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FIRST REPORT ON THE HARMONISATION OF RISK ASSESSMENT PROCEDURES

PART 2 :

APPENDICES

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Appendices *page*

APPENDIX 1

GLOSSARY OF TERMS

Risk analysis is an evolving field. An ever increasing number of publications by a wide range of national or international bodies as well as by individual authors address the issues related to risk assessment, risk management or risk communication. Many of these publications include glossaries, terminology, and other term lists that are intended to clarify the particular meaning attached to a term.

Such glossaries are occasionally at variance with each other. Whereas minor differences may have their value when referring to a specific context, ambiguous terminology may give an impression of confusion and may lead to misunderstanding. A typical example is provided by the terms "risk analysis" and "risk assessment". Whereas it is increasingly accepted that the term risk analysis is the encompassing term used to describe the three major sub-fields of the discipline (risk assessment, risk management and risk communication), many individuals still use the terms risk analysis and risk assessment synonymously.

Considering the above, the Working Party on "Harmonisation of Risk Assessment Procedures" identified the need to agree on definitions as far as possible. The aim was to have a common glossary of terms compiled for all Scientific Committees which, as far as practicable, would be in line with the definitions proposed by major international bodies.

The Working Party identified a few key terms for which agreed definitions are provided in the following list, in bold italics. They are not listed alphabetically, but arranged in functional groups.

When taking forward their task on terminology, the Working Party has been aware of a project on risk assessment terminology launched under the auspices of the International Programme for the Good Management of Chemicals (IOMC), with the active involvement of the International Programme on Chemical Safety (IPCS) and the Organisation for Economic Co-operation and Development (OECD). This programme involved a) - the listing of 50 selected terms together with the corresponding definitions collected from reference materials (the number of definitions per term ranged from 1 to 23) and b) - a consensus building exercise where each of the 200 experts identified has been invited to indicate, for each of the selected terms, the preferred definition. Only one choice was permitted. A total of 10000 records were received. A critical review has been conducted and published (P. Lewalle. Risk Assessment Terminology. Methodological considerations and provisional results. Report on a WHO experiment. *Terminology Standardization and Harmonization*, Volume II (1999), n° 1-4). This publication gives a snapshot picture of the terminology understanding that emerged from the survey. It is provisional in the sense that the corresponding definitions have not yet been subjected to an agreement. Nevertheless, the Working Party considered it useful to mention, for the key terms they have selected and where available, the outcome of this survey. In the text below, the survey definitions are presented as indents, between square brackets.

Some other terms of current use have been utilised in this report. These terms have not been discussed for agreement by the Working Party. They are listed separately in alphabetic order and a definition (in some cases two) from reference documents is provided, with mention of the source. At times, a short text provides some additional explanations.

The list and the definitions suggested should not be considered a definitive work.. Rather, it is expected that it would provide to the EU Scientific Committees an opportunity to review the

terms they currently use, clarify their definitions and, where appropriate, suggest the amendments necessary to ensure a greater compatibility of their nomenclatures. This list is not at all complete regarding related issues not directly focusing on risk assessment. Therefore, attention is drawn on regularly updated glossaries of terms in the environmental chemistry and medicinal chemistry/toxicology areas published by the respective IUPAC Commissions and easily accessible at the IUPAC Website (www.iupac.org).

- **KEY TERMS :**

HAZARD

- The potential of a risk source to cause an adverse effect (s)/event(s).

[Inherent property of an agent or situation capable of having adverse effects on something. Hence, the substance, agent, source of energy or situation having that property]

RISK

- The probability and severity of an adverse effect /event occurring to man or the environment following exposure, under defined conditions, to a risk source(s).

[The probability of adverse effects caused under specified circumstances by an agent in an organism, a population or an ecological system]

RISK SOURCE

- Agent, medium, commercial/industrial process, procedure or site with the potential to cause an adverse effect(s)/event(s)

RISK ANALYSIS

- A process consisting of three components: risk assessment, risk management and risk communication.

[A process for controlling situations where populations or ecological systems could be exposed to a hazard. It usually comprises three steps, namely risk assessment, risk management and risk communication]

RISK ASSESSMENT

- A process of evaluation including the identification of the attendant uncertainties, of the likelihood and severity of an adverse effect (s) /event(s) occurring to man or the environment following exposure under defined conditions to a risk source(s). A risk assessment comprises hazard identification, hazard characterisation, exposure assessment and risk characterisation.

> [A process intended to calculate or estimate the risk for a given target system following exposure to a particular substance, taking into account the inherent characteristics of a substance of concern as well as the characteristics of the specific target system. The process includes four steps: hazard identification, dose-response assessment, exposure assessment, risk characterisation]

HAZARD IDENTIFICATION

- The identification of a risk source(s) capable of causing adverse effect(s)/event(s) to humans or the environment species, together with a qualitative description of the nature of these effect(s)/event(s).

> [The first stage of risk assessment consisting in the determination of particular hazards a given target system may be exposed to, including attendant toxicity data. (Depending on the context, another definition emerged: the determination of substances of concern, the adverse effects they may inherently have on target systems under certain conditions of exposure, taking into account toxicity data)]

HAZARD CHARACTERISATION

- The quantitative or semi-quantitative evaluation of the nature of the adverse health effects to humans and/or the environment following exposure to a risk source(s). This must, where possible, include a dose response assessment.

> [The qualitative and, whenever possible, quantitative description of the nature of the hazard (alternative: of the nature of the possible adverse effects) associated with a biological, chemical or physical agent, based on one or more elements, such as mechanisms of action involved, biological extrapolations, dose-response and dose-effect relationships, and their respective attendant uncertainties]

DOSE-RESPONSE ASSESSMENT

- The determination of the relationship between the magnitude of exposure to risk source(s) [dose] and the magnitude or frequency and/or severity of associated adverse effect(s) [responses].

> [The analysis of the relationship between the total amount of an agent absorbed by a group of organisms and the changes developed in it in reaction to the agent, and inferences derived from such an analysis with respect to the entire population]

EXPOSURE ASSESSMENT

- The quantitative or semi-quantitative evaluation of the likely exposure of man and/or the environment to risk sources from one or more media.

> [The quantitative and qualitative analysis of the presence of an agent (including its derivative) which may be present in a given environment and the inference of the possible consequences it may have for a given population of particular concern]

RISK CHARACTERISATION

- The quantitative or semi-quantitative estimate, including attendant uncertainties, of the probability of occurrence and severity of adverse effect(s)/event(s) in a given population under defined exposure conditions based on hazard identification, hazard characterisation and exposure assessment.

> [Integration of evidence, reasoning and conclusions collected in hazard identification, dose-response assessment and exposure assessment and the estimation of the probability, including attendant uncertainties, of occurrence of an adverse effect if an agent is administered, taken or absorbed by a particular organism or population.
> Or
> The qualitative and/or quantitative estimation, including attendant uncertainties, of the severity and probability of occurrence of known and potential adverse effects of a substance in a given population]

RISK MANAGEMENT

- The process of weighing policy alternatives in the light of the result of a risk assessment and other relevant evaluation and, if required, selecting and implementing appropriate control options (which should, where appropriate, include monitoring / surveillance).

> [Decision-making process involving consideration of political, social, economic, and technical factors with relevant risk assessment information relating to a hazard so as to develop, analyse, and compare regulatory and non-regulatory options and to select and implement the optimal decisions and actions for safety from that hazard]
>
> (N.B. *Codex Alimentarius Commission*, ALINORM 99/37 (report of the 23rd session of the CAC): the process, distinct from risk assessment, of weighing policy alternatives, in consultation with all interested parties, considering risk assessment and other relevant factors relevant for the health protection of consumers and for the promotion of fair practices, and, if needed, selecting appropriate prevention and control options)

RISK COMMUNICATION

- The interactive exchange of information and science based opinions concerning risk among risk assessors, risk managers, consumers and other actual or potential stakeholders.

[Interactive exchange of information about risks among risk assessors, managers, news media, interested groups and the general public]

(N.B. *Codex Alimentarius Commission*, ALINORM 99/37 (report of the 23rd session of the CAC): the interactive exchange of information and opinions throughout the risk analysis process concerning risk, risk-related factors and risk perceptions, among risk assessors, risk managers, consumers, industry, the academic community and other interested parties, including the explanation of risk assessment findings and the basis of risk management decisions)

- **OTHER TERMS USED IN THIS REPORT :**

Sources :
(Unless otherwise specified)

a = Principles for the Safety Assessment of Food Additives and Contaminants in Food. Environmental Health Criteria 70, World Health Organization, Geneva 1987.

b = Assessing Human Health Risks of Chemicals: Derivation of Guidance Values for Health-based Exposure Limits. Environmental Health Criteria 170, World Health Organization, Geneva 1994.

c = Principles for the Assessment of Risks to Human Health from Exposure to Chemicals. Environmental Health Criteria 210, World Health Organization, Geneva 1999.

d = Glossary of terms on chemical safety for use in IPCS publications. World Health Organization, Geneva 1989.

e = Food consumption and exposure assessment of chemicals. Report of a FAO/WHO Consultation. Geneva, 10-14 February 1997. World Health Organisation, 1997. (WHO/FSF/FOS/97.5)

f = P. Lewalle. Risk Assessment Terminology. Methodological considerations and provisional results. Report on a WHO experiment. *Terminology Standardization and Harmonization*, Volume II (1999), n° 1-4

g = suggested for this report

TERMS AND DEFINITIONS :

Acceptable daily intake (ADI) [a] : an estimate of the amount of a food additive, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk (standard man = 60kg).

Accuracy [d] : (i) the closeness of agreement between the "true" value and the measured values; (ii) the degree to which a measurement, or an estimate based on measurements, represents the true value of the attribute that is being measured.

Acute Reference Dose (Acute RfD) [e] : the estimated amount of a substance in food or drinking-water, expressed on a body weight basis, that can be ingested over a short period of time, usually one meal or one day, without appreciable health risk to the consumer on the basis of all the known facts at the time of the evaluation.
It is usually expressed in milligrams of the chemical per kilogram of body weight.

Adverse effect [b] : change in morphology, physiology, growth, development or life span of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects of other environmental influences.
Decisions on whether or not any effect is adverse require expert judgement.

Benchmark dose (BMD [b] : the lower confidence limit of the dose calculated to be associated with a given incidence (eg 5 or 10% incidence) of effect estimated from all toxicity data on that effect within that study.

Biotransformation [d]: a process in which a chemical is modified by a living organism.

Carcinogen [d]: an agent, chemical, physical or biological, that can act on living tissue in such a way as to cause a malignant neoplasm.

Critical effect(s) [g] : the adverse effect(s) that are relevant to human risk assessment and that occur at the lowest doses in the most sensitive animal species.

Default value [b] : pragmatic, fixed or standard value used in the absence of relevant data.

Effect [d] : a biological change in an organism, organ or tissue.

Exposure : [d] the amount of an environmental agent that has reached the individual (external dose) or has been absorbed into the individual (internal dose, absorbed dose).
In the document on quantitative risk assessment for toxic chemicals, exposure is taken to refer to the external dose.

[f] concentration, amount or intensity of a particular agent that reaches a target system. It is usually expressed in numerical terms of substance, concentration, duration, frequency and intensity.

Health : a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity (World Health Organisation)

Incidence [d] : the number of instances of illness commencing or of persons falling ill, during a given period in a specific population.
Incidence is usually expressed as a rate, the denominator being the average number of persons in the specified population during a defined period or the estimated number of persons at the mid-point of that period. The basic distinction between *incidence* and *prevalence* is that whereas incidence refers only to new cases, prevalence refer to all cases, irrespective of whether they are new or old. When the terms incidence and prevalence are used, it should be stated clearly whether the data represent the numbers of instances of the disease recorded or the numbers of persons ill.

Intake [d] : the amount of a substance or material that is taken into the body, regardless of whether or not it is absorbed.
The daily intake may be expressed as the amount taken in by a particular exposure route, e.g. ingestion or inhalation. The daily intake from food is the total amount of a given substance taken in during one day through the consumption of food. The daily intake by inhalation is calculated by multiplying the concentration of the substance (or agent) in air by the total amount of air inhaled during one day (24 hours). The total daily intake is the sum of the daily intake by an individual from food, drinking-water, and inhaled air.

Lowest-observed-adverse-effect-level (LOAEL) [b] : lowest concentration or amount of a substance, found by experiment or observation, which causes an adverse alteration of morphology, functional capacity, growth, development or life span of the target organism distinguishable from normal (control) organisms of the same species and strain under the same defined conditions of exposure.

Maximum tolerated dose (MTD) [a] : a term in common use in carcinogenicity testing meaning a dose that does not shorten life expectancy nor produce signs of toxicity other than those due to cancer.
Operationally, the MTD has been set as the maximum dose level at which a substance induces a decrement in weight gain of no greater than 10% in a subchronic toxicity test.

Mutagen [d] : an agent that induces mutation.

Mutagenicity [d] : the property of a physical, chemical, or biological agent to induce mutations in living tissue.

Mutation [d] : any heritable change in genetic material.
This may be a chemical transformation of an individual gene (a gene or point mutation), which alters its function. On the other hand, this change may involve a rearrangement, or a gain or loss of part of a chromosome, ,which may be microscopically visible. This is designated a chromosomal mutation.

No-observed-effect-level (NOEL) [a] : the greatest concentration or amount of a chemical, found by experiment or observation, that causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target.

No-observed-adverse-effect level (NOAEL) [b] **:** greatest concentration or amount of a substance found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development or life span of the target organism under defined conditions of exposure.
Alterations of morphology, functional capacity, growth, development or life span of the target may be detected which are judged not to be adverse.

Precision [d] **:** the closeness of agreement between the results obtained by applying the experimental procedure several times under prescribed conditions.

Quantal effect [d] **:** an effect that can be expressed only as "occurring" or "not occurring".
Typical examples of quantal effects are death or occurrence of a tumour.

Reference Dose (RfD) [term used in certain contexts, e.g. in US EPA's non-cancer health risk assessments] : an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.
It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used.

Response [d] **:** the proportion of an exposed population with an effect or the proportion of a group of individuals that demonstrate a defined effect in a given time.

Risk estimation : [d] the quantification of dose-effect and dose-response relationships for a given environmental agent, showing the probability and nature of the health effects of exposure to the agent.

[f] quantification of the probability, including attendant uncertainties, that a chemical, physical or biological agent administered, taken or absorbed by a system will have a specific effect, based on hazard identification, dose-response assessment and exposure assessment for that particular agent in relation to that particular system.

Risk evaluation : [d] the comparison of calculated risks of exposure to a given agent with the risks caused by other agents or societal factors and with the benefits associated with the agent.

[f] establishment of a qualitative or quantitative relationship between risks and benefits, involving the complex process of determining the significance of the identified hazards and estimated risks to those organisms or people concerned with or affected by them. It is the first step in risk management.

Note: in the report of the Joint FAO/WHO Consultation, Rome, Italy, 27-31 January 1997, *Risk Management and Food Safety* (FAO Food and Nutrition Paper n°65), the term "risk evaluation" is applied to a grouping of steps in risk management which includes identification of a food safety problem, establishment of a risk profile, ranking of the hazards, establishment of a risk assessment policy, commissioning of risk assessment, and consideration of risk assessment results (see part 1, table 3.1).

Risk perception : the attitudes and intuitive judgements about risk
(Slovic, P. 1992. Perception of risk: reflections on the psychometric paradigm. In S. Krimsky and D. Golding (Ed) *Social Theories of Risk*. Praeger, Westport, Con.)

Safety (of a drug or other chemical substance for human health) [d] **:** the extent to which a chemical substance may be used in the amounts necessary for intended purposes with a minimum risk of adverse health effects.

Safety factor [a] **:** a factor applied to the no-observed-effect level to derive an acceptable daily intake.
The non-observed-effect level is divided by the safety factor to calculate the ADI. The value of the safety factor depends on the nature of the toxic effect, the size and type of population to be protected and the quality of the toxicological information available.

Sensitivity analysis : a method used to examine the behaviour of a model by measuring the variation in its outputs resulting from changes to its inputs
(Codex Alimentarius, ALINORM 99/13A)

Target organ(s) [d] **:** organ(s) in which the toxic injury manifests itself in terms of dysfunction or overt disease.

Threshold : [f] dose of a substance or exposure concentration below which a stated effect is not observed or expected to occur.

[g] intake or dose below which homeostatic changes are able to reverse any adverse effects; or an intake or dose below which homeostatic change are unable to compensate; or an intake below which a stimulus ceases to be perceptible.

Toxicity [d] **:** the capacity of a substance to cause injury to a living organism.
A highly toxic substance will cause damage to an organism if administered in very small amounts and a substance of low toxicity will not produce an effect unless the amount is very large. However, toxicity cannot be defined in quantitative terms without reference to the quantity of substance administered or absorbed, the way in which this quantity is administered (e.g. inhalation, ingestion, injection) and distributed in time (e.g. single or repeated doses), the type and severity of injury, and the time needed to produce the injury.

Toxicodynamics [b] **:** the process of interaction of chemical substances with target sites and the subsequent reactions leading to adverse effects.

Toxicokinetics [b] **:** the process of the uptake of potentially toxic substances by the body, the biotransformation they undergo, the distribution of the substances and their metabolites in the tissues, and the elimination of the substances and their metabolites from the body.
Both the amounts and the concentrations of the substances and their metabolites are studied. The term has essentially the same meaning as pharmacokinetics, but the latter term should be restricted to the study of pharmaceutical substances.

Uncertainty analysis : a method used to estimate the uncertainty associated with model inputs, assumptions and structure/form.
(Codex Alimentarius, ALINORM 99/13A)

Uncertainty factor (UF) [b] **:** a product of several single factors by which the NOAEL or LOAEL of the critical effect is divided to derive a TI [*Tolerable Intake*].
These factors account for adequacy of the pivotal study, interspecies extrapolation, inter-individual variability in humans, adequacy of the overall data base, and nature of toxicity. The term uncertainty factor was considered to be a more appropriate expression than safety

factor since it avoids the notion of absolute safety and because the size of this factor is proportional to the magnitude of uncertainty rather than safety. The choice of UF should be based on the available scientific evidence.

APPENDIX 2

REPORT ON EXPOSURE ASSESSMENT

Contents:

1. EXECUTIVE SUMMARY

Risk assessments and specifically exposure assessments are conducted in different regulatory frameworks, both on EU and member state level. The different types of products, their possible uses, and national/regional conditions inevitably require equally different exposure assessments to be done, using different sets of information and levels of precision. Therefore, harmonisation throughout all member states and regulatory frameworks has to be restricted to achieve consistency of approaches.

However, there exist some differences which are not justified by sectorial or national requirements and therefore should be examined further for potential harmonisation. An example for this is, that food safety assessments use exposure (= consumption) data close to the regional/sub-group maximum consumption possible ("reasonable worst case") while for cosmetics an EU-wide average consumption value is used for all countries and consumer groups.

The real, total exposure, both for consumers and the environment, can only be assessed if all pathways are considered in an integrated approach. The exposure assessments by the Scientific Committees follow the respective legislation and it is only the chemical substances legislation/Directives which follow this integrated approach. The others only consider a certain use of chemicals, e.g. in plant protection, or a pathway, e.g. in food safety. The same chemicals, however, may be used for other purposes or exposure may be by other media than those in the focus of legislation. A realistic description of the exposures of consumers and environment requires a stratification of input-data in relation to ways and means of primary production and primary products and the production chain.. Interaction between the different regulatory agencies and scientific committees in this regard is an important issue (e.g. sequentiation of pathways; where the competence of a committee or agency stops, another committee/agency should take over the assessment in a concerted approach. Legal (mandate) constraints to this should be addressed at EU level (ref. White Paper on Food safety).

In order to improve and demonstrate consistency and/or differences, there is a need for a common and precise "language" in exposure assessment ("semantic homogeneity" both in the data utilised and in the approach taken for the assessment). While obvious to the experts commissioned for doing the assessment, there is a need to communicate to the users the nature and meaning of the assumptions made and of the approach taken and how these would influence the interpretation of the results provided

Scenarios/models
Essentially in all approaches to exposure assessments as a systematic problem-oriented exercise evaluative or interpretative scenarios are used. In principle, all scenarios do not reflect one specific local situation, but have the objective to be representative of either mean, typical or most sensitive situations in a region or throughout the European Community. Such scenarios should be described clearly as to their representativeness (region/group; which degree of worst case/which probability of exposure they stand for). Ideally, they would be derived from minimal homogenous data gets and be integrated at higher levels, where appropriate. Where sufficiently representative data sets are lacking, measuring critical exposures may also produce scenarios close to a worst case.

Where possible, the common development (including updating and validation) of scenarios and models should be adequately supported by the Commission (ref.. pesticides; FOCUS initiative for fate and exposure modelling).

Probabilistic approaches are essential to represent and describe the complexity of real situations, for taking into account variability and uncertainty, and for quantitative description of uncertainties. They are also important for transparent risk communication both to the public and to risk managers. It is recognised that the development of this approach will rely on the collection of more, accurate, quantitative data, preferably using EU-wide compatible standards for data sampling and monitoring (EUROSTAT; EEA).

