemical reactions across species (Boxenbaum, 1982; Davidson *et al*, 1986). The bodyweight (bw) of the organism is the most easily and accurately obtainable measure of body size to provide a quantitative base for interspecies comparisons. Several investigators have described a simple mathematical relationship between bodyweight and a number of biological parameters including liver weight, creatinine clearance and haemoglobin synthesis which were fairly consistent over a wide range of species (see, for example, Voisin *et al*, 1990). This relationship may be written as follows:

$$\text{physiological parameter} = f(bw^n),$$

where bw is the organism bodyweight and n is a species-independent constant for the parameter of interest. However, body surface area (BSA) and the metabolic rate i.e. caloric requirement of the organism (CR) have also been used as the basis for such comparisons and a proportional relationship exists between these and bodyweight (Freirich *et al*, 1966; Davidson *et al*, 1986; Vocci and Farber, 1988; Feron *et al*, 1990).

Body weight can be raised to the power of 1, 0.75 and 0.67 for extrapolations based on the parameters bw, CR and BSA, respectively. It follows that extrapolation from animal toxicity data based simply on body weight (mg/kg) would result in a predicted NOAEL higher than if body surface area or caloric requirement were used.

The traditional approach has been to base extrapolations on body weight (i.e. same NOAEL for animal and human), but then to divide this figure by an arbitrary factor of 10 to take account of the widespread view that humans are more sensitive than animals. This approach, while it has been favoured for it simplicity, often exaggerates the differences between animals and results in overly conservative estimates of risk.

A more appropriate approach to extrapolations for the oral route is provided by metabolic rate (or caloric requirement), particularly where the substance is metabolised, and $bw^{0.75}$ thus provides a more meaningful basis (Feron *et al*, 1990). Recently, the US EPA has also supported the use of allometric relationships as a tool for interspecies extrapolation and has shown that equivalence based on an

exponent of 0.75 is appropriate in many cases. This allometric relationship takes account of known caloric requirements of the test species compared to man. Using this relationship, extrapolation to man of oral toxicity data obtained in an animal study (assuming an average body weight for man of 65 kg) requires division of the animal NOAEL by a factor of approximately 4 for the rat or 6-7 for the mouse (both factors will depend on the test animal body weight) (Feron *et al*, 1990; see Table 3). This method of extrapolation thus takes into account the known differences in metabolic rate between the test species and man and allows reduction of the arbitrary factor of 10 in a scientifically justifiable way. The following example illustrates the calculation. An absolute "No-effect dose" (NED) of, say, 1 mg in a 250 g rat (i.e 4 mg/kg bw) would be extrapoled to a 65 kg human being on the basis of the following equation:

$$\frac{NED_{human}}{NED_{rat}} = \frac{65^n}{0.25^n} \qquad (2)$$

This gives values of the NED_{human} as follows:

for n=1 the NED_{human} becomes 260 mg absolute or 260/65 = 4 mg/kg bw;

for n=0.75 the NED_{human} becomes 64.7 mg absolute or 64.7/65 ≈ 1mg/kg bw.

Thus, the extrapolation on the basis of CR (n=0.75) requires the division of a 250g rat NOEL by a factor of 4 in order to obtain a human NOEL. If the test animal used has a different bodyweight, other factors should be used as presented in Table 3.

In summary, the interspecies variability can be described by use of the 0.75 exponent of bodyweight for dose levels in mg/kg bw. In the case of the rat (the most commonly-used test species), the adjustment factor is approximately 4 and those for other species are shown in Table

Table 3: Factors for Interspecies Extrapolation (Oral Route) Based on Caloric Requirement as a Measure of Body Size (after Feron *et al*, 1990)

Animal Species	Bodyweight (kg)	"Scaling" Factor for Interspecies Adjustment
Mouse	0.025	7.1
Mouse	0.050	6.0
Rat	0.200	4.3
Rat	0.250	4.0
Rat	0.300	3.8
Guinea-pig	0.500	3.4
Dog	10	1.6
Dog	15	1.4

(The test species NOAEL (expressed as mg/kg/day) is divided by the corresponding factor above derived on the basis of $bw^{0.75)}$.