EU-wide compatible surveilling and monitoring schemes for consumers and the environment of real exposure data would be essential for validation of input data and assessment methods.

2. EXPOSURE ASSESSMENT IN PERSPECTIVE

2.1 Background

Risk assessment and specifically exposure assessment(s) are conducted in different legislative/regulatory frameworks. There is a range of ultimate goals of exposure assessments for consumers and the environment which also result from different technological sectors of the use of chemical substances as well as from the consideration of basic differences in hazard potentials for groups of substances. While the ultimate goal of consumer protection is to protect each individual, for the environment only populations and systems need to be protected. In the framework of exposure assessment this implicates principally differing sets of information as well as precision required. These principal differences of groups of products for which exposure assessment has to be done, clearly show that a full harmonisation of exposure assessment aiming at using identical approaches is impossible. This constraint can easily be understood when comparing different sectors:

Establishing food safety e.g., with regard to contaminants needs an entirely different approach as compared to cosmetics safety e.g., to which humans are intentionally exposed. Plant protection agents being intentionally biologically active need a more precise exposure assessment than low hazard chemicals. An important source of differences in exposure assessment, from a practical point of view, relates to the way in which exposure of the final consumer is determined (e.g. use of mean exposure; use of standardised consumption patterns such as the FAO food balance sheet; treatment of specific sub-groups of consumers/specific at-risk groups). For the assessment of the environmental exposure there are similar practical differences, e.g. using monitoring information or estimates from model calculations.

The major objective of harmonisation therefore should be to have for all areas a compatible assessment leading to results most appropriate for the required level of risk assessment. Where different approaches to exposure assessment have to be taken, the primary question is whether exposure assessment is carried out at similar levels with regard to safety considerations. Refined national exposure assessment for consumers and the environment should be increasingly used to be combined to the EU-level.

There is a need for a common and precise "language" in exposure assessment ("semantic homogeneity" both in the data utilised and in the approach taken for the assessment). While obvious to the experts commissioned for doing the assessment, there is a need to communicate to the users the nature and meaning of the assumptions made and of the approach taken and how these would influence the interpretation of the results provided.

2.2 Use of Scenarios

Essentially in all approaches to exposure assessments as a case-by-case exercise evaluative or interpretative scenarios are used. Depending on information availability and final assessment (deterministic or probabilistic), they are undergoing improvements with the advancement of scientific understanding and data availability. Details on scenario building concept are given in the following reports on specific Scientific Committees. In principle, all scenarios do not reflect one specific local situation, but have the objective to be representative of mean, typical or most sensitive situations in a region or throughout the European Community.

Nevertheless, when a standard scenario is used, it is currently still difficult to determine its representativeness. Such scenarios are either build on available data or are the basis for collection of data. Therefore, attention should be given to the comparability of data collected in different contexts. An important issue is the identification of the database utilised and the availability of this database to other potential users.

2.3 Integrated Exposure Assessment

An integrated exposure assessment is important in addition to the specific ones, e.g. via food, since the total exposure of humans and the environment have to be considered in risk assessments. The exposure assessments by the scientific committees follow the respective legislation and it is only the chemical substances legislation/Directives which follow this integrated approach. The others only consider a certain use of chemicals, e.g. in plant protection or a pathway, e.g. in food safety. The same chemicals, however, may be used for other purposes or exposure may be by other media than those in the focus of legislation. A realistic description of the exposures of consumers and environment requires a stratification of input-data in relation to ways and means of primary production and primary products and the full life-cycle of the product. This means that this rigid sectorial scheme is not only un-realistic, but also limited in its ability to cope with exposures in a timely and efficacious way. Where a given chemical is used in different sectors or exposure is via different media, important pathways may be overlooked resulting in a problem from the consumer point of view.

A fully "integrated" exposure assessment may be difficult to be carried out in practice. Sources of difficulties may include for instance: the provision of an appropriate figure of all relevant pathways (difficulties for the assessors specialised in one sector to identify all relevant pathways in other sectors); the potential variability of such pathways; the treatment of specific groups of consumers/at-risk groups (difficulties in determining specific exposure rate for particular groups; percentage of the particular groups in the population); the differences in metabolic pathways vs. different exposure routes.

Nevertheless, when different pathways (routes of transmission) can be envisioned, there is a need to take all of these into consideration. Interaction between the different scientific committees and regulatory agencies in this regard is an important issue (e.g. sequentiation of pathways; where the competence of a committee stops, another committee should take over the assessment in a concerted approach).

2.4 General Issues Related to Data Availability

For economical reasons exposure related data are usually estimated or measured following the requirements of the usually formalised steps in the sequence of assessment. At the higher levels of assessment monitoring data provide a crucial tool.

There is a need to improve the comparability of data critical for the conduct of exposure assessments (data sets should be homogenous in the sense, that their comparability has been established. Harmonisation should be at least to the extent, that data provided should follow a similar format and giving minimum information for the requested purpose.)

To that aim, there is also a need to study and experimentally implement EU-wide surveillance systems to generate "minimal homogeneous data sets". It is unrealistic to consider average exposures to an agent to be assessed for the whole European Community. Even the extrapolation of data in a given geographical area to the entire Union is as inappropriate.

A "probabilistic" approach is essential to represent the complexity of real situations and taking into account variability and uncertainty. Although complicated, a probabilistic treatment of exposure information improves the comprehension of the consumer in risk communication. It is recognised that the development of this approach will rely on the collection of more, accurate, quantitative data. While such data collection will in many cases be dealt with at member state level, common guidance for the data collection should be established at EU-level in order to facilitate data exchange and comparability.

Apart from these issues, following experience of exposure assessments, there are exposure related problems, which are not systematically dealt with and consequently no reliable data are available. One of these issues is the accumulation of contaminations by recycling of technical and biological materials, which may lead in the long-term to an increased exposure without being attributable directly to use in a technological sector.

On the other hand, for the trend assessment of exposure, banked environmental and human specimen provide an important tool which has not been used so far according to its potential.

3. EXPOSURE ASSESSMENT IN SCIENTIFIC COMMITTEES

3.1 SCIENTIFIC COMMITTEE ON FOOD

Overview of current practices for exposure assessment within the Scientific Committee on Food (SCF)
The SCF currently uses a stepwise procedure for long term exposure assessment.

3.1.1 Screening tools

The first step does not correspond to an intake assessment but much more to a crude estimate which is used for a screening purpose. In practice, in the field of food additive, the so called “budget method” is used to determine if a concerned substance can be ingested above the Acceptable Daily Intake (ADI). The assumptions are that the additive is used at the maximum authorised level and that a consumer is eating on a regular basis, the maximum quantity of food which can be physiologically eaten (1.5 kg of solid foods and 1.5 litre of beverage). This method is also used by both the Joint FAO/WHO Expert Committee for Additives and Contaminants (JECFA) and the Codex Committee on Food Additives and Contaminants.

In the field of flavouring substances, the so called “per capita time ten method” originally designed by US FDA is currently used by SCF and JECFA. This method consists to divide the total annual production of a substance by the number of consumers possibly exposed and to multiply this quantity by 10 as a safety factor link to the uncertainty of the distribution within the population.

In the field of veterinary drugs, the establishment of maximum limits at an international level assumes the consumption of large amounts of animal derived products (1.5 l of milk and 600 g of solid food per day on a regular basis).

3.1.2 Exposure assessment

The second step which corresponds properly to an exposure assessment consists to use two types of data : food consumption and food contamination data.

Food consumption data

At an international level, 2 sources of information are available for food intake data i.e. the FAO/WHO gems food program and the report of the E.U. Scientific Co-operation (SCOOP 4.1). The exposure assessment from these data correspond to a crude estimate which is managed to overestimate the mean exposure. Nevertheless, the exposure assessment for high percentiles of the distribution curve or special groups at risk is not possible using these data. The other possibility consists to analyse and possibly to combine national data. These data, despite the lack of reliability of the methodology of collection are recognised to be more accurate. In general, the exposure assessment is compare to an Acceptable or Tolerable intake expressed in mg/kg body weight. In those cases, the mean body weight is assumes to be 60 kg for an adult.

Food contamination data

Only national data are available. Those should be ideally based on recent individual results, randomly selected and representative. In certain cases, the complete distribution curves of contamination in foodstuffs is not available and it could be necessary to combine data from different sources i.e. from both individual and pooled samples or from different countries of a region. The combination of these data permits to obtain a mean contamination level, weighted as a function of the number of samples.

3.1.3 Quantification of the exposure[1]

The third step consists to quantify the exposure using the distribution of both consumption and contamination curves for stochastic modelling. As described previously, only national data provides distribution curves for food consumption which can be crossed with contamination results.

Regarding contamination curves, when a distribution based on individual samples is available, it is possible to use it directly in a Monte-Carlo simulation. When available contamination data are from different sources, assuming a lognormal distribution of contaminants, it is then possible to derive the standard deviation of the mean by a log-transformation of the available values. A lognormal curve characterised by the mean and the standard deviation can be used to build a theoretical curve of distribution to input in a Monte Carlo simulation. It must be noted that using this kind of statistical derivation increase the uncertainty of the exposure assessment.

[1] At that time, the SCF had never formely adopted opinion using this methodology

3.1.4 References

- Food consumption and exposure assessment of chemicals, Report of a FAO/WHO consultation, Geneva, Switzerland 10-14 February 1997, WHO/ FSF/FOS/97.5, WHO, Geneva (1997)
- Methodology for exposure assessment of contaminants and toxins in food. Report of a joint FAO/WHO Workshop, Geneva, 7-8 June 2000.

3.2 SCIENTIFIC COMMITTEE ON PLANTS

3.2.1 Mandate/Context of exposure assessments of the SCP

The mandate of the SCP covers scientific and technical questions relating to plants intended for human or animal consumption, production or processing of non-food products as regards characteristics liable to affect human or animal health or the environment, including the use of pesticides. The SCP therefore provides advice on related scientific issues, performs risk assessments (including exposure assessments) and/or reviews risk assessments done by member states in two areas:

a) relating to an EU decision on the placing on the market of a genetically modified organism in the context of directive 90/220
b) relating to an EU decision on the inclusion of an active substance (of a plant protection product = PPP) into Annex I of directive 91/414

So far, the SCP has been involved prior to such decisions. The mandate, however, covers also scientific issues which arise after a decision under the mentioned directives. The SCP works on the basis of those directives (i.e., the data requirements and decision-making criteria established by them) and uses - as far as possible and where they exist - harmonised or established procedures/methods which are also used by the relevant regulatory authorities.

3.2.2 Exposure assessments of the SCP

3.2.2.1 Plant Protection Products

It should be kept in mind that the following summary is based on the high level of harmonisation and standardisation already achieved for chemical plant protection products (PPPs). For PPPs with a micro-organism as the active agent, methods of exposure assessment are less far harmonised, and there is a high need to perform case-by-case assessments based on the specific biological properties and use of the active agent.

Human exposure

From the use of plant protection products (PPPs), exposure of humans may occur from

1. preparing and performing the application (mixer/loader, applicator, re-entry worker and possible bystanders)
2. residues in treated plants (consumers of food)
3. residues in the environment (e.g., groundwater as drinking water, in air).

Routes of exposure and uptake include contact and inhalation (farm workers, bystanders) and oral (consumer, from residues). All routes are addressed during the evaluation of a PPP and its active substances (including metabolites).

re: 1) Main factors driving the level and type of exposure of ***applicators, re-entry workers and bystanders*** are the ***use conditions*** of a PPP:

- application rate and frequency
- type of formulation (liquid sprays cause different exposure than applying granules)
- crop to be treated (spraying in orchards or greenhouses causes higher operator exposure than spraying a low cereal crop)
- method of application (which is partly but not completely determined by the previous two points. Hand-held knapsack sprayers are to be distinguished from several tractor-mounted types of equipment).

Those important input data for the exposure assessment are part of the data requirements and are thus ***known***. Applicator and bystander exposure through dermal uptake and inhalation can then be assessed either by using established standard scenarios (deterministic models based on experimental data; like the Predictive Operator Exposure Model [POEM]) or by specific measurements of external and/or internal exposure with the PPP in question being used as intended (i.e., simulating the real exposure). For re-entry exposure in a previously treated crop, estimations and/or measurements (including field data) of dislodgeable residues are used in the calculation.

re: 2) For ***consumer*** exposure, again the use conditions are important and known input data. They are used to determine (in ***specific studies***, representative for the treated crops and regions/climates) the uptake of a PPP by the treated plant, its metabolism in the plant and during processing (here, established processing factors may also be used). Where relevant, feeding studies with treated plants and e.g. lactating cows are performed to assess animal metabolism and residues in food of animal origin. Thus, the possible concentration and identity of ***residues in food is determined*** and used in the human health risk assessment, both long-term (setting of maximum residue limits [MRL's]; comparison with the acceptable daily intake [ADI]) and acute (comparison with Acute Reference Dose [ARfD]). The amount of food (and hence, residues) taken up by consumers is estimated by applying typical diets (regional, national, certain groups of the population) which vary between countries (e.g., the amount of olive oil in a mediterranean and a scandinavian diet). Some of those diets are also used by FAO/WHO. Diets are probabilistic data, being statistically derived from food surveys. Further, standard scenarios (food eaten per day, body weight) exist for specific consumer groups (adults, children) in different countries.

re: 3) Residues in **environmental compartments** may also be relevant for the human health assessment. This applies mainly to soil and groundwater (while the air path is assessed for local inhalative exposure of operators and bystanders, the assessment of long-range transport of PPP's in air is still under development).

Persistent residues in **soil** might be taken up by subsequent crops and thus enter the food chain. This is assessed by studies on the fate of the PPP in soil and also the residue trials (see above).

Residues which enter **groundwater** may cause exposure to the consumer of drinking water. Hence, the leaching behaviour of active substances and their metabolites is assessed in a tiered procedure, starting with laboratory studies in small soil columns, progressing to computer models and finally lysimeters which simulate field conditions. As to the computer models, several are in use within the EU. They have been evaluated by FOCUS (Forum for the Coordination of pesticide fate models and their use; report to be published in 2000). They are mechanistic models, i.e. they quantitatively simulate the fate processes as they occur in the environment. They use data on soil types and long-term weather data, hence the model output is probabilistic and may be regionalised (e.g., using Geographic Information Systems GIS). Many years of experience with some of those models in conjunction with lysimeter data has greatly contributed to their being widely accepted.

Environmental exposure

When PPP's are applied, all three environmental compartments (air, soil, water) may be exposed, depending on use conditions and the physical-chemical properties of the substances (e.g., vapour pressure and water solubility which drive the partitioning between those compartments).

Air: Volatile and UV-stable substances are most likely to partition into the atmosphere. Such substance-inherent properties are determined by laboratory studies. However, the assessment of exposure via the air path and possible effects is still under development in the scientific community. Issues include persistence, long-distance transport, influence on the ozone layer, global distillation, and bioaccumulation.

Water: For leaching into groundwater, see above. For surface water, routes of entry from the use of PPP's include spraydrift, surface runoff, drainflow, and groundwater. Of those, the first two are currently the focus of the assessment. All are driven by the use conditions of a PPP as well as the fate and distribution in the environment (degradation in and above soil, adsorption to soil particles, water solubility, leaching behaviour), all of which are known from standard tests as part of the data requirements. In addition, local conditions are important especially for runoff and may be less well known: soil types, slopes, intensity of rainfalls, time between last application and first (erosive) rainfall, etc.

The amount that is transported offsite via the different routes is then assessed by different means:
Spraydrift: Germany established standard values for the amount (percentage) of spraydrift to be expected from typical application equipment in the main crop types. The so-called 'Ganzelmeier tables' are based on extensive, standardised field experiments of which the 95%iles were initially chosen as a reasonable worst case. Other percentiles may be applied. For the receiving water bodies, standard scenarios exist in member countries.
Mechanistic computer models are increasingly applied to estimate the concentration of a substance and its metabolites over time in surface waters, including dilution and repeated applications.

Recently, probabilistic approaches are being put forward. These include regionally specifying the dimensions of surface water bodies and the probability of a treated area to be bordered by surface waters.
Runoff: This assessment is less standardised than the spraydrift one, possibly due to the additional driving factors. Standard factors are often applied in a screening step. Mechanistic computer models exist but may require adaptation to European or regional conditions. Validation seems to be important for their acceptance.
Drainflow: This assessment is recently starting to receive more attention. It requires a leaching component which can probably be adapted from the groundwater assessment.

Soil (terrestrial compartment): In the terrestrial compartment, several sub-compartments and various exposure routes must be distinguished:

- within the soil
- on the soil surface
- on plants

When a PPP is applied, terrestrial organisms can be exposed depending on where they live:

- within the soil, via soil particles with absorbed PPP (contact, oral uptake)
- on the soil surface, via soil particles or plants (contact, oral uptake) and by direct contact/uptake (spray liquid, granules)
- on plants, via contact and oral uptake of plant material or other animals, or by direct contact/uptake (spray liquid, granules).

This multitude of cases is addressed in different ways. Often, for non-target invertebrates, the exposure is not assessed separately from the effects but is included in the effects testing in a quantity and way which mimics more or less closely worst cases of the intended use conditions (e.g., the PPP is mixed into soil, or onto a surface, which is then used directly in a toxicity test.) Thus, the effect of the combined, overall exposure is often measured directly, without quantifying the respective contributions of the different exposure routes. In addition, effects of direct application of spraying liquid to the arthropods are often measured.

For birds and mammals, however, the assessment is similar to the one for human health, using the residue levels in/on food items (treated plants, granules, drops of spraying liquid) and estimations of daily food uptake (from general biological/ecological data).

Recently, probabilistic approaches are being put forward especially focused on birds and mammals. These include the use of field observations on the time spent for foraging in treated crops/orchards, in order to specify the likelihood, type and duration of exposure.

broad area	*who is exposed*	*by what (main) route*	driving factors	*quantitative? standard models?*
toxicology - humans	mixer/loader operator bystander	contact, inhalation	- use conditions: - formulation type (granular vs liquid) - application technique - application rate and frequency	- use conditions known - operator exposure models exist (derived from measurements) - can be replaced by specific studies
toxicology - humans	consumer	residues in food	- application rate/frequency - uptake by plant - metabolism - influence of processing - regional/national diets	- use conditions known - uptake, metabolism and processing measured - diets exist for several groups
environment – groundwater	humans by drinking water	oral (drinking water)	- use conditions - degradation and leaching in soil	- use conditions known - tiered testing schemes, include computer modelling widely harmonised in the EU by FOCUS; generally validated by lysimeters
environment	terrestrial organisms	contact, oral (depending on species and crop)	- use conditions - crop type/stage - uptake by plant - fate in the environment - activity of non-target species	- use conditions known - tiered testing schemes - often, toxicity tests designed according to use conditions, to simulate real exposure
environment	aquatic organisms	spraydrift, runoff, drainflow	- use conditions - crop type/height - weather - soil - mobility/degradation	- use conditions known - standard models for spraydrift; less standardised for runoff and drainflow - computer models evaluated by FOCUS

3.2.3 Genetically Modified Organisms

The Scientific Committee on Plants assesses genetically modified plants in the context of Directive 90/220/EEC. The objective is to identify and evaluate potential adverse effects of the GMO, either direct or indirect, immediate or delayed, on human health and the environment which the deliberate release or placing on the market of GMOs may have. Potential adverse effects of GMOs may include:

- possible effects on human health resulting from potential direct and indirect interactions of the GMO and persons working with, coming into contact with, or in the vicinity of the GMO release(s);
- possible effects on animal health and consequences for the feed/food chain resulting from animal feed use of the GMO and any products derived from it.

It should be noted that the safety assessment of GMOs in (human) ***food*** falls under the Regulation on Novel Foods and Novel Food Ingredients (EC No. 258/97), and, thus, is not among the tasks of the SCP but of the SCF.

Exposure assessments for GMOs are not (yet?) formalised to the extent of assessments of chemical PPPs. Rather, the assessments of GMOs are to a large extent case-by-case, as is the case also for PPPs based on micro-organisms which seems to be a notable similarity (both involving organisms rather than chemicals).

For GMOs, exposure assessments are mainly driven by the following factors:

- species of the GM plant; its uses (*e.g., is the GM plant used for industrial purposes like starch or oil production, or for feed/food production*) and its biology (*e.g., is it visited by pollinating insects or eaten by non-target species; does it form hybrids with native plants; is it likely to'escape' the agricultural management, become established in the environment and become a competitor of native species; etc*.)
- identity, natural origin and location of the incorporated sequences (*to assess the potential for gene transfer from plant material to microbe(s) in the human or animal digestive tract and to soil micro-organisms; i.e., to determine potential exposure routes other than via the GMO itself*)
- identity of expressed products, level of expression in different parts of the plant, and its stability in digestive tracts or in processing (*this will depend on the specific crop, its uses, and if any parts of it will be processed further or remain in the environment after harvest. For example, processing might destroy the expressed products, or only plant parts without expressed GM products might be used. Stability in digestive tracts may increase the potential for uptake by other organisms. Environmental exposure could occur to soil organisms (e.g. earthworms, micro-organisms; especially when plant material is incorporated into the soil after harvest), non-target arthropods (including pollinators, beneficial arthropods), grazing birds and mammals or, less often, the aquatic environment*.)
- information on biology/behaviour (including consumption of GM plant material) of organisms living in the vicinity of GM plants, or being fed with it or products derived from it.

As to the **effects assessment**, a wide variety of information is used, again depending on the particular case. For example, where the GM product is a substance otherwise used in a plant protection product, it would be assessed like PPP residues (see above). Else, the assessment would largely follow the approach of *substantial equivalence*. This principle has been developed for food/feed assessments within the OECD and endorsed by FAO and WHO. Determination of substantial equivalence comprises the molecular characterisation of the new food source, the phenotypic characterisation, and the compositional analysis of the new food *compared with a conventional counterpart (the non-modified plant)*. Where substantial equivalence can not be established, a range of toxicity and/or feeding studies, designed according to the nature and characteristics of the newly expressed substances, would be applied as in a conventional toxicological assessment.

For the environment, the type of studies and test species again depend largely on the nature of the GMO and its modification. Often, study designs as used for a PPP assessment are equally useful. A concept similar to that of substantial equivalence is often applied, by comparing e.g. in semi-field or field studies the influence of both the GM plant and the non-modified plant

on behaviour and ecological performance of the non-target species, without establishing single toxicity values of newly expressed proteins on test species. However, where such data exist (e.g., where the GMO expresses a known PPP substance), risk assessments follow the same principles as for PPPs.

3.3 SCIENTIFIC COMMITTEE ON COSMETIC PRODUCTS AND NON-FOOD PRODUCTS INTENDED FOR CONSUMERS

3.3.1 Exposure of the Environment to Cosmetic Products

Pathways to be considered regarding environmental exposure are via sewage treatment systems, where only persistent compounds might result in substantial concentrations, and direct release into surface waters upon swimming. Solid waste may also be a source for environmental release of certain products. So far, cosmetic products are not dealt with systematically as regards environmental exposure, they are dealt with only in case-by-case basis and then are handed over to the SCTEE. One example of exposure assessment of cosmetic products is the occurrence of musk compounds in aquatic systems. Emissions from production into the environment are not considered by the SCTEE.

3.4 SCIENTIFIC COMMITTEE ON TOXICITY, ECOTOXICITY AND THE ENVIRONMENT

CSTEE exposure assessments

Since the Scientific Committee for Toxicity, Ecotoxicity and the Environment (CSTEE) was formed late 1997 the committee has done just a few risk assessments. The compounds dealt with are chemicals that are not regulated and therefore the databases are often very limited and it is not possible to force the producer/user to deliver data. The committee also has a very wide responsibility and has, in most cases, to take both the human health and the environment into account. For the exposure assessment this imply that the distribution of the substances should to be followed until they are broken down to harmless products. This is normally not possible, but the assessments have to be performed on a case-by-case basis.

A major task for the CSTEE has been to review reports from other sources, and most of these reports deal with risk assessments, including exposure assessments. Today a large number of reports are sent to the committee from the work with risk assessments of existing substances for reviewing.

Exposure assessment for existing substances

The basis for risk assessments of existing chemicals is laid down in the Council Regulation (EEC) 793/93, where it is mentioned that

- “in order to ensure the protection of man, including workers and consumers, and of the environment, it is necessary to carry out at Community level a systematic evaluation of the risks involving existing substances appearing in the Einecs”.

A description of the risk assessment procedure is given in the Commission Regulation (EC) No 1488/94. Exposure assessment is dealt with in articles 2, 3, 4 and 5, where the following texts can be found:

- “'Exposure assessment' is the determination of the emissions, pathways and rates of movement of a substance and its transformation or degradation, in order to estimate the concentrations/doses to which human populations or environmental spheres (water, soil and air) are or may be exposed”.
- “In conducting an exposure assessment, the rapporteur shall take into account those human populations or environmental spheres for which exposure to the substance is known or reasonably foreseeable in the light of available information on the substance, with particular regard to manufacture, transport, storage, formulation into a preparation or other processing, use and disposal or recovery”.
- Risk assessment for human health includes “exposure assessment for whichever human population-group (i.e. workers, consumers or man exposed indirectly via the environment) is exposed or likely to be exposed to the substance”.
- Risk assessment for environment includes “exposure assessment for the environmental spheres exposed or likely to be exposed to the substance”.

In Annex 1 of the same regulation (1488/94), further details are given for the exposure assessment:

- “3. EXPOSURE ASSESSMENT
  3.1. An exposure assessment shall be conducted for each of the human populations (workers, consumers and man liable to exposure indirectly via the environment) for which exposure to the substance is known or can reasonably be foreseen. The objective of the assessment shall be to make a quantitative or qualitative estimate of the dose/concentration of the substance to which a population is or may be exposed. Such estimation shall take account of spatial and temporal variations in the exposure pattern.
  3.2. In particular, the exposure assessment, where appropriate, shall take account of:
  (i) adequately measured exposure data;
  (ii) the quantity in which the substance is produced and/or imported;
  (iii) the form in which the substance is produced and/or imported and/or in which the substance is used (e.g. substance itself or as component of a preparation);
  (iv) use pattern and degree of containment;
  (v) process data, where relevant;
  (vi) physico-chemical properties of the substance including, where relevant, those conferred by the process (e.g. aerosol formation);
  (vii) breakdown products and/or transformation products;
  (viii) likely routes of exposure and potential for absorption;
  (ix) frequency and duration of exposure;
  (x) type and size of specific exposed population(s) where such information is available.
  3.3. Where adequately measured, representative exposure data are available, special consideration shall be given to them when conducting the exposure assessment. Where calculation methods are used for the estimation of exposure levels, adequate models shall be applied. Relevant monitoring data from substances with analogous

use and exposure patterns or analogous properties shall then also be considered.
3.4. If a substance is contained in a preparation, consideration of exposure to the substance in that preparation shall be necessary if the latter is classified on the basis of the toxicological properties of the substance in accordance with Council Directive 88/379/EEC (1), or if there are other reasonable grounds for concern."

In Annex 2 of 1488/94 the risk assessment for human health effects is described and the regarding exposure the following text is given:

- "2. EXPOSURE ASSESSMENT
  If risk characterization has to be conducted in accordance with Article 4, it shall be necessary to determine the known or the reasonably foreseeable conditions of use."

In Annex 3 of 1488/94 the environmental risk assessment is described with the following text for the exposure assessment:

- "3. EXPOSURE ASSESSMENT
  3.1. The objective of the exposure assessment shall be to predict the concentration of the substance which is likely to be found in the environment. That concentration is known as the predicted environmental concentration (PEC). However, in some cases, it may not be possible to establish a PEC and a qualitative estimation of exposure would have to be made.
  3.2. A PEC or, where necessary, a qualitative estimation of exposure need only be determined for the environmental spheres to which emissions, discharges, disposal or distributions are known or are reasonably foreseeable.
  3.3. The PEC or qualitative estimation of exposure shall be determined taking account of, in particular and if appropriate:
  (i) adequately measured exposure data;
  (ii) the quantity in which the substance is produced and/or imported;
  (iii) the form in which the substance is produced and/or imported and/or in which the substance is used (e.g. substance itself or as component of a preparation);
  (iv) use pattern and degree of containment;
  (v) process data, where relevant;
  (vi) physico-chemical properties of the substance, in particular melting point, boiling point, vapour pressure, surface tension, water solubility, partition coefficient n-octanol/water;
  (vii) breakdown products and/or transformation products;
  (viii) likely pathways to environmental spheres and potential for absorption/desorption and degradation;
  (ix) frequency and duration of exposure.
  3.4. Where adequately measured, representative exposure data are available, special consideration shall be given to them when conducting the exposure assessment. Where calculation methods are used for the estimation of exposure concentrations, adequate models shall be applied. Where appropriate, on a case-by-case basis, relevant monitoring data from substances with analogous use and exposure patterns or analogous properties shall then also be considered."

For the classification, packaging and labelling of new substances similar texts can be found in the Council Directive 67/548/EEC, Council Directive 92/32/EEC, and Commission Directive 93/67/EEC.

Technical guidance document

To support the practical work with risk assessments under the above mentioned Directives, European Chemicals Bureau (ECB) at the JRC in Ispra in co-operation with member states, have produced a Technical Guidance Document (TGD). The existence of this document also harmonise the methods used by member states in the risk assessment work and make the final reports more easy to compare. The TGD has two major sections, one on human health and one on environment, and smaller chapters describing QSAR, use categories, emission scenarios and the risk assessment report format.

According to the TGD, the exposure assessment in the human health risk evaluation shall predict a reasonable worst case but also consider upper estimates of the extreme use and reasonably foreseeable misuse. “It may, however, often be useful initially to conduct an exposure assessment based on worst case assumptions, and to use default values when model calculations are applied.” Whenever possible, high quality and relevant measured data should be used in the risk characterisation. The procedure of deriving an exposure level by applying model calculations should be made transparent, and it is essential to use expert judgement to check the realism of the exposure value derived from a model, particularly if default or “reasonably worst case” values have been used. Where exposure levels have been determined on the basis of measured and on the basis of modelling, the values obtained should be compared. If the differently derived values are not in agreement, an analysis and a critical discussion of the approaches used is necessary in order to identify the cause of the divergences. Models for the prediction of exposure in different scenarios (workplace, consume, indirect exposure via the environment) are also described.

The risk assessment for the environment is based on a comparison of predicted environmental concentrations (PEC) and predicted no-effect concentrations (PNEC). PEC values are to be derived on three different geographical scales: local, regional, and continental. The first is based on a generic local environment, which is a hypothetical site with predefined environmental characteristics (a so called “standard environment”). The region is also a generic, but larger (40 000 km^2), environment, while the continent is Europe. For many existing chemicals there are measured concentrations that can be used in the exposure assessment, but for others, and for new substances, model predictions are the only way to determine the exposure. To run the models some basic information on the chemical under evaluation is needed, and also knowledge about production/use volumes and use pattern. There are default values for releases from different processes in the TGD, but all available specific information for the chemical is useful. The fate (transport and transformation) of the released chemical can also be predicted by models. There is also a model for the behaviour of a chemical in a wastewater treatment plant in the model package (EUSES) in the TGD.

During this work the CSTEE has observed some difficulties in the exposure assessments and has formed a work group to highlight these and to try to suggest possible solutions. The committee has also formed a working group to develop a method for risk assessments for the terrestrial environment, something that has been lacking so far. These two activities will be briefly described, but first a couple of risk assessments done by the committee, where the exposure assessments were difficult, will be described.

Exposure assessments performed by the CSTEE

One of the first tasks the CSTEE was given was to assess the risks connected with the use of plasticised PVC in children's toys, especially teethers. It is difficult to mimic what is happening in the child's mouth when it is sucking and biting on these items and the CSTEE adopted a worst case scenario and used the high exposures indicated by a Danish investigation. This resulted in an unacceptable low margin of safety (MOS<100) for several of the actual phthalates and some member states banned the use of some, or all, of these compounds in toys.

Phthalates are used in many materials and the assessment of other exposure routes is difficult. The use of a fraction of the TDI for the route via toys, as is suggested in a CEN work group assessing chemicals in toys, was not accepted by CSTEE. Available data on other exposures were described, but not used in the MOS calculation.

An *in vivo* study verified the high releases of plasticisers from teethers, and a new CSTEE assessment gave similar result as the first one. The consortium that performed the study used probabilistic methods, which gave a more favourable risk situation. The reason was that there was one individual that produced high release results. The high release rate has later been observed also in other studies.

When the use of phthalates is restricted there is a possibility that other plasticisers will be used. Two of the possible groups of compounds are adipates and citrates, and the CSTEE was asked to do risk assessments of these two groups. The data base for release of these substances from polymers was very limited, as well as the data toxicity data. The conclusion of the committee was that it was not possible to do a proper risk assessment for the adipates and citrates due to limitations in the available data bases, but a couple of the individual substances were regarded as unsuitable plasticisers in toys due to their sensitising potentials.

CSTEE experiences from exposure assessments.

During the review work of risk assessments delivered to CSTEE, a number of difficulties have been identified. To bring this experience back to the risk assessors, the committee has formed a working group to report the observations and, if possible, to suggest improvements in the procedure. Some areas where difficulties have been seen are listed below, and for some of them there may also be reasons to see if there is a need for harmonisation between the different scientific committees.

1. Basic data
    a. Production volumes
    b. Use pattern and volumes, including content in goods
    c. Export and import
    d. Substance properties
2. Measured data
    a. Availability
    b. Representativity
    c. Accuracy

3. Predicted data
    a. Emissions and emission factors
    b. Degradation rates
    c. Model limitations
4. General difficulties in the exposure assessment
    a. Speciation and transformation
    b. Extreme exposure situations
    c. Estimations of exposure from diffuse sources
    d. Formation/degradation
    e. Hot spots
    f. Units
    g. Steady-state levels
    h. Other sources, high natural background
    i. Mixtures
    j. Bioavailability
    k. Lifecycle emissions

Especially for the work with risk assessment of existing substances it is also essential that the comparisons between predicted data and measured data are done carefully and that the results are brought back to the model developers for possible improvements of the models.

The work group has just started its work and will work on a report along the above given outline and the work is expected to be finish by the end of 2000.

The CSTEE work group on "Scientific basis for the hazard and risk assessment of chemical substances for the terrestrial environment".

The committee has also recognised the lack of guidance documents for the risk assessment of chemicals in the terrestrial environment and thus formed a work group to produce such a document. A draft is available and the chapter on the exposure assessment is part of this report. This chapter deals with the transfer of pollutants to air, soil, vegetation and animals and also with the fate of the chemicals in those compartments. The possibilities to estimate the exposures of different organisms using predicted and measured data is also discussed. The first discussion in the CSTEE of this report is expected in the early autumn.

3.5 BIOCIDES

The Biocides Directive has not been yet fully implemented. Considering the range of sectors where they are used, that identical chemicals are used as biocides and for other purposes, an appropriate exposure assessment, both for consumers and the environment, will only be possible following the above discussed integrated exposure assessment. It is also important from the very beginning to include data acquisition allowing for a probabilistic interpretation and evaluation.

3.6 HUMAN AND VETERINARIAN MEDICINES

Consumer exposure to veterinarian medicines is dealt with by the Scientific Committee on Food . For environmental exposure there exists a detailed guideline which is not elaborated

here (no representation in Working Group). It considers appropriately the specific requirements resulting from this sector. For human medicines human exposure is not relevant in the context of this report, whereas exposure of the environment is considered similarly to veterinarian medicines.

4. CONCLUSIONS

Exposure assessments are conducted in different legislative/regulatory frameworks. There is a range of ultimate goals of assessments for consumers and the environment, which also result from different technological sectors of the use of chemical substances as well as from the consideration of basic differences in hazard potentials for groups of substances. This range of conditions are reflected in the work of the scientific committees. It would be difficult, and even is not desirable, to fully harmonise their work to achieve identical exposure assessments.

The different scenarios applied by the committees are aiming at the identification of worst case, realistic worst case or even exposure for average consumers. This information has to be transferred to the risk assessment and included in the final risk communication.

It is also obvious that all committees are not expected to look at the integrated exposure. This may end up in an underestimation of the total exposure if a certain compound has several applications, and in extreme cases the acceptable exposure can be "used" by several committees. Methods for improved integration of different exposure pathways would therefore be welcome.

Exposure assessments should take available *measured data* of acceptable quality into account. The availability of such databases should be improved. It would also be advantageous if monitoring programmes could be harmonised to increase comparability. The often rigid structure of these programmes also makes it difficult to include additional substances or additional parameters. Risk assessment is a tiered process, and if in the first tier a reason for concern is identified for a certain exposure route, it is very valuable if this can be validated by either representative or at least strategic measurements.

To improve the possibility to do *integrated exposure assessments*, the definition of a minimal data set for this purpose would be very useful. The implementation of a EU research programme in this field could prove fruitful. This data set would also cover diffuse sources, such as chemicals in the technosphere including recycled materials. It is also essential that the experiences from the presently ongoing risk assessments (e.g. for existing chemicals) are fed into such a programme.

The *scenarios* used in the different exposure assessments are usually improved according to the development of knowledge. Considering the increasing importance of stochastic and more specific assessments, the development of additional scenarios to cover specific subgroups (e.g. children), endangered ecosystems, regional differences.

The methodology to deal with data uncertainties, their representativity, validation procedures, minimum data requirements and their role in deterministic and stochastic approaches is the crucial basis for valid exposure assessments.

5. RECOMMENDATIONS FOR HARMONISATION

- It is recommended to focus the harmonisation efforts in exposure assessments to achieve consistency in principles and methodologies and to improve harmonised data acquisition and quality.

- Implement research programmes for EU wide surveillance systems to generate minimal data sets for integrated exposure assessments, also to be used in the sectors.

- In order not to overlook important pathways of exposure, it is suggested that in exposure assessment within the sectors an integrated approach is at least considered.

- It is important that in the exposure assessment area a homogeneous language (semantic homogeneity) is achieved both in respect to data, their interpretation and assessment concepts (tiered approaches, etc.).

- With advances in the use of stochastic procedures, a consistent development of scenarios representing specific groups of population, endangered ecosystems, regional and national differences and dealing with uncertainties is inevitable.

APPENDIX 3

REPORT ON

QUANTITATIVE RISK ASSESSMENT OF CHEMICALS IN

RELATION TO HUMAN HEALTH

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7a The use of biomarkers as a bridge between exposure assessment, toxicokinetics and toxicodynamics
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10. APPENDIX 1 (Examples of quantitative risk assessment for threshold toxicity)

This paper has been prepared in relation to risk assessment for chemicals present in food, beverages and the environment. Because of differences in terminology between different areas of risk assessment, a glossary of the terms used has been given at the end of this document. This working paper will describe the approaches adopted traditionally for risk assessment of environmental chemicals and will propose methods of quantitative risk assessment.

It should be recognised that with very few exceptions the data available for quantitative risk assessment will not be closely related to the exposure scenario that has given rise to the request from risk managers for such a quantitative estimate. In consequence, there will be a number of uncertainties in the quantitative risk estimate, most of which cannot be clearly defined or quantified. In addition, quantitation will require the application of a mathematical model to the available biological data, and the selection of the mathematical model will also have a potential impact on the quantitative risk estimate.

Inherent in any quantitative risk assessment is the assumption that the risk is related to the dose. In consequence it is possible to separate the concept of the hazard associated with the chemical (ie the inherent property of the compound) and the risk arising from exposure. Whilst this is true for the majority of toxic effects, it is possible that certain reactions, for example immunologically-mediated idiosyncratic reactions, may not be clearly related to the dose. In addition, other risks for which the author does not have expertise, for example, microbiological risks or respiratory sensitisation and occupational asthma, may be associated with a less clearly defined dose-response relationship.

1. INTRODUCTION

Traditionally risk assessment procedures have adopted one of two approaches.

- quantitative risk assessment involving the use of the dose-response relationship in order to quantitate the magnitude of any risk associated with particular levels of exposure,
- "safety assurance" involving the assessment of the dose-response relationship in order to define the threshold below which an adverse effect would not be detected, and then to estimate the exposure threshold for sensitive human subjects.

Each of these approaches requires information in four areas (WHO 1999a):

- hazard identification
- assessment of human exposure to the chemical
- dose-response characterisation for the hazard and risk assessment
- risk characterisation

Hazard identification is the recognition of a potential adverse effect, of relevance to human health, which may be associated with exposure to the chemical. The hazard is an inherent property of the chemical. A single chemical may represent more than one hazard, and risk assessment may be required for each hazard. The risk is the likelihood of the hazard being produced, or caused, at a particular level of exposure (see Glossary for full definitions). Chemical hazards are usually identified from a series of *in vitro* and *in vivo* studies in animals, which are designed to investigate different endpoints or target systems. There are established internationally recognised testing guidelines

(which are outside the scope of this paper). In some cases the initial hazard identification has arisen from human epidemiology studies. Characterisation of the dose-response relationship, determined from epidemiology studies or from *in vivo* studies using suitable animal models, is an important part of risk assessment. Chemicals are usually tested and assessed individually, and the risk assessment is for that chemical alone. Consideration of interactions between chemicals sharing common features (combination toxicology) is normally a separate exercise performed after assessment of the chemical alone.

Exposure assessment is an essential part of risk characterisation, because it provides the basis for the risk management question. Risk management questions are usually in the form of either "What is the magnitude of the risk associated with a given level of exposure?" (quantitative risk assessment) or "What is the maximum level of exposure that is associated with negligible risk?" (safety assurance). Measurement of exposure will depend on the exposure scenario, eg workplace or environmental, and the medium and route of exposure. The exposure to chemicals in food can be measured based on concentration data, and information on the consumption of foods containing the toxicant. Workplace exposure may be determined by suitable monitoring methods. In some cases, the exposure estimates will indicate very low exposure levels, such that a more restricted programme for hazard identification may be acceptable (FDA; Draft Redbook II; discussed in Renwick (1999d). Extremely low exposure may be considered not to represent a safety concern even in the absence of hazard identification data (WHO, 1999c).