Inhalation route

It is generally agreed that for inhalation toxicity studies of systemically acting substances, no adjustment factor for body size is required in interspecies extrapolation (see for example, Van Genderen, 1988). Implicit in this is the assumption that laboratory animals and humans breathe at a rate related to their need for oxygen, thus automatically at a rate depending on their metabolic rate or caloric requirement, CR. Therefore, in practice, no adjustment factor for difference in body size relative to man is needed for an NOAEL obtained in an animal inhalation study. Failure to recognise this can result in an error of double adjustment in the extrapolation process resulting in an exaggerated assessment factor which is not toxicologically supportable.

For substances acting locally (e.g. irritants), the physiological and anatomical differences between test species and man (e.g. obligate nose breathers, minute volumes) should be considered on a case-by-case basis and may require the selection of an extrapolation factor greater or less than 1.

Thus where inhalation is the route of interest, extrapolations from animals to man may appropriately be based on a factor of 1 (i.e. no adjustment), provided the substance is acting systemically. For

substances with local effects on the respiratory tract, extrapolation needs to be considered on a case-by-case basis.

Toxicodynamics

Toxicodynamics is the activity or potency of a substance at the site of toxicity and reflects the sensitivity of the organism's response. An additional factor may be used to account for suspected differences in toxicodynamics. Where man is considered to be more sensitive than the most sensitive species tested (e.g. the case with methanol), then this factor should be > 1. When this is not the case, the use of additional factors can not be scientifically justified. However, for interspecies extrapolation in the area of toxicodynamics, it is essential to verify that the test species is a relevant model system for man particularly in terms of similar metabolic processing of the substance of interest.

3.6.2 Intraspecies Variability

Factors may be needed to account for greater variability in toxic response within the human population as compared with the exposed test animal population from which the critical effect NOAEL is derived. It is assumed that the variability in toxic response within the potentially exposed human population is greater than for the exposed animals. This is justified by a wider variation in such parameters as, for example, genetic disposition, age, health status etc. Consequently, the intraspecies factor must always be greater than 1.

In an attempt to provide a scientific rationale for the use of a 10-fold intraspecies factor in deriving ADIs, Dourson and Stara (1983) retrospectively analyzed the data of Weil (1972), which comprised determinations of acute lethality for 490 chemicals in rats administered single oral doses. For 92% of the studied chemicals, a reduction of the median-lethal dose (LD_{50}) by a factor of 10 was adequate to protect nearly all animals (approximately 99.9%); for 85% of the tested agents, a reduction by a factor of 6 was sufficient to provide the same level of protection, while a factor of 3 provided similar protection for 67% of the studied chemicals. This demonstrates that there is considerable variation between laboratory animals of the same strain.

With respect to the variability of responses in the human population evidence is derived from a limited database of studies on the pharmacokinetics of chemicals, mostly drugs. Hattis and coworkers (1987) retrospectively examined 49 chemicals for 3 parameters likely to be related to susceptibility to toxicity: elimination half-lives, Area Under Curve (AUC), and peak concentration in blood. They further

compared the human variability for the above pharmacokinetic parameters with the variability suggested in the Weil (1972) data set for acute oral lethality in rats. For the median chemical, a 10-fold difference in these pharmacokinetic parameters corresponded to 7-9 standard deviations in populations of normal healthy adults, implying significant conservatism if a 10-fold factor were applied.
Also the human variability in these pharmacokinetic parameters did not depart markedly from the Weil distribution of total variability to acute lethal effects in rats.