There is an extremely wide variability in both the quantity and the quality of data available on different chemicals and other hazards. In some cases there are sufficient data to establish species differences in toxicokinetics between test animals and humans, and also information related to the biological mechanism causing the toxicity. In such cases it is possible to develop a biologically-based, dose-response model such that the extrapolation across the species and from high to low doses is securely based on scientific principles and data. However, in the vast majority of cases risk assessments may be necessary for compounds for which only limited data are available (Figure 1). Such data may be extremely restricted and not allow a full characterisation of the dose-response relationship or an understanding of metabolic or mechanistic differences between the test species and humans. In consequence, risk assessment procedures have to offer a range of possible options from relatively unsophisticated default approaches for sparse data sets, to sophisticated dose-response modelling for data-rich compounds (Figure 1 and Table 1).

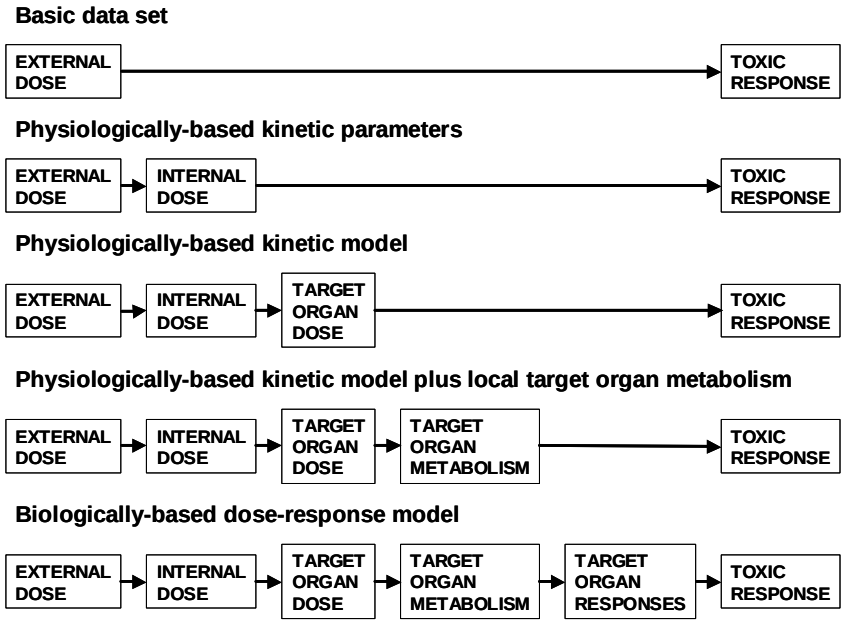

Figure 1. The different databases on which quantitative risk assessment may be required.

The risk assessment approaches shown in Figure 2 have historically resulted in different risk characterisations. Quantitative risk assessment by low-dose extrapolation provides an estimate of the risk, or incidence, associated with a particular level of exposure, or can be used to estimate the exposure associated with a particular pre-defined level of risk. Standards can be set based on low-dose risk estimation to ensure an appropriately low level of risk. "Safety assurance", based on an assumption that there is a threshold, is used to characterise an exposure considered to be of negligible risk, and is used for standard setting such as an acceptable daily intake or an occupational exposure standard. It is widely accepted that there is a threshold in the dose-response relationships for the majority of adverse effects and therefore low-dose extrapolation methods would be inappropriate. This paper reviews current approaches and proposes a method that would allow quantitative estimates of risk arising from individual variability in the threshold for response.

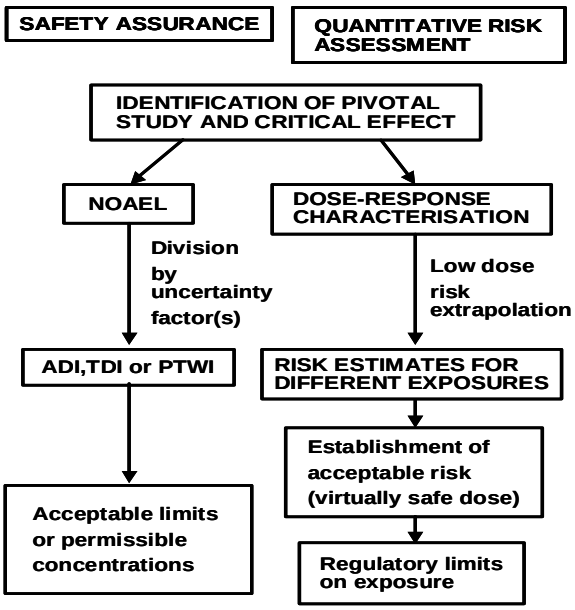

Figure 2. **Alternative approaches adopted for establishing acceptable levels of human exposure (from Walker R, personal communication).**

The risk assessment approach that is adopted depends on the nature of the toxic effect or hazard, which is the basis for risk assessment (Figure 2). For some hazards, such as genotoxic chemicals, it is considered that there may be no threshold for the effect and therefore estimates are made of the possible magnitude of the risk (usually incidence) at human exposures (dose-response extrapolation). In contrast, for other hazards, such as non-genotoxic effects, it is considered that there is a threshold of exposure below which no biologically significant effect will be produced. Each of these approaches usually involves the uncertainties of extrapolating from high-dose animal studies to low-dose human exposure, and from small groups of genetically homogeneous animals to the larger and more diverse human population.

2. DOSE-RESPONSE RELATIONSHIPS

2a Dose-response data in humans

Dose-response data in humans may be available from either epidemiological studies or very rarely by direct experimentation (for example, the effect of compounds on enzyme activity, such as acetylcholinesterase). Such data require information on, and measurements of, effects in humans and, therefore are not relevant to the vast majority of risk assessment procedures, in which data from animal studies are used to prevent the development of unwanted adverse effects in humans arising from exposure to chemicals and other risk factors. There are ethical issues relating to the intentional production of adverse health effects in humans by direct experimentation, although response measurements using biomarkers of minor and reversible changes can provide valuable human data for risk assessment. Therefore, the majority of risk assessments involve the

interpretation of studies in experimental animals, and the extrapolation of data across species.

The dose-response relationships available from epidemiology studies typically involve estimates of current levels of exposure of humans and the current incidence or risk of the adverse effect of concern. Such a temporal relationship would be suitable for acute effects or effects produced soon after exposure, but it would not provide a reliable risk estimate if there was an interval between exposure and development of the adverse effect, for example, carcinogenicity. Cumulative exposure estimates may be available in some rare cases, but these are usually following workplace exposures and data may be limited to recent years following the establishment of monitoring procedures. A further problem with epidemiology studies is that quantitation of exposure is frequently imprecise. In contrast, a distinct advantage of the use of human data is that quantitation of the risk for either higher or lower exposures would not normally require extrapolation of the dose-response relationship far beyond the available data (see later).

2b Dose-response data in animals and model systems

An advantage of the use of experimental models (both *in vivo* and *in vitro*) is the ability to increase the incidence, and hence the ability to identify a potential hazard, by increasing the dosage. Because of the high incidence of adverse effects produced in experimental studies (allowing hazard identification), compared with the potentially acceptable risks in the human population, the dose-response relationship from experimental studies in animals is usually extrapolated three or more orders of magnitude outside the range of the experimental data. Such extrapolation has to make assumptions about the slope of the dose-response relationship beyond the range of the experimental observations.

For adverse effects believed to be associated with a threshold, such low-dose extrapolation is not appropriate, and quantitative risk assessment would involve determination of the possible incidence of individuals for whom their threshold for response was less than the level of exposure, in other words the incidence of "at risk" subjects. The nature and magnitude of any risk would then be related to the experimental dose-response data.

2c Types of response data

The effect or response data may be determined either as quantal data or as a continuous variable. An example of quantal data would be the incidence of a specific lesion, such as a tumour, whilst examples of a continuous variable would be a change in organ weight or body weight. Quantitative risk assessment could, therefore, produce either an exposure-related incidence of a specific lesion or an exposure-related change in a particular body function. Continuous variables can be converted to quantal data provided that a range of normality can be defined; in other words upper and lower level limits can be set, below and above which any observation would be considered abnormal (outside the usual range), and hence the response in an individual converted to quantal effect.

2d Hormesis – a problem for quantitative risk assessment or a stimulus for change?

A major problem for the risk estimation procedures outlined above is the recognition that low doses in experimental animals sometimes produce a response which is statistically significantly less than the background incidence in untreated animals, a phenomenon known as 'hormesis' (Calabrese and Baldwin, 1998). Although hormesis remains controversial, it is not without biological plausibility (Sielken *et al*, 1995) because a low exposure may serve to stimulate cytoprotective and homeostatic processes in excess of the amount of added insult to the system. At higher exposures the magnitude of the added adverse stimuli would exceed the induced cytoprotective or homeostatic mechanisms so that an adverse response would become measurable. The presence of hormesis would not significantly affect risk estimations based on assumptions that there is a threshold to the biological response. However, hormesis would profoundly affect, and largely invalidate both low-dose risk extrapolation and the principle of ALARA (as low as reasonably achievable), because such approaches would be excessively conservative if low doses were not associated with an increased risk.

3. NON-THRESHOLD vs. THRESHOLD - THE HISTORICAL DICHOTOMY

Although the proof of the presence or absence of a threshold remains a matter for debate in risk assessment, subdivision of toxic effects into threshold and non-threshold has been the basis for risk assessment for the past 30-40 years (WHO 1999a). The presence of a threshold cannot be demonstrated readily from experimental data, because even a non-threshold, linear dose-response relationship could give no measurable response in groups of experimental animals given low doses (Figure 3).

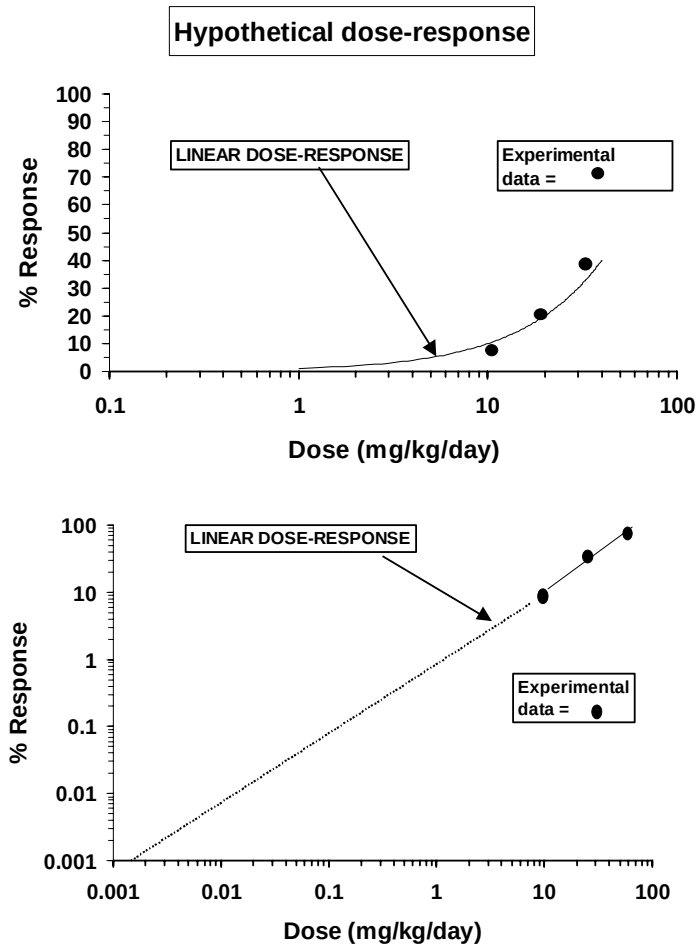

Figure 3. **Dose-response data in the experimental range and its extrapolation to low risk estimates. Low doses in the experimental range may indicate the presence of a threshold due to limitations of group size and variability in the data. The line represents the data for low-dose linearity without a threshold.**

Therefore any experimental dose-response relationship (whether or not it has a threshold) may include doses without a measurable (or statistically significant) biological effect in the test system. In consequence, the existence of biological thresholds cannot be proven or disproven, and the possibility of a level of exposure that does not produce any effect (rather than any measurable effect) has to be based on experience and expert judgement of the underlying biology of the test system. Although it can be argued that thresholds cannot exist in absolute terms, ie a very low concentration will still interact with the biological system, in reality the presence of homeostatic and cytoprotective processes means that the interaction between the chemical and the biological system has to exceed the homeostatic or other protective processes in order to elicit a response. Therefore, the concept of thresholds can be converted into quantitative terms by defining the magnitude of any measurable response that would not be considered to be adverse (Slob, 1999). Because different risk

assessment procedures have been adopted depending on whether there is or is not a biological threshold, this issue is critical for the risk assessment procedure.

The difficulty in relation to determination and interpretation of thresholds is illustrated well by the development of cancer following exposure to genotoxic compounds, which are normally considered not to show thresholds. The two-stage clonal growth model described by Moolgavkar *et al* (1988, 1990) incorporates two processes giving rise to increased numbers of cancer cells. An initial genotoxic effect on the cells gives rise to transformed cells that is followed by an effect on cell division and proliferation. The basic assumption for genotoxic compounds is that the initial mutagenic effect does not show a threshold; recent data on the production of DNA adducts (Turteltaub *et al*, 1997; Dingley *et al*, 1998) indicate that a linear relationship between DNA adduct formation and dose applies down to very low exposure levels. However, the production of DNA adducts is not equivalent to mutation or initiation, because of the presence of DNA repair mechanisms, and it is possible that capacity limited repair processes may be able to prevent very low levels of adducts from resulting in cell mutations and initiation. The second proliferation stage may be linked to cytotoxicity and as such the *a priori* hypothesis would be that a threshold would be present for this aspect. However, the mechanism of cytotoxicity may be linked with a change of a continuous variable, such as receptor binding and activation, so that a small increase in the continuous variable over background levels would theoretically result in an increase in risk. Thus at a mechanistic/biochemical level the presence or absence of thresholds is a matter for interpretation rather than demonstration. In addition from a mathematical (probabilistic) perspective, dose-responses relations would not show a mathematical zero risk for very low exposures, even if cytoprotective and homeostatic processes are incorporated into the model. Slob (1999) has argued that dose thresholds cannot exist in a strict quantitative sense, but that thresholds can be defined in relation to the magnitude of any change in a continuous variable which would not be considered adverse.

A recent meeting organised by the Society of Toxicology in the USA, discussed the harmonisation of cancer and non-cancer risk assessments and concluded that biological thresholds are probably present in the mechanisms of action for both genotoxic and non-genotoxic compounds. Ideally the risk assessment for animal carcinogens should integrate all relevant information (Butterworth and Bogdanffy, 1999) to produce a biologically-based model, but in reality the vast majority of cases will require assumptions and default approaches.

Major developments in toxicology since the 1950's have related to good laboratory practice (GLP) (FDA, 1976; OECD, 1982; Turnheim, 1993) (which has ensured the quality of the data), studies on mechanisms of toxicity (which define the cellular events within the target organ for toxicity), and data from metabolism and disposition studies (which allow the external dose to be related to the internal dose and delivery of the chemical to the target organ). Such data have a major impact on the selection of the risk assessment approach adopted, and chemical-specific data can be used to reduce uncertainties and refine the risk assessment procedure. However, risk assessments are frequently required on databases which do not contain mechanistic or toxicokinetic data, and in consequence no single risk assessment approach can be proposed to cover all possible circumstances.

3a Non-threshold toxicity (e.g. genotoxicity)

Quantitative risk assessment for non-threshold effects (eg cancer) usually uses the dose-response for the incidence data from the animal study to estimate a risk for levels of exposure more relevant to human exposures. The incidence of the risk detected in an *in vivo* animal study would normally be greater than 1 in 20, but a "virtually safe dose" for a genotoxic compound is usually considered as 1 in 100,000 or 1 in 1,000,000 (this is a risk-management decision). Therefore, this approach normally requires extrapolation of the dose-response relationship over at least 4 orders of magnitude (Figure 3). Such extrapolation is based on the assumption that there is a theoretical possibility of an effect with exposure to a single molecule of the substance. Although this proposition was defensible when first introduced about 20 years ago, our increasing understanding of DNA repair mechanisms, and other cytoprotective and homeostatic processes, means that the risk at very low doses is a probabilistic estimate, rather than a biologically-based risk.

A difficulty of this approach is that a risk management decision has to be made on what is an "acceptable" risk in order that the risk assessment can estimate the exposure associated with this level of risk, ie give a defined level of risk equivalent to a "virtually safe dose". In reality, this is a "societal" decision, which would require information on the hazard, the cost of establishing a particular exposure standard, and the benefit (if any) of the compound. If this decision is not made, then the output of the quantitative risk assessment has to be given as a series of risks associated with a range of doses relevant to the risk management question (WHO, 1999b).

An alternative risk assessment approach is to conclude that a safe dose cannot be defined, due to the uncertainties inherent in the extrapolation procedures and lack of knowledge of the biological consequences of very low exposures; the consequent risk management option is limited to ensuring that exposures are reduced to the minimum technologically practicable or as low as reasonably achievable (ALARA), or as low as reasonably practicable (ALARP).

3b Threshold toxicity

A generally accepted paradigm has been used for the past 40 years (Lu, 1988; Truhaut, 1991) for the establishment of intakes of non-genotoxic chemicals that would be associated with unquantified, but "negligible" risks when consumed by humans daily throughout life.

A key principle in this approach is that there is a threshold of daily intake below which measurable toxicity will not be produced; therefore it is possible to calculate exposures for humans, which would be without significant adverse health effects (safety assurance). Safety assurance is an example of quantitative risk assessment with the level of risk being considered to be "insignificant" rather than a specific quantitative estimate. The term "safety assurance" gives the implication of complete absence of risk, but all outputs such as the ADI etc are defined as "without significant" or "without appreciable" adverse health effects. In reality "safety" is not an absolute freedom from risk, but represents a balance between risk, benefit and cost (Williams, 1998). The use of default uncertainty factors (see Figure 4 and later) is considered to reduce the risk to

negligible proportions compared with the perceived benefits (for a food additive or pesticide approved onto a positive list) or the perceived costs (for the removal of an environmental contaminant). Therefore the uncertainty factors used contain an implicit societal dimension (Illing, 1999), but for exposure of the general population the use of a general 100-fold default factor has been considered adequate for the past 40 years. The scientific basis for this default and approaches to introduce more scientific data into the selection of uncertainty factors are discussed below.

Not all effects detected in animal studies are predictive of possible adverse health effects in humans. The high doses used in animal studies may produce nutritional imbalances, or adaptive responses that would not be relevant to lower levels of intake. In addition, some adverse effects in animals are not relevant to humans. Therefore, an important initial decision, requiring expert judgement, is definition of the *critical effect*, which is the relevant adverse effect in the animal studies that is detected at the lowest exposures, and therefore is the most sensitive endpoint. It is assumed that any risks related to other hazards detected at higher doses, will be lower than those relating to the critical effect.

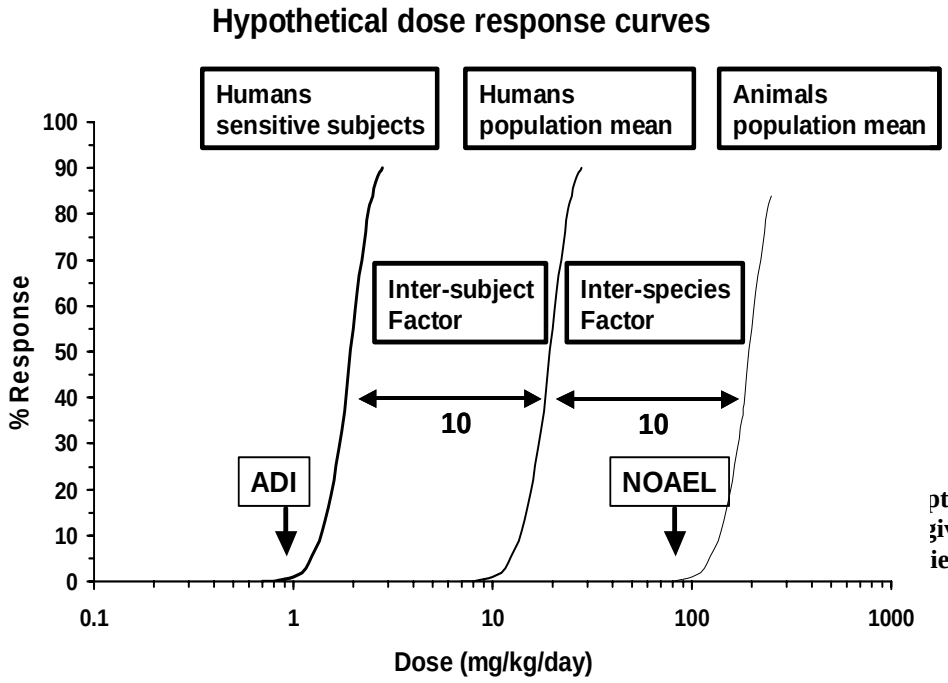

Figure 4 **ptable or given for ied to the**

Safety assurance is based on using the dose-response relationship to define an approximation of the threshold for toxicity in the animal study. The endpoint normally used as a surrogate for the threshold is the no-observed-adverse-effect-level (NOAEL) (WHO, 1999a), which is a sub-threshold dose. The term no-observed-effect-level (NOEL) is also used, but not all observed effects are adverse and would be the basis for quantitative risk assessment. In consequence, NOAEL has tended to be used more in recent years, although in reality NOAEL and NOEL are interchangeable, because the term "adverse" is included in the definition of NOEL (see glossary).

When a compound produces 2 or more different adverse effects, the NOAEL used to calculate the intake for humans associated with negligible risk, is that for the most sensitive, relevant endpoint in the most sensitive species (the critical effect). Usually,

adverse effects are detected at lower doses in chronic studies, than in sub-chronic tests, and in consequence the NOAEL used when there is chronic low level human exposure is usually based on data from chronic bioassays: sometimes 90-day studies show greater sensitivity, because the adverse effect due to the compound is not masked by the effects of ageing.

The approach adopted for non-genotoxic carcinogens, in food and drinking water, varies between different bodies and includes the use of standard uncertainty factors (see below), an additional uncertainty factor, and low-dose risk-extrapolation. Linear low-dose extrapolation is difficult to justify because non-genotoxic mechanisms arising from altered physiological or metabolic processes would be expected to exhibit a threshold. Non-genotoxic mechanisms include excessive secretion of trophic hormones that control endocrine function, the activation of cytosolic receptors regulating DNA transcription, and chronic cell proliferation and hyperplasia. The outcome of either the use of uncertainty factors or low-dose extrapolation is the definition of a daily or weekly exposure to a non-genotoxic carcinogen that is considered to be "acceptable", "tolerable" or "virtually safe". Alternatively, the human exposure can be compared with the dose-response data in animals to calculate a margin of exposure or "safety margin" (Doull *et al*, 1999; Wilkinson and Lamb, 1999).

The NOAEL expressed on a body weight basis (eg mg/kg body weight/day) is divided by an **uncertainty factor** or **safety factor** to derive the level of human exposure that will be without significant adverse effects (Figure 4). Although the terminology differs between regulatory bodies (NOEL *vs* NOAEL; acceptable daily intake (ADI) *vs* tolerable daily intake (TDI) *vs* reference dose (RfD – used in the USA); safety factor *vs* uncertainty factor), there is a common underlying approach. The "safe" human exposure is usually termed "acceptable" (for an additive) or "tolerable" (for a contaminant) together with a time base, which is related to the potential for accumulation, eg acceptable daily intake (ADI) or provisional tolerable weekly intake (PTWI) for chemicals that accumulate. These assessments may be dated to indicate the time at which the database was assessed (Ruberey *et al*, 1990). Despite the commonality of approach, there are frequently wide differences in the values derived by different bodies assessing the same compound (Dourson and Lu, 1995).

The simple nature of the current methods applied to threshold toxicity, means that they can be applied readily to a wide range of different databases. In addition, the inexact nature of the "science" used is readily apparent (Felter and Dourson, 1998), whereas the equally simplistic linear low-dose extrapolation appears more sophisticated, because of the data fitting undertaken, but in reality is supported by less biological plausibility, and largely ignores certain aspects, such as human variability.

4. EXTRAPOLATION PROCEDURES IN RISK ASSESSMENT

The available dose-response data for the adverse effect may be analysed in a number of ways, each of which involves a number of assumptions and uncertainties. Measurements which can be taken from the dose-response relationship and used for quantitative risk assessment include:-

a) the slope of the dose-response curve,
b) a fixed point on the dose-response curve, and

c) the threshold, or a surrogate for the threshold, such as the NOAEL

Assuming there is no biological threshold, the slope of the incidence data in the experimental range can be extrapolated by a mathematical model to low dose levels in order to provide a quantitative risk estimate directly. In contrast, dose-response extrapolation below a threshold would not give a meaningful estimate of the risk: therefore, analysis of low dose risks in relation to thresholds has to be on the basis of the number of individuals in a population whose individual thresholds for a response are less than the exposure level of concern (and the basis of the risk management enquiry).

4a Non-threshold effects

Extrapolation of the dose-response curve outside the range of the observations is the subject of both assumptions and errors (Tables 2 and 3). These relate to the choice of the starting point and data used for extrapolation, the slope of the curve used for the extrapolation and the mechanisms by which interspecies differences and interindividual variability are taken into account in the extrapolation process. Potential errors arise from the extent to which unquantified assumptions have to be made in relation to these criteria (see Tables 2 and 3).

4a (i) Use of human response data

The presence of a dose-response relationship is one of the criteria defined by Bradford-Hill (1965) to establish causation in epidemiological studies (Table 4). Epidemiology studies have the potential to minimise both assumptions and errors in quantitative risk assessment, because of the lack of interspecies extrapolation and the need for extrapolation from very high to low doses. However, epidemiology studies frequently suffer from a lack of precision in the exposure estimates in different exposed groups, and also the presence of confounding factors (which influence response outcome in different groups) and different populations, and bias (Choi and Noseworthy, 1992). A recent example of the use of human epidemiological dose-response relationships was the evaluation by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) of aflatoxins (WHO, 1999b). Aflatoxin is a known animal and human carcinogen affecting primarily the liver in humans. It arises from contamination of the food supply by mycotoxins produced by species of *Aspergillus*, and there are wide geographical variations in potential intake related to agricultural practices. However, the geographical variations in exposure and liver cancer incidence are confounded by similar variations in hepatitis B and possibility hepatitis C virus, which are also risk factors for liver cancer. Despite the extensive database available on aflatoxins, including *in vivo* animal data and mechanistic studies, and the large number of studies defining the extent of contamination, the JECFA was unable to define the dose-response relationship clearly. The reasons for this were:-

a) The epidemiological data related to geographical areas with high prevalence of hepatitis B antigen positive individuals and contamination, and there were few data available from low prevalence areas.

b) The reliability and precision of the estimates of exposure to aflatoxins are unknown.

c) The shape of the dose-response curve is unknown and, therefore, the selection of a mathematical model for interpolation analysis resulted in another potential source of errors.

Additional sources of error and bias were i) only studies showing a positive association between aflatoxin exposure and liver cancer were included, ii) current levels of intake were related to current levels of liver cancer which may be inappropriate for a carcinogen, iii) the earlier studies underestimated the prevalence of hepatitis B in the patients and iv) histological confirmation for the cases of primary liver cancer was limited in most of the studies. This analysis of aflatoxins illustrates the difficulties in the use of epidemiological dose-response.

4a (ii) Use of animal dose-response data

There are very few epidemiological databases which are as data-rich as the aflatoxins, and therefore the majority of risk assessment analyses will have to be based on dose-response relationships under experimental conditions usually using animal models.

The use of dose-response data from animal experiments to predict the risk in human populations incorporates a number of assumptions (Tables 2 and 3). Interspecies differences may be taken into account by the production of a physiologically-based pharmacokinetic (PBPK) model which allows the dose delivered to the target organ to be used in the dose-response relationship rather than the external or applied dose. When species differences in the target organ response in relation to the concentration of the compound have also been investigated, this can also be included to modify the response relationship so that the biologically-based dose-response model (Table 1) is used instead of just a simple external dose-response relationship. However, although this degree of sophistication will improve the characterisation of the risk within the dose-response range, there is still the major issue of the selection of the appropriate mathematical model for extrapolation outside the range of dose-response data (see below).

Human variability is rarely taken into account in these dose-response extrapolation procedures. An approach that has been adopted is the use of the upper 95^{th} percentile of the dose-response relationship since the variability in response will be reflected in the variability in the experimental data. However, much of this will relate to variability arising from the small size of the experimental groups, and will relate to variability within the test species not within the humans. The use of the 95^{th} percentile to produce a dose-response relationship which allows for variability in the test animals may not be appropriate to represent human variability and the slope arising from human variability. Therefore, simple extrapolation of the slope of the animal dose-response curve or its upper 95^{th} percentile confidence intervals will not represent the dose-response relationship present in the human population.

The slope of the dose-response and the model used will be the major variable in the estimate derived by quantitative risk assessment when extrapolation has to be made over 3 or 4 orders of magnitude (ECETOC, 1996). If the actual slope of the animal dose-response curve is not extrapolated (Figure 3) then an arbitrary choice about the appropriate model and slope has to be made.

A number of different models have been proposed (Figure 5), although only a restricted number have been used (ECETOC, 1996).

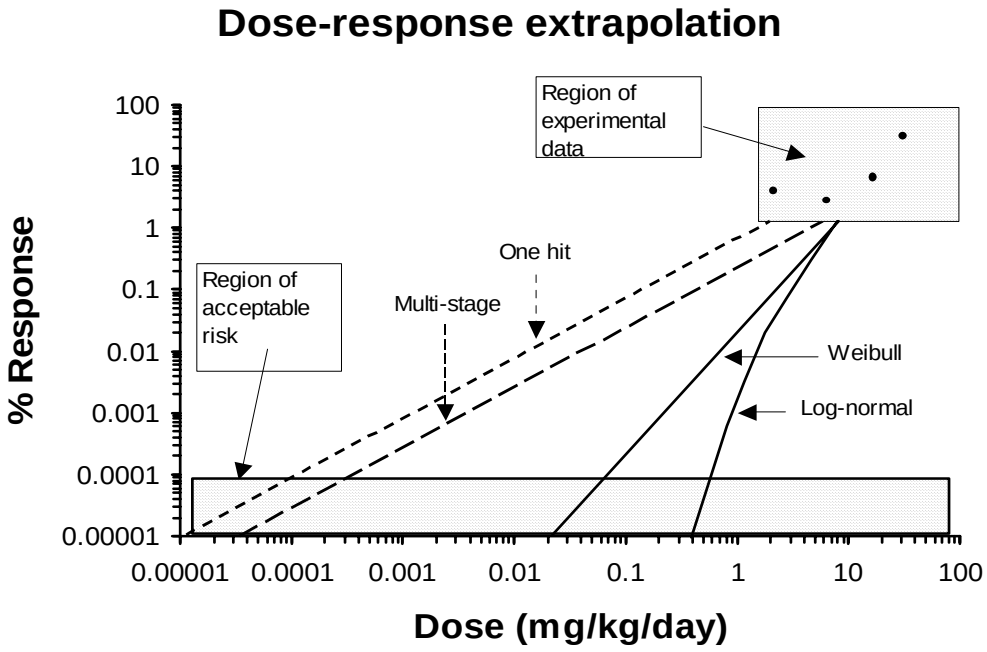

Figure 5. Mathematical models for low-dose risk estimation (based on ECETOC, 1996)

The different models are:-

Stochastic models (eg one hit, and linearised multi-stage). The linearised multi-stage model assumes that cancer arises from a sequence of events, that at least one event is linearly related to dose, and that a background incidence is always present. In consequence this gives a linear extrapolation at low exposures (Figure 5) and the slope is determined largely by the top dose used in the study (Lovell and Thomas, 1996).

Tolerance distribution models (eg Weibull, log-probit and logit). The log-probit and logit give a sigmoid curve in the experimental range but differ in low-dose extrapolation. The Weibull model is capable of representing thresholds, and is sensitive to the slope of the dose-response curve.

Time to tumour models (eg Weibull distribution). These models are considered to be better because they do not use quantal data. These models have not been adequately validated and generally offer no advantage over incidence data that have been corrected for differences in life span between different experimental groups.

Biologically-based models (eg Moolgavkar-Venzon-Knudson (MVK) model). Although stochastic models were introduced because low-dose linearity was considered to be a conservative interpretation of the underlying biology, they do not adequately represent the processes involved. The MVK is a biologically credible model, but requires data on rates of cell division and cell death at different stages of tumour growth, from the stem cell to the initiated cell to the transformed cell, and such data are not currently available.

In consequence the available models range from simplistic, easy to apply but biologically dubious, to sophisticated, impractical but biologically credible. In practice, low-dose risk extrapolations have historically adopted the simpler models, because they can be applied to a wide range of databases of variable quality. The simplest approach (sometimes termed "model-free") is to select an arbitrary starting point on the dose-response curve, such as the LOAEL or the dose producing a 25% response (ED_{25}) and then apply an arbitrary slope (usually a simple linear decrease) to doses below that point. The starting point may be derived by fitting a model to the experimental data, but that model is not used for extrapolation below the starting point. The US-EPA have used a simple linear extrapolation from the dose estimated to give a 10% tumour incidence (TD_{10}).

In practice all models tend to fit equally well to the experimental data, and model selection has to be based on perceptions of biological plausibility and practicability, rather than mathematical appropriateness.

Thus a major problem with low-dose risk extrapolation is that the mathematical model or equation selected for the extrapolation process becomes the major variable in the final risk estimate when extrapolating to very low exposures (Figure 5). Fitting the different models to the same dataset can give risk-specific doses (e.g. the dose giving a 1 in 10^6 risk) that differ by several orders of magnitude! Despite the precision frequently reported for extrapolated risk estimates, there remain a number of uncertainties relating to inter-species differences and inter-individual variability in toxicokinetics and sensitivity within the heterogeneous human population compared with the test species. At low doses, the confidence intervals may span a risk from zero up to the upper-bound risk estimate. The virtually safe dose is usually presented as o-x where x is the upper-bound estimate of intake per day associated with the defined risk (eg 1 in 10^6). The uncertainties in the risk estimate are rarely taken into account, and the higher value is usually taken as the possible risk, and the precision of the estimate not questioned.

Although low-dose risk extrapolation appears to be a sophisticated process, in reality the normal default model is a simple, linear-extrapolation from some part of the dose-response curve, eg the lowest-observed-adverse-effect-level, or possibly a fixed incidence (eg 25% response). With a simple, linear-extrapolation there is a 10-fold decrease in incidence for every 10-fold reduction in dose, and zero risk is associated only with zero exposure. For carcinogenic compounds the extrapolation is usually from an incidence of about 1:10 or 1:100 in animal studies down to $1:10^6$ for humans. In consequence, extrapolation from the lowest-observed-adverse-effect-level to a virtually safe dose in humans involves extrapolation over approximately 10^4.

Whenever possible inter-species differences in toxicokinetics are incorporated into the extrapolation by the introduction of PBPK modelling, so that the external dose is replaced by a "target organ dose". A commonly used method is to correct the dose in animals to a human equivalent dose by scaling based on body weight$^{0.75}$. This will allow for simple physiological differences but not for differences in xenobiotic metabolism.

It is considered that inter-individual variability within the test species is taken into account to some extent by the use of the upper 95th percentile confidence interval on the dose-response extrapolation; however, true human variability is rarely taken into account in low-dose risk-extrapolation based on animal data.

Because the cancer dose-response in animals is usually closely related to the maximum tolerated dose (MTD) (Gaylor and Gold, 1998), and a simple linear model is normally applied to the animal data the human "acceptable" risk or "virtually safe dose" could be estimated simply by dividing the MTD by 740,000 (Gaylor and Gold, 1995), without the need for a cancer bioassay. While this approach has never been adopted for quantitative risk assessment, it does illustrate the very simplistic nature of current low-dose risk-extrapolation procedures.

4b Threshold effects

4b (i) Use of human response data

The discussion concerning the use of epidemiology data for non-threshold effects (Section 4a (i)) applies equally to assessment of threshold effects, but data for threshold effects may also be obtained by direct experimentation in volunteers. Although it would be unethical to determine the dose-response for toxic effects in humans, it is ethical to produce data on an innocuous surrogate endpoint for the toxic effect, or on general "tolerability" (for example gastro-intestinal side effects).

Once the dose-response relationship has been characterised from either human epidemiology data or experimentation it is necessary to decide if the exposed population represents the full spectrum of human variability. When data are available from direct experimentation in small groups of volunteers, the NOAEL is usually divided by an uncertainty factor of 10 to allow for human variability (see below).

4b (ii) Use of animal doses-response data

The starting point for threshold effects is definition of a surrogate for the threshold-dose (such as the no-observed-adverse-effect-level (NOAEL) or benchmark dose (BMD)) which is divided by uncertainty factors to determine an intake which would be without significant adverse health effects in sensitive humans. This approach also has assumptions and uncertainties (Table 5). (Adaptation of this approach for quantitative risk estimation is discussed later).

No-observed-adverse-effect-level (NOAEL)
The NOAEL is a level of exposure in which the treated animals do not differ significantly from untreated control animals in measurements related to the critical

effect recognised at higher doses. The NOAEL is a dose without measurable activity (Figure 6), and therefore can be considered to be below the threshold in animals.

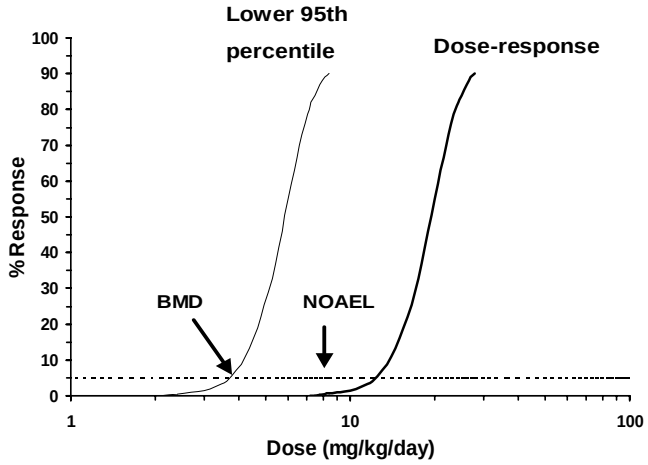

Figure 6. Comparison of no-observed-adverse-effect-level (NOAEL) and the benchmark dose (BMD)

The value of the NOAEL is dependent on three main factors of the study design:-

- *Group size* - the larger the group size, the greater will be the sensitivity. The group sizes currently recommended in testing guidelines represent the best compromise between sensitivity and practicability: group sizes would have to be increased considerably in order to provide a measurable increase in sensitivity over the current recommendations.
- *Test sensitivity* - the more sensitive the method of detection, the lower the NOAEL. The consequence of poor or inadequate methods of assessment of adverse effects is that the NOAEL is higher - thereby rewarding poor techniques. It is this problem which is the basis for the requirement that studies which are submitted for regulatory purposes should comply with GLP or be reported in sufficient detail to provide quality assurance to those undertaking the risk assessment.
- *Dose spacing* – a major determinant of the NOAEL in real databases is the choice of the spacing between doses given to the animal. The NOAEL is the next dose down from the minimally effective dose: hidden in this simple statement is the fact that the experimental NOAEL may be a gross underestimate of the true threshold, especially if the doses are separated by factors of 10-fold. For example, if the doses in a study were 10, 100 and 1000mg/kg body weight per day and the biological threshold was 80mg/kg/day, the NOAEL (10mg/kg/day) would be a factor of 8-fold below the true threshold. The NOAEL from modern databases, in which the doses differ by a factor of 3-fold or 5-fold, are closer to the true threshold.

These different aspects affect the relationship between the NOAEL and the biological threshold for toxicity in different directions; they probably cancel each other out, because group size and test sensitivity would result in the true threshold being below the

NOAEL, but due to dose-spacing (selection) the threshold would be above the NOAEL (this is an important consideration discussed later).

Benchmark dose (BMD)
The BMD (Figure 6) is an alternative method of defining an intake close to the threshold (Crump, 1984). Unlike the determination of a NOAEL, this method uses the full dose-response data to determine the incidence associated with a defined low level of response (WHO, 1999a). The value is derived by modelling the experimental data in the observed range and selecting the 95^{th} percentile lower confidence limit on the dose causing a particular incidence of the effect, for example 5% of the maximum response (Auton, 1994; Barnes *et al*, 1995). A 5% difference in a continuous variable, such as an organ weight, may be within the background variability in control animals and therefore not represent a clear "adverse" effect. In consequence, the BMD is most suitable for application to quantal variables, such as the incidence of a histological lesion, or the incidence of abnormal liver weight (where the normal range has been defined based on the variability in control animals). Because the dose-response relationship is not extrapolated far beyond the experimental observations, the BMD is not subject to the errors, or the dependency on the model, which are inherent parts of low-dose risk-extrapolation. Advantages of BMD are that it rewards good dose-response data because this will be associated with narrower confidence intervals, and also it is not subject to the limitations discussed above for the NOAEL. The BMD is by definition greater than the threshold and the way that this can be used in risk assessment and the choice of uncertainty factor are still the subject of debate. Unlike the NOAEL, a BMD cannot be calculated when none of the experimental observations produce an adverse effect, and is very approximate when the adverse effect is detected at the top dose only.

Lowest-observed-adverse-effect-level (LOAEL)
The LOAEL is used instead of the NOAEL when all test groups produce a significant effect compared to controls. In consequence, this estimate is above the threshold and in risk assessment this is usually taken into account by the use of additional uncertainty factors (see below). The LOAEL, like the NOAEL, is an experimental observation and dependent on the design of the study as discussed above for the NOAEL. Consequently, the BMD would represent a more scientifically credible way of dealing with risk assessment for databases which do not allow determination of a NOAEL.