HRMC (1992) cite a review of the pharmaceutical literature on age-related kinetic differences and conclude that even the most extensive variations in treatment regimens require an adjustment of ad mi nistered dose by no more than 5-fold , although adequate documentation to support th is figure was not included. From a separate very limited database (8 chemicals), Renwick (1993) has considered interindividual differences in kinetics within the human population using a statistical approach. An adjustment factor of 3-4 appears sufficient from these limited data to account for differences between the 99th percentile and the mean for kinetic parameters (e.g. clearance) for most compounds.

In summary, there is no scientifically supportable evidence from the above to justify any numerical value for the increased interindividual variability in humans relative to that within the test species examined. However, due to variations in genetic disposition, age and health status within the human population the expectation is that the factor should be >1. The limited data related to human variability in pharmacokinetic parameters described above, together with observed but unquantifiable variability within animal test species, suggests that this number is likely to be <10. Where selection of a single default figure is necessary we recommend a default of 3 (approximately the geometric mean of 1 and 10).

The exposed population in the workforce typically is less heterogeneous than in the general population. Thus, adult subjects typically 16-65 years of age and of "reasonable health" status in the average work force contrast with the increased incidence in the general population of potentially sensitive subpopulations (i.e. children, older persons, and the chronically sick). Therefore, the factor recommended for an occupational population may reasonably be less than that recommended for the general population; accordingly, a factor of between 1-3 (default value 2) is recommended for occupational situations.

3.7 DERIVATION OF HUMAN PNAEL

The factors outlined in Table 4 should be used as appropriate to derive human PNAELs from animal or human NOAELs or LOAELs.

Table 4: Adjustment factors (recommended default values) for use in deriving Human PNAEL(s) from human or animal NOAEL(s)/LOAEL(s)

Element	Factor Default Value
Short-term repeated/subchronic/chronic extrapolation	
short-term repeated to subchronic	3
subchronic to chronic	2 - 3
LOAEL to NOAEL extrapolation	3*
Route-to-route extrapolation	no default (case by case calculation)
Interspecies extrapolation	
oral route	4
inhalation route	1
Intraspecies extrapolation	
general population	3
occupational population	2

* An additional factor of 4 may be required where the human PNAEL refers to continuous inhalational exposure and the animal data base involves intermittent (6-8 h/d) exposure.

The values of the relevant factors should be determined for each individual case and the human PNAEL(s) obtained by dividing the NOAEL(s) or LOAEL(s) by the product of these factors (the overall 'adjustment' factor). A human PNAEL so derived will represent the best scientific estimate of the highest dose or exposure concentration which will not lead to adverse effects in humans exposed by the route and under the exposure regime for which the PNAEL is intended. The human PNAELs do not contain any allowance for political, socio-economic or risk perception factors, or for the degree of scientific uncertainty inherent in their derivation.

3.8 DEGREE OF CONFIDENCE / SCIENTIFIC UNCERTAINTY

The risk assessor should formulate a statement about the degree of confidence he has in the PNAELs derived by the above process. This statement should guide the risk manager in selecting between risk management alternatives. The degree of confidence may be high, medium or low. The following examples give a short overview what is meant by these three categories.

- ***High degree of confidence***

  The database contains high quality human or animal studies. Findings should be confirmed by the existence of two or more studies with the same endpoint. Human studies may be volunteer or workplace studies and must be conducted to a satisfactory protocol, particularly including adequate controls. Animal studies should preferably conform with GLP requirements, and must contain an adequate group size and be well documented and reported. Animal studies must have been conducted by the relevant route of administration and be of appropriate duration. The critical effect should be one where the mechanism(s) is (are) well understood, both in animals and humans. The database should be sufficiently extensive to give confidence that the correct critical effect has been selected, and that there are no major uncertainties in this respect.

- ***Medium degree of confidence***

  The human or animal studies fall short of the quality described above in some significant respect. This may be due to the critical effect having been characterised in only a single study. The studies may fall short of the highest standards in respect of some aspects of the protocol or reporting, but they must be by the relevant route and be adequately controlled. If a LOAEL/NOAEL or duration extrapolation is involved this will limit the overall confidence to 'medium', even if all other aspects of the database are satisfactory.