4b (iii) <u>The use of safety/uncertainty factors to convert the NOAEL (or alternative) from animal studies into a "safe level" of human exposure</u>

A number of different types of numerical factor are used in risk assessment, and these have been termed “safety factor” or “uncertainty factor”. Neither term is ideal because the term safety factor has implications of absolute safety, whereas uncertainty factor may be difficult to translate into other languages (for example into an insecurity factor). “Uncertainty factors” are applied to a number of different aspects of dose-response characterization (WHO, 1994). This is illustrated in Figure 7, with those factors normally applied within the EU shown with solid lines, and the factors used by other bodies, such as the IPCS (International Programme on Chemical Safety) and the US-EPA (United States-Environmental Protection Agency) are shown with dotted lines. In the USA, different factors are used for oral toxicity causing systemic effects (typically 10) and for inhalation (with dosimetric correction for deposition) causing local toxicity (typically 3).

The use of extrapolation factors (see below) is normal for the approval of compounds onto a positive list, for example the approval of new food additives, or pesticides. However with vitamins and minerals, toxicity is often seen at intakes (on a mg/kg body weight basis) in animals that are only slightly above those recommended for nutritional needs, and attempts to apply the usual numerical factors would create adverse health effects because of deficiency.

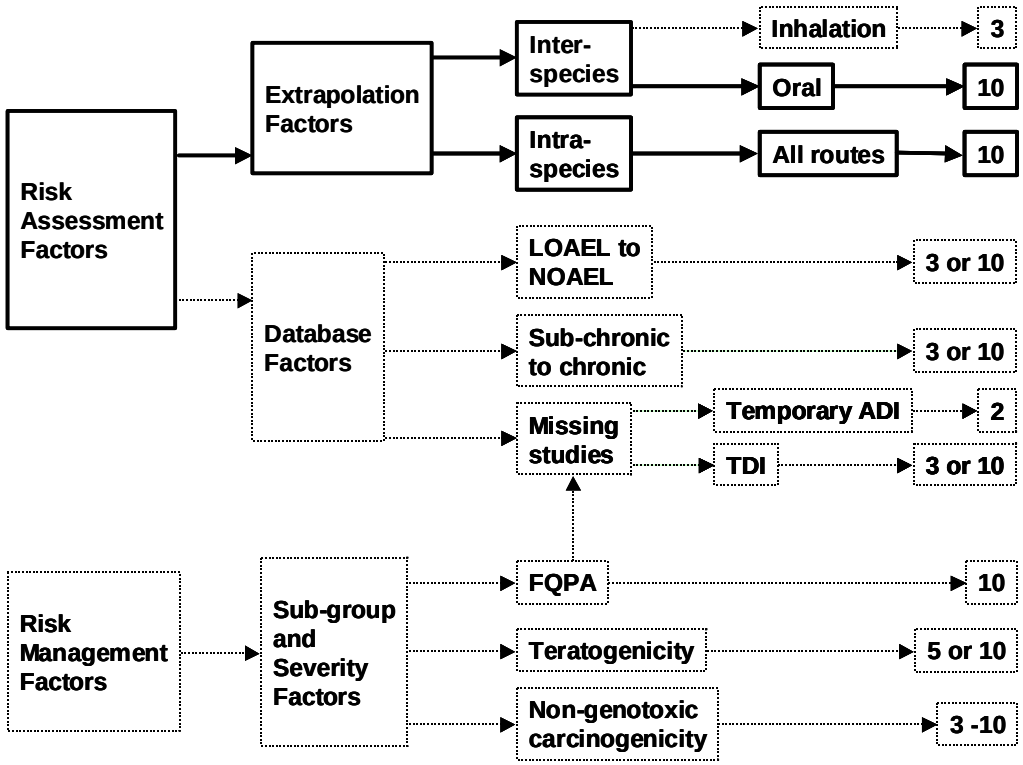

Figure 7. **Uncertainty factors used to establish acceptable levels of human exposure based on animal databases. The factors shown with continuous lines are those usually used in the EU for the assessment of food additives and pesticides. Other factors may be applied for other types of chemicals (e.g. contaminants) and by authorities and bodies outside the EU. The numerical values represent usual practice and are not recommendations.**

Extrapolation Factors

Extrapolation factors (also called uncertainty factors) are used to allow for extrapolation from test animals to humans, and from average humans to sensitive subgroups, i.e. to convert the NOAEL from animal data into a surrogate for the threshold in sensitive subjects. For animal data, a 100-fold uncertainty factor is usually applied to the NOAEL, with a 10-fold factor to allow for differences between animals and an average human, and 10-fold to allow for differences between average humans and sensitive sub-groups (WHO, 1987). Thus, one 10-fold factor is considered to move the intakes (expressed per kg body weight) from a population sub-threshold value for a group of test animals down to a population sub-threshold value in a similarly sized, and relatively homogeneous, group of humans. The second 10-fold factor is to allow for sensitive humans and is equivalent to moving the intake from a population sub-threshold value for humans down to the value for sensitive individuals (Figure 4). The basis for the

common practice of applying a 100-fold factor to the NOAEL from studies in animals and a 10-fold factor to the NOAEL from studies in humans has been the subject of numerous reviews (Dourson and Stara, 1983; Calabrese, 1985; Hattis, Erdreich and Ballew, 1987; Sheenan and Gaylor, 1990; Lewis, Lynch and Nikiforov, 1990; Renwick, 1991; Calabrese, Beck and Chappell, 1992; Naumann and Weideman, 1995; Dourson, et al, 1996; Renwick and Lazarus, 1998). These reviews have been post-hoc analyses of the validity of the "uncertainty factors" which were selected in the 1950's, before recent advances in the fields of toxicology and risk assessment.

Database Factors

There are established guidelines for the extent and design of toxicity studies necessary for the approval of a chemical, such as a food additive or a pesticide, onto a positive list (SCF, 1980; FDA, 1982; WHO, 1987; EC, 1989; FDA, 1993; OECD, 1993). The concept of good laboratory practice (GLP) and the adequacy of the database affect the selection of appropriate uncertainty factors (WHO, 1994). For contaminants where a risk assessment may have to be undertaken on a non-ideal database, additional uncertainty factors may be used, in order to allow for deficiencies in the database (Table 6). Extra uncertainty factors may be used to allow for database deficiencies (Figure 7) (Beck *et al*, 1993; WHO, 1994; Vermeire *et al*, 1999) such as the absence of a NOAEL, or of a chronic (long-term) study in animals (especially in cases where there is expected to be chronic exposure of humans).

Risk Management Factors

In contrast to aspects related to the scientific database and extrapolation procedures, additional factors, which have a less clear scientific rationale, may be applied for risk management reasons. These include an extra factor for severity of toxicity, such as teratogenicity, and to allow for special groups (such as infants and children under the Food Quality Protection Act (FQPA) in the USA – Figure 7). The proposal for an extra 10-fold factor for infants and children would be logical if the equivalent ages had not been investigated in the animal toxicity studies; but under these circumstances, this could be considered a database deficiency, rather than a risk management decision. Alternative risk management options include specifically limiting the exposure of presumed susceptible or sensitive individuals or groups. This could take the form of restrictions on uses, or the issuing of specific advice for special groups.

4b (iv) <u>The replacement of default uncertainty factors</u>

The same 100-fold default factor is generally applied to a wide range of compounds with diverse chemical structures, and metabolic fates and a wide range of target organ effects in the common test species such as rats, mice and dogs. This approach is open to criticism because of its simplicity, and the appropriateness of a single default has been questioned (Calabrese, 1985; Hattis, *et al*, 1987). Alternatives such as probabilistic methods have been proposed (Baird, *et al*, 1996; Price *et al*, 1997; Slob and Pieters, 1998), however probability-based approaches normally require assumptions about the nature of the distribution of the uncertainty factors.

From the perspective of the new millennium it is naive to expect 10-fold factors to allow for differences between the various test animals and humans, or for the range of human variability. The processes giving rise to an adverse effect can be divided into two main aspects, delivery of the compound to the target organ (toxicokinetics) and the

response of the target organ to the compound (toxicodynamics). This sub-division was used as the basis for an analysis of the adequacy of the usual default factors (Renwick, 1991), which concluded that while the value of 100-fold was a reasonable default, different situations could occur for which the value was either excessive or inadequate.

The inter-species differences comprise both kinetic and dynamic aspects. Ideally, compound-specific data should be used instead of defaults (see later). Alternative defaults are possible for the kinetic aspects, such as the ratio between the test animals and humans of body weight$^{0.75}$, or body weight$^{0.66}$, or a generic kinetic default of 4.0 ($10^{0.6}$) (see below) to allow for species differences in parent compound after oral dosage. These kinetic defaults, or a compound-specific inter-species adjustment factor, would be multiplied by a default for dynamics of 2.5 ($10^{0.4}$) (see below).

The 10-fold factor for human variability is to allow for inter-individual differences in response to the external dose. In classic dose-response terms it is to allow for differences in the position of the dose-response curve for the individual, compared with the population mean. In relation to risk assessment and the ADI/TDI/RfD, the 10-fold factor allows for inter-individual differences in the position of the NOAEL. Differences between dose-response curves are usually defined by estimates such as the ED_{50} (the dose in that individual which results in an effect which is 50% of the maximum); for parallel dose-response curves, the difference between individuals will be the same at any particular effect level, including the NOAEL. The 10-fold factor has to allow for variability in both kinetic and dynamic processes and default factors of 3.16 ($10^{0.5}$) (see below) have been proposed for each of them (WHO, 1994). Ideally, compound-specific data should be used instead of defaults (see below). The analysis of human variability by Renwick and Lazarus (1998) demonstrated that the 10-fold factor was an adequate default, but that situations could be envisaged in which the compound might show metabolic characteristics that would greatly increase human variability (for example polymorphisms in xenobiotic metabolism, such as CYP2D6, or polymorphisms in cytoprotective pathways, such as G6PD deficiency).

Mechanistic and toxicokinetic data provide important information for risk assessors, but rarely contribute to the selection of the uncertainty factor for inter-species differences or for human variability. A major problem with the pragmatic and simple/simplistic default procedure of using a 100-fold factor has been the introduction of quantitative, chemical-specific data, PBPK data etc. It has been proposed (WHO, 1994) that the 100-fold factor can be regarded as comprising 4 sub-factors which when multiplied together give the usual default of 100. Each of the 10-fold factors is considered to allow for differences in 2 aspects; *toxicokinetics* (which determines the delivery of the chemical to the target site) and *toxicodynamics* (which determines the reaction of the target site to the presence of the chemical).

Thus:-

	Interspecies differences			Inter-individual differences	
100 =	10		times	10	
	kinetics	dynamics		kinetics	dynamics
100 =	4.0	x 2.5	times	3.16	x 3.16

The overall scheme developed by the IPCS (WHO, 1994) is shown in Figure 8.

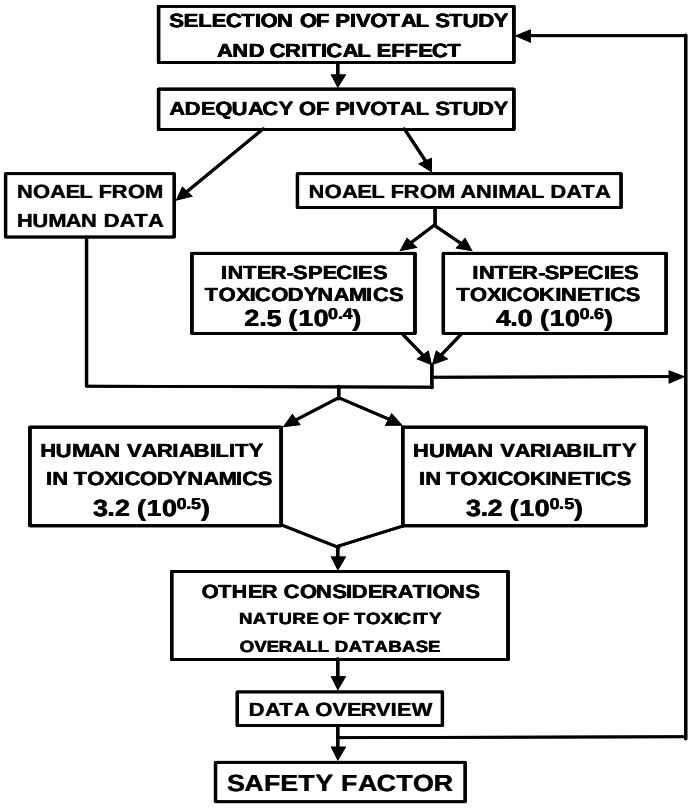

Figure 8. Scheme for risk assessment of threshold toxicants (based on WHO, 1994). At a recent IPCS meeting on the harmonization of risk assessment procedures (August 2000) it was recommended that when a default value is replaced by a value based on quantitative chemical-specific data the value should be termed an adjustment factor, and the term uncertainty factor retained for the default values shown in the risk assessment scheme above. Thus the "safety factor" in the above scheme would be the product of chemical-specific adjustment factors (for aspects where data are available) and default uncertainty factors (for the remaining aspects where data are not available).

The replacement of a default value for either interspecies differences or human variability by a quantitative chemical-specific adjustment factor requires experimental data generated from *in vivo* or *in vitro* studies in humans. In consequence, the term toxico*kinetics* should be taken as equivalent to pharmaco*kinetics*, ie the mathematical description of the *movement of the compound (and its metabolites) around the body*. This description may be a classic multi-compartmental model, or the more relevant non-

compartmental parameters such as clearance and bioavailability, or a PBPK model. Partitioning of xenobiotic chemicals between blood and tissues is usually by simple diffusion, and is not a major cause of inter-species differences or human variability. In consequence valid comparisons can be made based on concentrations in blood or plasma. Interactions occurring within the target tissue (including any local bioactivation/inactivation processes) are not readily amenable to toxicokinetic analysis in humans, and in the context of sub-dividing uncertainty factors should be considered to be a part of toxicodynamics.

The principal aim of the sub-division of the 10-fold factors was to allow compound-specific data to be used quantitatively in risk assessment and the determination of chemical-specific, data-derived uncertainty factors (Renwick, 1993). In fact, there are few databases currently available which contain the appropriate information to allow replacement of one of the sub-factors (Kroes *et al*, 1993). However, the sub-division into kinetics and dynamics has proved to be a particularly useful approach for the analysis of special situations.

Sub-division of the 10-fold factor for human variability into kinetic and dynamic aspects
Subdivision of the 10-fold factor requires separation of the variability in response due to kinetics and that due to dynamics. The *kinetic factor* is to allow for individual differences between the external dose and the concentration delivered, *via* the circulation, to the site of action (the internal dose). Since most ADI/TDI/RfDs are based on chronic oral toxicity data, the kinetic factor should reflect the chronic blood concentration or body burden, and therefore measurements such as area under the plasma concentration-time curve (AUC) are of most relevance. Data for the kinetics of 60 compounds in humans (Renwick and Lazarus 1998) were identified which represented a range of pathways of metabolism or clearance, and gave a mean coefficient of variation of the kinetic parameters of 38% with a minimum of 9% and a maximum of 114%. Concentration-effect data, mostly *in vivo* plasma concentration-response data in humans, were identified for 49 compound-related effects, and gave a mean coefficient of variation in dynamics was 51% with a minimum of 8% and a maximum of 137%. Most of the dynamic data were for the clinical treatment of patients, and ageing and disease processes may have contributed to the greater variability in dynamics compared to kinetics. This analysis supported the subdivision proposed by the IPCS Working Group (WHO, 1994), with an equal weighting for kinetics ($10^{0.5}$ or 3.16) and dynamics ($10^{0.5}$ or 3.16).

5. FUTURE METHODS FOR QUANTITATIVE RISK ASSESSMENT

Quantitative risk assessment has been used in many countries for non-threshold effects, such as cancer, by the application of linearised dose-response extrapolation. As discussed above, such estimates are heavily dependent on the mathematical model applied to the data. In consequence, some countries consider that the resulting risk estimates are not scientifically credible and have adopted alternative risk management strategies. The acceptance and use of such estimates is probably related to the severity and potential irreversibility of the hazard, such that a highly conservative, worst-case estimate is considered justifiable by some risk assessors as a default approach.

Methods of quantitative risk assessment have not been developed for threshold toxicants, probably because the default approach of using uncertainty factors has been considered adequate. However, reviews of the adequacy of the default uncertainty factors (see above) have identified various situations where they may be inappropriate. The circumstances under which quantitative risk assessment may be necessary for threshold effects include, a) assessment of specific sub-groups of the population, such as infants and children, which can be identified, b) assessment of specific sub-groups, such as genetic polymorphisms, which cannot be readily identified and c) exposures in excess of the "approved" intake (eg ADI, TDI etc).

The following discussion presents a summary of quantitative risk assessment for non-threshold effects, because there is a long history of use of this approach. This is followed by a more extensive discussion of population analysis for the quantitative risk assessment of threshold toxicants based on the application of a 10-fold uncertainty factor to allow for human variability.

5a Non-threshold effects

The current approaches for low-dose risk extrapolation have been outlined briefly above. Attempts to provide estimates of exposure associated with risks in the region of 1 in 10^6 have been attempted for the past 40 years and a number of mathematical models of increasing sophistication have been developed.

Quantitative risk estimation based on mathematical modelling outside the dose-response range is increasingly insupportable based on biological principles, unless the underlying biology is incorporated quantitatively into the model. Despite the difficulties various approaches have been used internationally, but without consensus and harmonisation. Approaches include the linearized-multistage model, and simple linear extrapolation from a fixed point on the dose-response curve such as the TD_{50}, TD_{25}, TD_{10} or LOAEL. The main criterion for acceptance seems to be that the model should be applicable to a wide variety of dose-response data, ie it is a simplistic but pragmatic approach. The historic application of a common, simple mathematical models such as the one-hit or linearised multistage model allows useful comparisons between different compounds, but the actual numerical values are determined more by the model than the data. In consequence the same comparative ranking of different compounds would have been obtained without the low-dose extrapolation (eg by comparison of TD_{10} values). Because the risk-specific exposure estimates are determined largely by the model, which is not clearly related to the biology of the hazard, comparisons of different hazards (eg carcinogenicity, biological hazards, sensitisation) will be comparing the models not the actual risks.

The model-dependency of historic approaches would be avoided by the development of biologically-based dose-response models. Such models require extensive knowledge of both the toxicokinetics of the compound, and details of its mechanism of action and the rate limiting stages. Major current problems with the adoption of biologically-based dose-response models include the absence of data suitable for incorporation into the more biologically relevant models for extrapolation, and sufficient knowledge of low-dose effects to be able to determine whether there is a biological threshold at very low levels of exposure.

Quantitative dose-response extrapolation to low doses would be inappropriate if hormesis were an established phenomenon for the compound under assessment.

5b Threshold effects - analysis of the proportion of a population not covered by the uncertainty factors

The use of default uncertainty factors to allow for interspecies differences and human variability (see above) are designed to move the dose-response curve from the mean for a group of experimental animals down to the curve for sensitive humans. The 10-fold factors are multiplied on the assumption that these factors are independent variables and that for some compounds the test species and humans will vary by a factor of 10, and a factor of 10-fold will separate average and sensitive humans.

The application of probabilistic methods can be used to analyse the likelihood that such factors will be appropriate. Such analyses are usually based on assumptions about the variability between different compounds in characteristics such as interspecies differences, rather than the inherent interspecies differences or human variability for the compound under assessment. Therefore this approach will give information about the probability of a value being adequate, but cannot greatly inform decisions relating to specific compounds and/or specific risk management enquiries.

The procedure outlined below is based on a conservative assumption that the factor applied for interspecies differences (10-fold or data-derived) is necessary, and that the slope of the dose-response curve in animals is relevant to humans. It is based on an analysis of the proportion of the human population that would not be covered by factors of 3.16 for kinetics and 3.16 for dynamics, giving a composite 10-fold factor. (The analysis would need to be modified if a different factor was applied to allow for human variability).

The risk associated with any level of exposure to a compound showing threshold toxicity can be estimated providing certain aspects are taken into account:-

a) the difference between the NOAEL and the biological threshold (Renwick and Walker, 1993). Because the NOAEL is a sub-threshold dose in experimental animals, calculations using this as a surrogate for the threshold will tend to over-estimate the possible risk.
b) the dose-response for average humans (population mean) occurs at doses 10-fold lower than those in animals, ie the 10-fold factor is necessary for interspecies differences (if compound-specific data are available these should be used to replace the default). Probabilistic approaches can be used to define the likelihood that the 10-fold factor may be an over- or under-estimate (Slob and Pieters, 1998).
c) the dose-responses for sensitive humans occur at doses 10-fold lower than for average humans (population mean)
d) sensitive humans are those with adverse kinetic and dynamic characteristics (ie their internal dose is >3.16-fold away from the population mean, and their individual internal dose threshold for response is >3.16 lower than the population mean) (Renwick, 1999a) (Figure 9).