- ***Low degree of confidence***

  The human or animal studies fall short of the highest standards in some important respect(s). Route-to-route extrapolation will normally lead to 'low' overall confidence, as will significant uncertainty over the choice of critical effect; old, poorly reported animal studies or those with inadequate group sizes will lead to a similar conclusion. Studies without appropriate controls

would not normally be regarded as providing an adequate starting point for the derivation of human PNAELs.

In considering the way in which the degree of confidence in the human PNAEL should be taken into account, the following is suggested as a guide:

- *High degree of confidence:* no additional numerical 'uncertainty factor' required (i.e. the factor is 1);

- *Medium degree of confidence:* assess on a case-by-case basis, perhaps consider to use a low numerical uncertainty factor (in the range of 1 - 2);

- *Low degree of confidence:* consider the need to generate more data (either on effects or on exposure) to increase the degree of confidence or, alternatively, use a larger uncertainty factor.

4. RECOMMENDED APPROACH - CONCLUSIONS

The human Predicted No Adverse Effect Level (PNAEL) established by the procedure described below represents the best scientific estimate of the dose or exposure concentration which will not lead to adverse effects in humans exposed by the route and under the regime for which the PNAEL was derived. It does not contain any allowance for scientific uncertainty or "safety" factors.

The preceding chapter has described in some detail the elements considered necessary in the process of establishment of a human PNAEL (or PNAELs). These elements may be put together into an overall recommended approach to this task, and are summarised in sequence as follows.

1. **Exposure**

   Review exposure database - establish route(s) and patterns of exposure and define human PNAELs required.

2. **Hazard**

   Review hazard database - decide whether adequate starting point exists for derivation of the required PNAELs. If so, proceed; if not, recommend that risk management be considered.

3. **Critical Effect**

   Identify critical effect(s) and establish NOAEL(s) or LOAEL(s).

4. **Short-term repeated/Subchronic/Chronic Extrapolation**

   Consider need for and determine size of factor to take account of short-term repeated/subchronic/chronic extrapolation.

5. **LOAEL/NOAEL Extrapolation**

   In the event that NOAEL(s) have not been established, determine value of factor(s) required to extrapolate from LOAEL(s) to NOAEL(s).

6. Route-to-route Extrapolation

If the experimental data have been generated by a route of administration other than that relevant to the human exposure situation, consider validity of route-to-route extrapolation and, valid, calculate equivalent NOAEL by relevant route.

7. Interspecies Variability

In the event that the hazard data are derived from animals, determine the validity of interspecies extrapolation and the value of the factor required to take account of differences between experimental animals and man.

8. Intraspecies Variability

Determine value of the factor required to take account of human variability in response to toxic chemicals.

9. Human PNAEL(s)

Using the overall adjustment factor derived by multiplying together the factors determined in steps 4 to 8 above, derive the appropriate human PNAEL(s) from the starting LOAEL(s) or NOAEL(s).

10. Degree of Confidence/Scientific Uncertainty

Consider degree of scientific uncertainty inherent in each of the above stag and decide whether the overall confidence in the derived human PNAEL(s) is 'High', 'Medium' or 'Low'.

The human PNAEL(s) derived by the above approach, together with the attached degree of confidence, should then be discussed jointly by the Risk Assessor and the Risk Manager.

Any further numerical adjustment deemed necessary to account for the degree of scientific uncertainty should be jointly agreed. The Risk Manager will then determine any non-scientific 'safety' factors required before the resulting number is compared with the estimated or measured level of human exposure in the Risk Characterisation stage.

An example for a "Risk Assessment Worksheet" is provided in the Text Box 2 below.