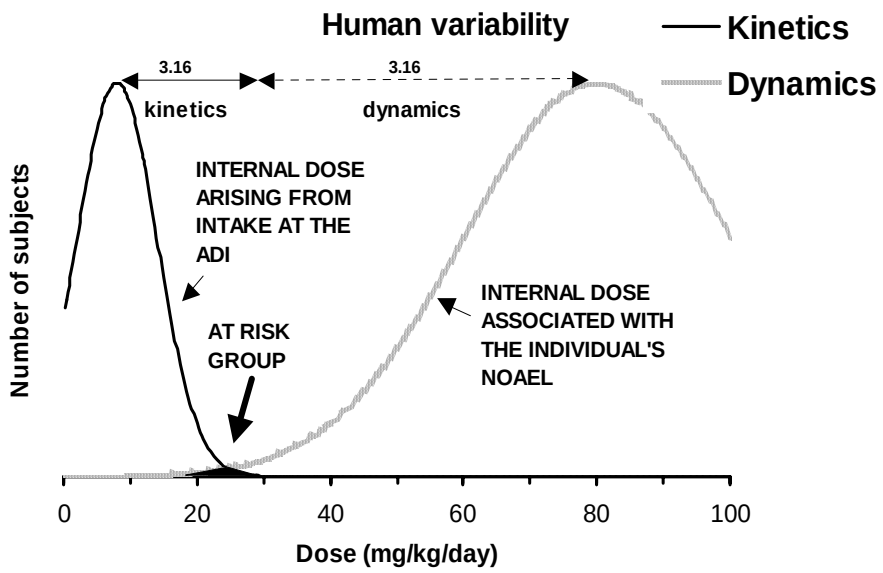

Figure 9. **The population distribution for toxicokinetic and toxicodynamic variability. The 10-fold factor has to allow for individuals with higher than average internal doses for the same external dose (toxicokinetic factor of 3.16) and for individuals with lower than average thresholds for adverse effects in relation to the internal dose (toxicodynamic factor of 3.16) "At risk" individuals will be those with high internal doses and low thresholds.**

e) the incidence of individuals with kinetic or dynamic characteristics >3.16 away from the corresponding mean values is determined by the coefficient of variation within the population distribution (Figure 10).

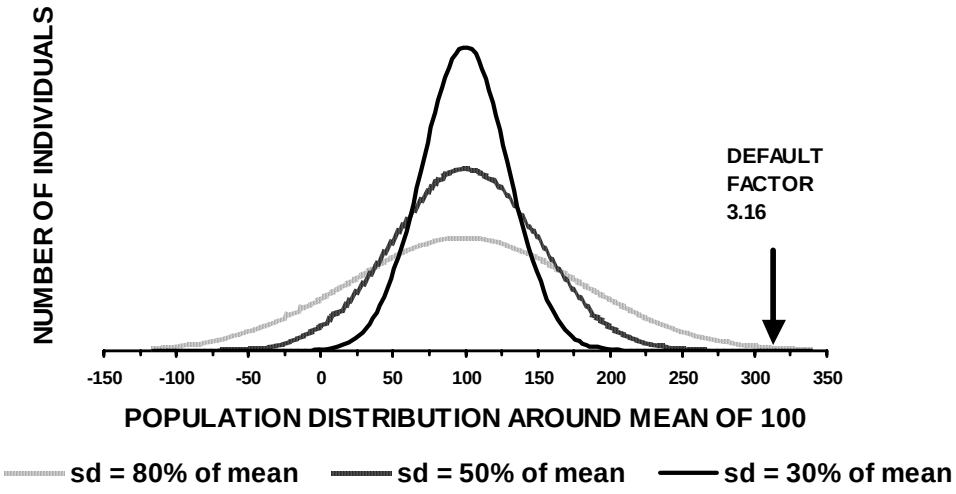

Figure 10. Interindividual variability in relation to the default uncertainty factor for kinetics or dynamics. The data represent the population distribution around a mean value of 100 for data showing standard deviations of 30%, 50% and 80% of the mean value (plotted for a normal distribution).

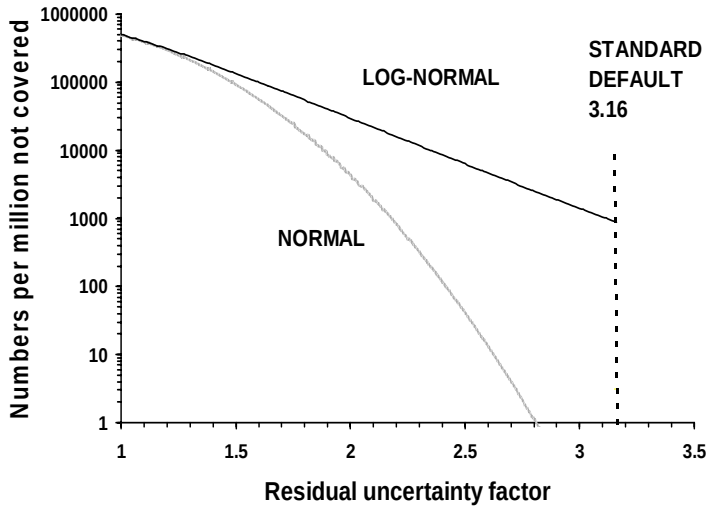

Figure 11. The influence of population distribution model (normal or log-normal) on the incidence of individuals not covered by the default uncertainty factor of 3.16 for kinetics or dynamics (plotted for illustration purposes using a coefficient of variation of 38%).

f) the nature of the population distribution of the relevant kinetic or dynamic parameter, for example, unimodal, bimodal, normal, log-normal, skewed etc (Figure 11). In reality, such detailed data will rarely be available and a pragmatic default nature of the distribution, such as unimodal and log-normal,

will be necessary. (If there are sufficient data from studies in humans to define the nature of the population distribution, then these data should be used to replace the appropriate toxicokinetic or toxicodynamics default with a data-derived value).

g) default assumptions would be that the % coefficients of variation for kinetics and dynamics would be 38% and 51% (Renwick and Lazarus, 1998; see above) and the data would fit a log-normal distribution. Such estimates may not cover all sources of variability (see below). An alternative and slightly more conservative approach would be to assume default coefficients of variation of 50% for both kinetics and dynamics. An advantage of this is that it would not link the method to a specific, and possibly non-representative database (Renwick and Lazarus, 1998).

h) the default assumption about the variability and nature of the distribution should be modified by compound-specific data whenever possible.

i) the incidence of individuals at risk (of the adverse effect detected at doses above the NOAEL), ie those not covered by the 100-fold uncertainty factors, would be the product of:-
   - the incidence of individuals with target organ sensitivity exceeding the available uncertainty factor (3.16 for healthy adults).
   - the incidence of individuals with internal doses which differ from the population mean by more than the available uncertainty factor (3.16 for healthy adults).
   - the median estimate of the incidence of animals affected at the NOAEL based on application of a non-threshold model to the experimental data, eg a logit or probit plot, or the use of the Hill equation (Barton *et al*, 1998).

Alternatively, the incidence and severity of effects could be analysed by categorical regression analysis, which has the advantage of using all adverse effect data, but has a number of difficulties and limitations (Gibson *et al*, 1997).

The proportion of a population which would fall more than 3.16-fold away from the mean, and therefore not covered by the default can be calculated based on the interindividual variabilitiy in the relevant parameter (e.g. the target organ dose, or AUC for kinetics). The incidence of subjects not covered by 3.16-fold factor is directly proportional to the standard deviation for the parameter estimate (Figure 10). The choice of distribution model; ie normal or log-normal, has a greater impact when the population estimate is in the tail of the distribution (Figure 11). It is generally accepted that most data fit a log-normal distribution and adoption of this as a conservative default assumption would be less critical than the selection of a mathematical model for low-dose extrapolation for non-threshold effects (see above).

The analysis by Renwick and Lazarus (1998) showed that:

for *kinetics* using the average coefficient of variation (38%) the number of subjects not covered by a factor of 3.16 away from the mean parameter estimate would be <1 per million of the population assuming a normal distribution, and 860 assuming a log-normal distribution, and
for *dynamics* using the average coefficient of variation (51%) the number of subjects not covered by a factor of 3.16-fold away from the mean would be 11 per million of the

population assuming a normal distribution and 8323 assuming a log-normal distribution.

The probability of the same individual falling outside the range for both kinetics and dynamics (Figure 9) can be approximated by the product of the 2 separate estimates for kinetics and dynamics, assuming that the kinetic and dynamic "risk factors" are independent variables. On average <1 person in a million would not be covered by combined factors of (3.16 times 3.16) assuming a normal distribution and 7 persons per million assuming a log-normal distribution. This demonstrates that the 10-fold factor is an adequate default assumption for the types of chemicals and biological effects considered by Renwick and Lazarus (1998).

The use of standard deviations, geometric standard deviations and population distributions involves a number of assumptions. An important assumption is that the variability in single measurements, as used by Renwick and Lazarus (1998), will be representative of chronic exposure and that outliers on one occasion will remain outliers during chronic treatment. Although few publications give sufficient details to analyse intra-individual variability, published data indicate that outliers will not necessarily be the same individual on repeat observations [unless there is some genetically determined reason]. Therefore, the coefficients of variation in the single estimates are probably over-estimations of the situation during chronic administration, and their use represents a precautionary approach. In addition the available data on inter-individual variability would include variability due to random experimental errors, so that the values used would further over-estimate true long-term human variability. However, the values of 38% and 51% for kinetics and dynamics would be inadequate to allow for major genetic polymorphisms (see Renwick and Lazarus, 1998).

The incidence of individuals in a population who would not be covered by the standard default factor for kinetics or dynamics would depend on the variability inherent in the critical kinetic or dynamic measurement (Figure 12).

In reality, such information is rarely available, and hence an assumption would be necessary on the extent of variability for the kinetic and dynamic parameters. The assumed variability for any chemical risk assessment could be based on the analysis in the publication of Renwick and Lazarus (1998) either as a mean variability in the data studied, the median or the 90^{th} percentile of distribution of the data that were analysed.

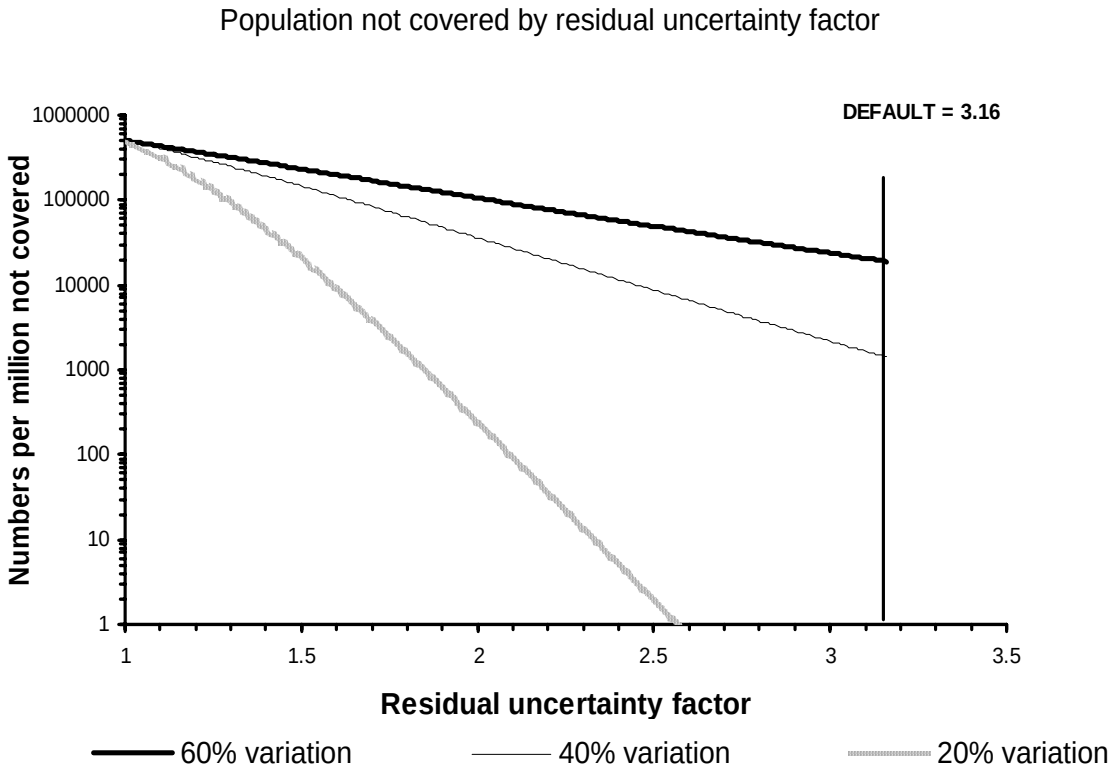

Figure 12. **Variability in kinetics or dynamics and the proportion of a population not covered by the default of 3.16 or by lower values when the uncertainty factor is reduced for a subgroup of the population. Data are plotted for illustrative purposes assuming a log-normal distribution with standard deviations of 20%, 40% and 60% of the mean value in the population which has a value of 1.**

At the present time this amounts to a common assumption, which would be applied to the majority of compounds, a situation that is similar to the use of the default linear model or low-dose risk extrapolation for carcinogens. In contrast to the low-dose risk extrapolation, this approach would allow the future incorporation of our increasing knowledge related to human variability in the enzymes involved in xenobiotic transformation and the enzymes linked to cytoprotective and homeostatic processes.

5b (i) Future refinements to uncertainty factors

Future developments will include pathway-related, categorical defaults (for kinetics) and, process or mode of action-related defaults (for dynamics), to allow fine-tuning of the factor to the chemical in the absence of detailed chemical-specific data (Renwick and Lazarus, 1998). The current, extensive database-analysis underway at Southampton University could be used to further refine these defaults in the future (Figure 13). In addition, these analyses should be able to provide pathway and process related default distributions for use in quantitative risk assessment for threshold toxicants.

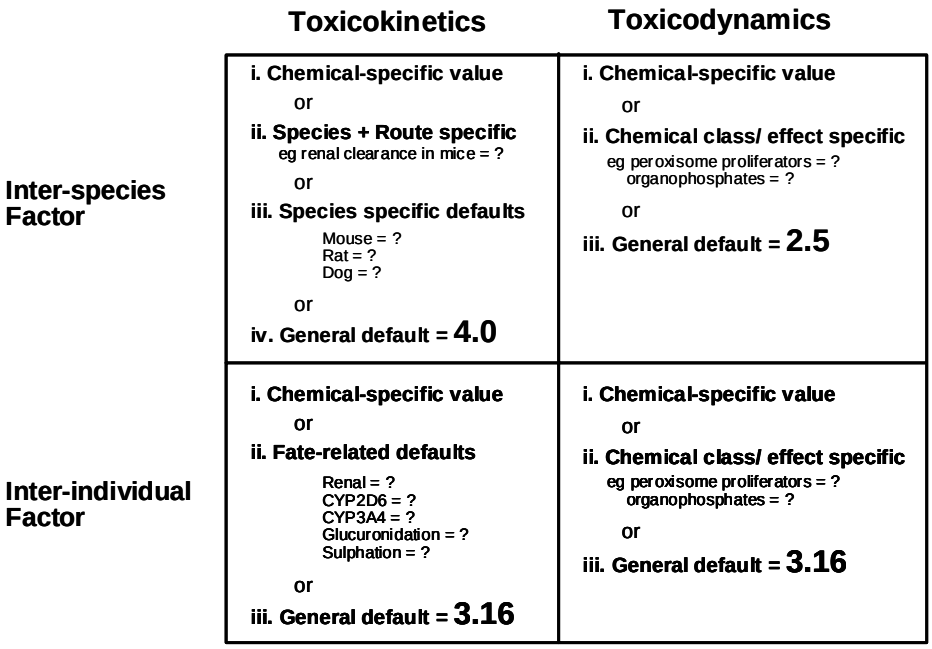

Figure 13. Future refinement of uncertainty factors based on replacement of general defaults with chemical-specific adjustment factors or categorical factors based on an analysis of compounds sharing common kinetic or dynamic properties (from Renwick and Lazarus, 1998)

Pathways of metabolism for a chemical can be identified by simple *in vitro* systems, and the role of specific isoenzymes can be defined by the use of heterologously expressed human isoenzymes of cytochrome P450. Such an approach may be particularly useful for the assessment of plant alkaloids, many of which may be substrates for cytochrome P450 isoenzymes and therefore subject to very wide inter-individual variability. In contrast, most food additives are metabolised by enzymes, which would be expected to show little variability, compared with the P450 enzymes which metabolise most drugs and alkaloids.

In principle, a similar approach could be adopted for toxic processes and responses. Data for humans are essential to undertake such an analysis and fortunately there are only limited data on human variability or species differences in toxic responses to non-therapeutic agents. However, it may be possible to develop specific defaults for some classes of effect that could be used to replace the general default values for dynamics. Relevant information could relate to *in vitro* responses of animal and human tissues (for example peroxisome proliferators) or to *in vivo* clinical toxicity (for example leukopenia). Theoretically, it may be possible to develop specific defaults for dynamics in different species compared to humans but it is unlikely that there will be adequate data on human variability in dynamics for non-therapeutic agents. Therefore, it is likely that the majority of chemicals will require the use of generic defaults for dynamics.

The use of separate factors for kinetics and dynamics will allow a knowledge of the fate of the chemical in the body to have a greater, and possibly quantitative, impact in the determination of the magnitude of the risk associated with different levels of exposure for humans. In addition, simple *in vitro* screens of pathways of metabolism will help to identify chemicals for which the common defaults may be inadequate.

6. APPLICATION OF QUANTITATIVE RISK ASSESSMENT TO RISK MANAGEMENT QUESTIONS

Quantitative risk assessment is not appropriate as the standard procedure for risk assessment/safety assurance, because of the problems and uncertainties involved at low risk estimates, and the spurious precision with which such estimates are usually presented. In addition, human exposures may be so low that the necessary allocation of research resources and further studies in experimental animals may not be warranted. Therefore, a tiered stepwise approach to the risk assessment of identified chemical hazards would be appropriate:-

Tier 1 — Estimation of the ratio between the doses reported to produce adverse effects in animal experiments and the estimated human exposures. Such a ratio would indicate the extent of any "margin of exposure" or "safety margin" and the potential magnitude of any problem, and could be used to prioritise different issues. Interpretation of the ratio should take into account the extent to which the nature of the animal study mirrored the human exposure of concern, for example the route and the duration of exposure, and also the nature of the possible hazard(s) associated with the chemical. For non-genotoxic compounds with a limited available database, a ratio of >10,000 would allow for the uncertainty factors that might be applied (see Figure 7 and WHO, 1994). For genotoxic compounds, the doses of different chemicals producing cancer in experimental animals are related to the maximum tolerated doses (MTD) in sub-chronic studies (see section 4aii). Because the same conservative model is usually applied to low dose risk estimation, the "virtually safe dose" for a genotoxic carcinogen is approximately 740,000 below the MTD. If human exposure are such that the margin of safety is less than these values then the assessment should proceed to the next tier.

Tier 2 — Consideration of mode of action and likelihood of a threshold at low exposures. Future harmonisation of non-threshold and threshold methodologies base on understanding of modes of action, may reduce the importance of this tier, but it is currently the major determinant of the approach adopted. Subsequent tiers will depend on the outcome of this tier.

Tier 3A (non threshold effects) — A variety of options could be given as advice to risk managers. These could include risk estimates using both highly conservative (linear) and conservative (linearised-multistage) models. These estimates would be presented with a description of the mechanistic assumptions made in the model used for extrapolation, together with an account of the uncertainties involved and the precision of the final risk estimate. The extrapolation model used for risk estimation should be the most sophisticated that is consistent with the data available on the chemical. An estimate of the risk would not be given if the database were considered to be inadequate, because of the uncertainties involved.

The margin of safety should be considered in the context of the usual uncertainty factors that would be applied, taking into account the nature and

Tier 3B (threshold effects)	duration of human exposures and the adequacy of the available database. Quantitation of the incidence of individuals who would not be covered by the usual uncertainty factors could be made, as outlined above, using as much data as possible. Any assumptions made should be explained, together with an account of the uncertainties involved and the precision of the final risk estimate.

An important consideration for future discussion, not addressed in this paper, is an assessment of the minimum data requirements (see Figure 1) before a quantitative risk assessment should be performed.

6a TIER 3A - Non-threshold effects

The currently adopted extrapolation procedures for low-dose risk estimation can take species differences in toxicokinetics into account by using PBPK models to convert the external dose (for animals and humans) into a target organ dose. However, differences in toxicodynamics cannot be incorporated without the development of a biologically-based, dose-response model.

Human variability is not really taken into account in current procedures for low-dose extrapolation (see discussion above). Toxicokinetic variability in humans could be incorporated by appropriate modification of the kinetic parameters (eg enzyme kinetics, liver blood flow etc) used in the PBPK model. The resulting output would be a risk assessment appropriate to those individuals within the population who show altered kinetic parameters. Human variability in dynamics could be taken into account by appropriate modification of a biologically-based, dose-response model.

6b TIER 3B - Threshold effects

An advantage of the population distribution analysis outlined above, is that it allows an estimate of the added risk associated with exposure scenarios for which the normal uncertainty factor (eg 100-fold) may be considered inappropriate.

6b (i) Analysis of special sub-groups of the population

A strength of using population distributions to estimate the incidence of individuals not covered by the usual default uncertainty factors is that data for sub-groups can be analysed either separately (Renwick and Lazarus, 1998), or by modification of the population distribution of the appropriate parameter estimate.