Text Box 2: Example of a Risk Assessment Worksheet

Review of Data Base				
Exposed populations: **Route of exposure:** **Pattern of exposure (single dose, intermittent, continuous):** **Human PNAEL(s) required:** **Critical effect(s):** **Pivotal study/studies:** **NOAEL or LOAEL (A):**				
Adjustment Factors				
	Occupational Exposure		**Non-Occupational Exposure**	
	Default Value	**Applied Value**	**Default Value**	**Applied Value**
Short-term repeated/subchronic/ chronic extrapolation				
short-term repeated to subchronic	3		3	
subchronic-chronic	2 - 3		2 - 3	
LOAEL-NOAEL	3		3	
Route-to-route	-		-	
Interspecies extrapolation				
oral	4		4	
inhalation	1		1	
Intraspecies variations	2		3	
Overall adjustment factor (B)				
Human PNAEL (A/B)				
Degree of confidence *				
Recommendations:				

* Guidance on how this degree of confidence should be taken into account is given at the end of Section 3.

5. APPLICATION OF THE APPROACH IN OCCUPATIONAL AND NON-OCCUPATIONAL SITUATIONS

There are sound scientific reasons for differentiating between occupational and non-occupational situations in respect of some of the elements in the recommended approach.

- Different human PNAELs may well be required. For example, occupational exposure is often by the inhalation route, thus calling for a PNAEL for repeated exposure by that route, while the non-occupational situation may involve lifetime exposure by the oral route, calling for a different PNAEL.

- As a result of the different routes of exposure, the critical effect may differ between the occupational and the non-occupational situation. There are many substances where the critical effect occupationally is irritation of the respiratory tract, whereas this effect may be of no relevance for lifetime oral exposure.

- Reflecting the different pattern and duration of exposure, it may be acceptable to use a smaller adjustment factor in the occupational context when the starting point is a short-term repeated exposure study, than that which would be required when considering lifelong non-occupational exposure.

- For the reasons expounded in Section 3.6.1, a lower factor is needed for interspecies extrapolation when the experimental data are generated by the inhalation route (as is often the case occupationally) than when considering the oral route.

- The exposure population in the workplace is typically less heterogeneous than the general population. Thus adults typically 16-65 years of age and in reasonable health contrast with the larger proportion of potentially sensitive sub-populations (i.e. children, older persons, the chronically sick) present in the general population.

The extent to which any or all of the above points will lead to a difference for any given substance will depend, of course, on the specific circumstances. In particular the nature of the critical effect(s) may be of overriding significance.

6. NON-SCIENTIFIC FACTORS

The risk assessor is considered to be the individual or group of individuals responsible for estimating the probability of injury, disease or death to mankind due to exposure to a potentially hazardous substance in the environment. The risk assessment should be based on adequate and reliable toxicity data and on sound scientific judgement following the principles of data review and uncertainty estimation as described in earlier sections.

Once a realistic estimate of risk has been established, the management of that risk for a specific population, e.g. workforce, or for society in general is decided by the risk manager. The risk manager may choose to add additional factors to account for, e.g.:

- the perception of the particular risk in society, based usually on the unacceptability of the response. The nature/severity of the critical effect may justify the use of an additional factor under this heading, since it is not possible to take a scientific approach to the relative acceptability (or unacceptability) of effects such as teratogenesis compared with, e.g., upper respiratory irritation;

- economic factors (cost/benefit considerations);

- political factors.

Ideally, the risk manager should work closely with the risk assessor to understand the real scientifically-based estimate of risk and to develop together the magnitude of these additional non-scientific factors where deemed necessary. The use of unnecessarily large "safety factors" should be avoided. Close cooperation between risk assessor and risk manager will allow identification of areas where conservatism has already been applied in the risk assessment process through the choice of factors which often represent a "worst-case" estimate. Clearly such areas where the risk assessor has chosen conservative factors would not normally need additional "factors" applied by the risk manager. Doing so would only result in overly-conservative measures which may be neither feasible nor practicable for society.

The risk manager is encouraged to provide transparency in the choice and use of additional factors and to justify the magnitude of these factors based on the population concerned.

7. RECOMMENDATIONS

- In the overall process of establishing acceptable levels for human exposure to chemical substances the methodology used should be transparent and permit clear distinctions to be made between the scientific and non-scientific aspects of the process.

- A methodology should be used which permits occupational and non-occupational situations involving the same chemical substance to be addressed on a consistent scientific basis and which allows justifiable distinctions to be made between the two.

- The roles of the risk assessor and the risk manager in the overall process should be clearly defined and distinguished.

- The approach recommended in this Report should be considered by the relevant authorities as an attempt to develop a methodology which will facilitate implementation of the above recommendations.

- Recognising the limitations of the database underpinning some of the numerical factors in the recommended approach, the data accumulating to authorities under Existing Chemicals legislation should be reviewed to see whether they will permit firmer recommendations to be made.

APPENDIX A. GLOSSARY OF TERMS

Adverse Effect

Functional impairment of toxicological relevance or pathological lesions.

Assessment Factor

The overall factor involved in moving from an animal or human NOAEL/LOAEL to an "acceptable" level of human exposure. Its derivation will include consideration of "adjustment", "uncertainty" and "safety" factors.

Adjustment Factor

The factor used to convert an animal or human NOAEL/LOAEL into a human PNAEL. This factor is based solely on scientific considerations.

Confidence/Uncertainty

The risk assessor should give a statement on the confidence (high, medium or low) he has in the accuracy of his risk assessment and the reliability of the resulting limit value.

Critical Effect

The adverse effect considered to be of most concern in relation to the population of concern. It may not always be the effect exhibiting the lowest NOEC.

Default Value

A pragmatic fixed value used in the absence of relevant data.

Exposure

The concentration within a time interval or dose with which a human population comes into contact.

Hazard

The inherent capacity of a substance to cause adverse effects.

LOAEL

Lowest-Observed-Adverse Effect Level is the lowest experimentally determined dose at which there was statistically or biologically significant increase in frequency or severity of an adverse effect in a treated group when compared to a control group.

NOAEL

No-Observed-Adverse Effect Level is the highest experimentally determined dose at which there was no statistically or biologically significant increase in frequency or severity of an adverse effect in a treated group when compared to a control group.

NOEL

No-Observed-Effect Level is the highest experimentally determined dose at which there was no statistically or biologically significant treatment related effect.

Pivotal Study

The study (animal or human) identified by the risk assessor as providing most information (qualitatively and quantitatively) on the critical effect and thus most likely to be of assistance in deriving a human PNAEL.

PNAEL

The human Predicted No Adverse Effect Level (PNAEL) represents the best scientific estimate of the dose or exposure concentration which will not lead to adverse effects in humans exposed by the route and under the regime for which the PNAEL was derived. It does not contain any "safety" factor and does not distinguish as such between occupational and non-occupational situations.

Risk

The probability that a substance will actually cause adverse effects in a given exposure situation. It is a function of hazard and exposure.

Risk Assessment

The overall process of determining whether and in what circumstances a substance will cause adverse effects. This involves consideration of both "hazard" and "exposure".

Risk Characterisation

Estimation of the incidence and severity of the adverse effects likely to occur due to actual or predicted exposure to a substance.

Risk Management

This process includes all those elements (e.g. "safety" factors, risk perception, socio-economic factors) involved in moving from a scientifically derived Human No Adverse Level (PNAEL) to a level of exposure deemed "acceptable" in its specific context.

Safety Factor

The factor used by the Risk Manager in determining an "acceptable" level of human exposure. It will include consideration of socio-economic, risk perception and other similar elements and is inherently non-scientific.

Structure Activity Relationship

The development of structure-activity relationships (SAR) is an attempt to express the relationships between the biological activity of chemicals, or series of chemicals, and their structure. These relationships can be described qualitatively and quantitatively.

Toxicodynamics

Toxicodynamics describes the development, duration and magnitude of the response of an organism to a given target organ dose.

Toxicokinetics

The processes which determine the disposition of a chemical substance in the body over time. Toxicokinetics therefore requires a consideration of the absorption, distribution, metabolism, excretion and retention properties of the substance.

Uncertainty Factor

The factor used to take account of the degree of scientific uncertainty involved in the derivation of the human PNAEL. This factor should be determined in individual cases by the Risk Manager in consultation with the Risk Assessor.

APPENDIX B. DESCRIPTIONS OF FACTORS USED IN THE APPROACH OF LEWIS/LYNCH/NIKIFOROV

The Scaling Factor, S, is used in the numerator of the algorithm to adjust the animal NOAEL upward or downward reflecting the known quantitative differences in toxicokinetics between the experimental test species and humans (interspecies toxicokinetics). Any positive value may be assigned to S; a value greater than 1 is chosen if, for example, it is known that a less toxic metabolite is produced in man than in the test species. If the reverse is true, then S should be assigned a value less than 1 but greater than 0. When there is no clear evidence supporting an alternate value, then the default value of 1 is assigned to S.

The Interspecies Adjustment Factor, R, takes account of the differences in susceptibility between animals and humans i.e. interspecies toxicodynamics. These adjustments should be clearly differentiated from those addressed by S. The factor R may be assigned any value between 0.3 and 3 with values less than 1 indicating lower susceptibility among humans when compared to the test species. The recommended default value is 1 suggesting that in the absence of other data, it should be assumed that animals and humans are equivalent in sensitivity to the critical effect.

The Heterogeneity Factor, H, is the adjustment factor used to take account of the anticipated greater heterogeneity between individual humans than was observed among the laboratory test animals. However, review of the literature on age-related differences in patients during the handling of drugs suggests that even the most extensive variations in treatment regimes require an adjustment of the administered dose by no more than 5-fold. The LLN approach recommends that a value of 3-5 should be selected for H if specific human sub-populations are identified which are particularly sensitive to the critical effect. Where the NOAEL was based on these sensitive populations, then a value of 1 for H is appropriate. A default value of 3 is recommended providing for some intraspecies variation without introducing overly conservative adjustments.

The Critical Human Health Factor, Q1, represents the likelihood that the critical effect observed in the animal study is also relevant for humans. The factor may have a value between 0.1-1; values lower than 1 indicate that the effect is considered to be of little significance to humans compared to the test species. The chosen default value is 1 indicating that the effect seen in animals is equally relevant for humans.

The Study Duration Factor, Q2, is used to cover the data extrapolation from studies of lower duration to estimating the risk from lifelong exposures and hence the likelihood that the effect might have been observed at a lower dose if the study had continued for a longer time. The range of appropriate values recommended is 1-5 and the default value of 3 is supported by other authors (Weil and McCollister, 1963).

The LOAEL to NOAEL Factor, Q3, is used to adjust a LOAEL in a study where no NOAEL was identified. The incidence of the critical effect at the LOAEL should be considered. If a large fraction of animals exhibit the effect, then a higher value of Q3 should be selected. The LLN approach recommends a default value of 3 when a LOAEL is used instead of a NOAEL but there are no data supporting any predictions for an estimate of the NOAEL. Of course where a NOAEL has been established, then Q3 becomes automatically 1.

The Uncertainty Factor, U, takes account of any residual uncertainty after all appropriate data have been used to provide best estimates for the preceding factors. Each factor is separately evaluated and is assigned a value equal to or greater than 1. By multiplying these factors, an overall uncertainty factor is achieved. The range recommended for the overall uncertainty (i.e. all factors considered) is 1-10 reflecting the belief that is sufficient data are available to use the approach, then there should be no greater than 10-fold uncertainty as a final outcome.

The Severity Factor, C, is used to adjust the NOAEL downward as a result of a "severe" critical effect. A range of 1-10 is recommended for this value representing a gradient of effects from less severe, reversible effects to those which are potentially disabling or life-threatening.

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