In some cases, the sub-group will be clearly identifiable, and the risk assessment could result in risk management options/actions applicable to the sub-group. An example would be neonatal exposure to an approved additive, where the approved uses could be modified as necessary. In other cases, for example genetic polymorphisms in enzymes involved in toxicokinetics or cytoprotection, the sub-groups will not be readily identifiable, and the overall risk assessment for the population will need to take the sub-group into account.

Simple theoretical examples of the application of the population approach for a threshold toxicant is given in **Annex 1**.

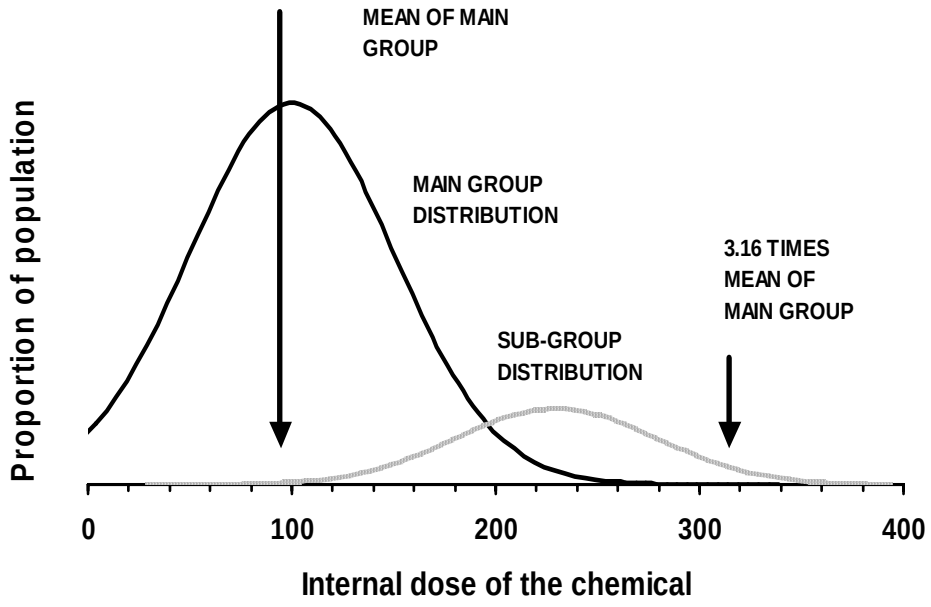

Figure 14. **Analysis of sub-groups by comparison of means and variability of main group (e.g. healthy adults) and the subgroup. The default factor of 3.16 (see Figure 8) would be applied to the mean of the main population group in order to cover variability within that group. Subgroups with higher internal doses, because of lower clearance, would show a higher incidence outside the usual factor. Subgroups with lower internal doses, because of higher clearance, would be covered to a greater extent than the main group in the population.**

Infants and Children

The immaturity of hepatic metabolism and low clearance in pre-term infants means that they represent a potentially vulnerable subgroup. Such vulnerability could be taken into account quantitatively by modification of the population distribution using the appropriate coefficient of variation and the magnitude of the difference between neonates and adults in order to estimate the risk for threshold effects (Figure 14). A recent review on the differences in kinetics between adults and children concluded that

young children frequently eliminate drugs and foreign compounds more rapidly by metabolism and excretion compared with adults (Renwick, 1998). In consequence, a smaller proportion of a population of children would be at risk compared with adults.

Quantitation of differences in sensitivity between neonates, or children, and adults in target organ response using *in vitro* studies, could be used to alter the default factor for human variability in toxicodynamics. If *in vivo* response data were available in human neonates (e.g. haemolysis associated with nitrate) such data would be used directly for risk assessment without the need for comparison with adult data.

Ethnic differences

Ethnic differences can arise from genetic and environmental factors and result in differences in both kinetics and response (Renwick, 1996). In many cases, differences in mean kinetic parameter estimates between different ethnic groups are small (Renwick and Lazarus, 1998) and ethnicity would not influence the validity of the default factor of 3.16. However, a 3.16-fold factor would be less adequate in cases where a different ethnic group showed a decrease in clearance, combined with an increase in variability, eg desipramine, diazepam, methylprednisolone and nifedipine. It is clear that ethnicity should be considered for some P450 mediated oxidation reactions, although this would need to be on a case-by-case basis.

Polymorphic metabolism

Calabrese (1985) illustrated that genetically determined biochemical differences could exceed greatly the 10-fold factor for human variability. That analysis interpreted variability in enzyme activities in relation to the full 10-fold factor and included *in vitro* estimations of activity as well as diagnosed clinical conditions. In cases of diagnosed clinical conditions, specific advice can be given; for example phenylketonurics are advised that the sweetener aspartame is a source of phenylalanine. Of greater potential concern are undiagnosed and unrecognised sources of variability, such as genetically determined differences in enzymes affecting kinetics, which have to be covered by the default uncertainty factor.

Genetically determined differences are of greatest relevance to risk assessment when the polymorphic pathway represents the major route of elimination. Poor metaboliser subjects would be at greater risk if the polymorphic pathway resulted in detoxication, but at less risk than the extensive metaboliser group in cases where the pathway is involved in a bioactivation process leading to toxicity. Therefore, knowledge that a chemical is a substrate for a metabolic pathway which shows polymorphic expression raises questions about the validity of the 3.16-fold default uncertainty factor for kinetics, (and therefore the combined 10-fold factor for human variability), but does not automatically invalidate the default values. Again known differences could be incorporated into an analysis based on thresholds and the population distribution (Figure 14), but could not be incorporated readily into low-dose extrapolation methods unless a PBPK model was part of the extrapolation model..

6b (ii) Consideration of intakes in excess of ADI, TDI or RfD

Excessive intake would affect the amount of chemical delivered to the potential target organ, but not the inherent sensitivity of the target organ (Figure 15).

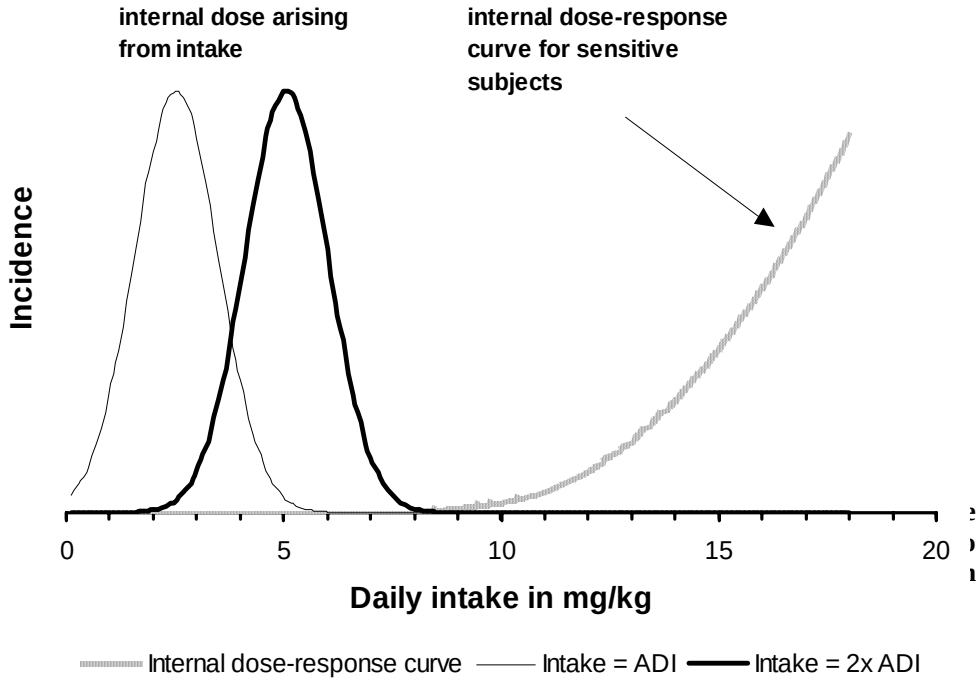

Figure 15.

The primary consequence is that the population mean internal dose at such elevated exposures will increase. This could be taken into account in low-dose extrapolation by requiring the output to predict the incidence at the higher dosage (note - with linear low-dose extrapolation an intake that is twice the virtually safe dose (1 in 10^6) must have an incidence of 2 in 10^6. For threshold effects, the available uncertainty factor would be reduced to 3.16 times (ADI or RfD/intake of concern), and the proportion of the population not covered by this value calculated from the assumed nature of the population distribution and the known or assumed variability (Figure 12) (Renwick, 1999b). The increase in the proportion of the population not covered by the default factor depends on the magnitude and duration of increased intake in humans, compared to the duration of the study that was the basis for calculating the ADI (Renwick, 1999b), and the assumed population distribution *ie* normal or log normal (Renwick, 1999c).

7. EXPOSURE ASSESSMENT AND RISK CHARACTERISATION

Exposure assessment is an essential step in risk characterisation (WHO, 1999a), which is subject to its own assumptions and errors and is outside the scope of this paper. As with the risk assessment procedures outlined above, assumptions tend to be conservative (Wolt, 1999) and therefore the final risk characterisation may be unrealistically conservative.

As outlined above, risk characterisation should incorporate as much compound-specific data as possible. Both low-dose extrapolation and threshold methods of quantitative risk assessment can be refined by the incorporation of toxicokinetic data (eg PBPK models) or toxicodynamic (mechanistic) data.

7a The use of biomarkers as a bridge between exposure assessment, toxicokinetics and toxicodynamics

Biomarkers of exposure and biomarkers of response provide a potential unifying link between exposure assessment and risk assessment. The *in vivo* dose-response data discussed above should ideally be replaced by *in vivo* biomarker-response data, and the dose and the response estimates based on actual measurements of the same biomarker. Although biomarkers of response would cover both kinetic and dynamic aspects, these could be misleading unless the biomarker represented the critical step in producing the response; therefore a detailed mechanistic understanding would be necessary. Biomarkers of exposure may relate to either the external dose, for example the daily excretion of a specific metabolite, or the internal dose, for example the steady-state blood concentration. Biomarkers of external dose are of use for exposure assessment only, whereas biomarkers of internal dose can be linked to both exposure assessment and to the parameters used in risk assessment. Such an approach would remove many of the assumptions and uncertainties of both risk assessment and exposure assessment and allow a more reliable risk characterisation.

7b Risk assessment outputs

Based on the discussion given above, the risk assessment process may result in one of 3 possible outputs:-

i) *For non-threshold effects* – a quantitation of risk based on extrapolation of the experimental data using an assumed mathematical model.

ii) *For threshold effects* – a quantitation of risk based on an assumed population distribution in relation to the surrogate for the threshold, and the level of human exposure.

iii) *For both threshold and non-threshold effects* – an estimate of the ratio between the surrogate for the threshold, or a dose giving a measurable incidence of a non-threshold effect (eg TD_{25}), and the level of human exposure. The use of the ratio is in association with a non-quantitative interpretation related to the exposure scenario. This approach is typically used for preventive standard setting, (eg establishing an "acceptable" exposure).

Each approach requires either a risk management decision on the magnitude of the risk which would be considered acceptable (i and ii), or the magnitude of the toxicity:exposure ratio ("margin of safety") that is appropriate for the exposure under consideration.

The "margin of safety" approach has a long history of use (for example a factor of 100 between the NOAEL and an acceptable intake for chronic exposure of the general population), and is defensible based on recent analyses. However, it does not allow interpretation of the risks associated with higher exposures, or the exposure of potentially sensitive sub-groups. The adequacy of any margin of safety or margin of exposure would need to consider the nature and quality of the available hazard identification and dose-response data, as well as the reliability and relevance of the exposure estimations (ie the robustness of the estimate). In addition, the adequacy of

any margin of exposure (safety) must depend on a combination of risk, benefit and cost (see definition of safety, and Williams, 1998).

There has been considerable controversy about the use of mathematical models for quantitative, low-dose, risk estimation of non-threshold toxicants. The outcome is determined largely by the mathematical model, which may have little or no biological relevance (see discussions on homeostatic processes and hormesis). Such approaches have not been accepted universally and are not appropriate for threshold effects.

The use of population distribution models to estimate the incidence of sensitive individuals who may be at risk based on their exposure and possible individual threshold provides an alternative approach for threshold effects. The approach retains biological plausibility and allows flexibility, but requires assumptions about the nature of the population distribution of individual thresholds.

RECOMMENDATIONS - PRIORITIES FOR FUTURE WORK

- Refinement of the models used for quantitative risk assessment to better reflect the shape of the dose-response relationship, including the presence of any thresholds.

- Research to address the nature and definition of biological thresholds in relation to the shape of the dose-response curves. (*Note* - probabilistic methods will usually give the possibility of a finite response for any dose above zero, and what is needed is a biological rationale for the development of mathematical models which include a threshold)

- Development of an international database on in vivo human variability in the major biochemical and physiological processes that affect xenobiotic disposition. Such a database could then be incorporated into risk assessments without the need for chemical specific data in humans in vivo, i.e. human variability could be derived using data from in vitro systems and animal studies which define the major processes involved in the fate of the chemical under consideration.

- **Table 1 Default approaches and risk assessment**

Default approaches are used in the absence of appropriate data on the compound being reviewed. Such default approaches can be refined by incorporation of compound-specific data of increasing complexity, until a full biologically-based dose-response model is developed.

General default approaches –approaches applied on the basis of general properties, eg linear extrapolation or uncertainty factors; similar approaches are used in the absence of chemical-specific data for compounds sharing similar general properties. Current standard default approaches (such as 100 when the NOAEL is for systemic threshold toxicity after oral administration to animals, or low-dose linearity for genotoxic carcinogens) are considered to be categorical, because they relate to simple categories, such as threshold/non-threshold, oral/inhalation and systemic/local effects. General default uncertainty factors include factors related to adequacy of database, inter-species differences and inter-individual variability.

Compound-related approaches – compound-specific data are used to convert the external dose to an internal dose, or to replace one or more of the categorical defaults uncertainty factors for inter- and intra-species differences. Examples include physiologically-based kinetic parameters such as area under the plasma concentration-time curve (AUC) (which are most appropriate when the parent compound is active), and *in vitro* target organ sensitivity data which can be used to replace part of a default uncertainty factor. PBPK (physiologically-based pharmacokinetic) models are useful for the parent compound, but add little to simple physiologically-based kinetic parameters. PBPK models are most appropriate when they include parameters for the conversion of the parent compound into an active metabolite, and for route-to-route extrapolation of the internal dose. PBPK analysis has been applied largely to take interspecies differences into account for low-dose extrapolation of animal data, and could be used to replace the kinetic component of the interspecies uncertainty factor. BBDR (biologically-based dose-response) models can be used to replace the toxicokinetic aspects plus part or all of the toxicodynamic aspects: historically such models have been applied to inter-species comparisons and rarely used to model human variability. Detailed knowledge of the toxicokinetics of the compound and its mode of action are essential for development of a reliable model.

Table 2 The strengths and weaknesses of dose-response extrapolation using an assumed default slope/mathematical model

Assumptions

1. A single molecule is theoretically able to produce a biological response (in the absence of a full biological dose-response model).

2. The dose-response relationship outside the experimental range is represented by an assumed default relationship (ie a mathematical model such as low-dose linearity), and is not a direct extrapolation of the slope of the relationship in the experimental range.

3. The starting point on the dose-response curve in the experimental range selected for extrapolation (eg the slope in the experimental range as fitted by the model, or upper confidence interval on the LOAEL, or 25% response for model-free approaches) is relevant for quantification of human risk.

4. Species differences can be taken into account by correcting the dose in the animal studies to a human-equivalent dose by interspecies scaling, or by the incorporation of a PBPK model giving the target organ dose of the active chemical species.

5. Human variability can be taken into account by using the upper 95^{th} percentile of the dose-response curve from the experimental data (usually in animals).

Sources of error/disadvantages

1. The low-dose risk estimate is not influenced by the slope of the experimental dose-response relationship.

2. The low-dose risk estimate is determined largely by the mathematical model chosen for the extrapolation procedure. In consequence, the low-dose risk estimate tends to be extremely stable and determined largely by the model rather than the experimental data.

3. Hormesis, or non-linearity at low doses, would invalidate the risk estimate.

Practical difficulties

1. Data on variability in human disposition (eg from *in vitro* systems) cannot be incorporated readily.

2. The more biologically credible models require extensive databases on cell turnover, which are rarely available and require extrapolation across species, or from *in vitro* to *in vivo* if human cell lines are used.

3. Selection of the appropriate dataset for extrapolation may be difficult for potent genotoxic carcinogens which increase the tumour incidence at a number of sites with different incidences and dose-response relationships.

4. Selection of the mathematical model cannot be based on the "goodness of fit" to the experimental data, because all models fit well in the experimental range.

5. Often the data for high doses do not fit well to the simple linear based models; such data (which may be the only statistically significant effect data) may be excluded for the purposes of extrapolation (Lovell and Thomas, 1996).

Advantages

1. The use of simple default linear models means that risk estimates based on data where the effect is seen at the top dose only will not differ greatly from data sets where there are two effect doses in the same experimental range.

2. The use of a default linear slope allows easy comparisons between different compounds showing the same effect (although in reality this could be made by simply comparing the doses giving the same fixed response such as the ED_{25}).

Table 3 The strengths and weaknesses of dose-response extrapolation using the slope from the experimental data

Assumptions

1. There is a probability that a single molecule could produce a biological response (ie there is no threshold).

2. The dose-response relationship outside the experimental range is a simple extrapolation of the experimental data, without the presence of a threshold or significant derivation at low doses.

3. The slope of the dose-response in the experimental data is relevant to humans.

4. Species differences can be taken into account by correcting the dose in the animal studies to a human-equivalent dose by interspecies scaling, or by the incorporation of a PBPK model giving the target organ dose of the active chemical species.

5. Human variability can be taken into account by using the upper 95^{th} percentile of the dose-response curve from the experimental data (usually in animals).

Sources of error/disadvantages

1. Extrapolation using the slope of the actual dose-response data will be influenced greatly by the number of doses producing a measurable response, and the precision of quantitation.

2. Errors or variability inherent in the experimental data will affect greatly the slope of the dose-response curve in the experimental range and this will be magnified by the extrapolation procedure. In consequence, the low-dose risk estimate would be an extremely unstable value and influenced greatly by precision in the experimental data. Because of these problems, the simple extrapolation of the slope in the experimental data is not used, and an approach outlined in Table 2 and the text is adopted.

Practical difficulties

1. Data on variability in human disposition (eg from *in vitro* systems) cannot be incorporated readily.

2. An ultra-conservative sub-linear slope (ie <10-fold decrease in risk for a 10-fold decrease in exposure) could arise from data sets with shallow dose-response curves or in which the response at the top dose was lower than predicted based on data at lower doses.

3. Selection of the appropriate dataset for extrapolation may be difficult for potent genotoxic carcinogens which increase the tumour incidence at a number of sites with different incidences and dose-response relationships.

Advantages

1. Provides the best possible estimate if the risk is derived from data for humans and by interpolation rather than extrapolation (see WHO, 1999b).

Table 4 The Bradford-Hill Criteria for Establishing Causality

1. Strength of association
2. Consistency of association
3. Specificity of association
4. Temporal relationship
5. Dose-response relation (biological gradient)
6. Plausibility
7. Coherence
8. Endpoint
9. Analogy

Based on Bradford-Hill (1965)

Table 5 The strengths and weaknesses of estimation of risks based on analysis of the proportion of a population not covered by the uncertainty factors applied to threshold effects

Assumptions

1. There is a biological threshold below which exposure does not produce a biological response (in reality this means a biologically significant response compared to inherent variability in the background and homeostatic mechanisms).

2. The threshold for biological response can be derived from the experimental data, and lower doses would not be associated with a risk.

3. The surrogate estimate of the threshold (eg the NOAEL) is a suitable starting point for human risk assessment.

4. Species differences can be taken into account by the use of a default uncertainty factor (usually 10 for oral dosage), by inter-species scaling to replace the toxicokinetic component of the factor, or by incorporation of chemical-specific data to replace either the toxicodynamic or toxicokinetic component.

5. Human variability can be taken into account by the use of a default uncertainty factor (usually 10-fold), or by the incorporation of chemical-specific data where they are available.

6. A default population distribution (normal, or log-normal) has to be assumed, because the nature of the population distribution in humans for overall sensitivity (to the external dose), or for the toxicokinetics and/or toxicodynamics in humans, will not normally be known.

Sources of error/disadvantages

1. The normal surrogate for the threshold (the NOAEL) is not derived using the slope of the dose-response curve (but this could be avoided by the use of the benchmark dose). The slope of the dose-response and the nature of the response data will influence the selection of the dose level that represents the NOAEL.

2. Available data on the distribution of the variability in humans to the overall response (or the toxicokinetic handling of the chemical) will never be sufficient to determine the actual incidences relating to a factor of 10-fold (or 3.16-fold for the toxicokinetic component) away from the population mean. In consequence, the incidences will be determined by both the distribution model applied (normal or log-normal) and the extent of variability (known or assumed).

Practical difficulties

1. Quantitation of risk has to use information on the nature of the population distribution of the biological threshold. In some cases, data may be available for the human variability in the toxicokinetics of the compound but default assumptions will normally be necessary for the toxicodynamic component.

2. When data are available on responses, or kinetics, these will normally be in relatively small numbers of subjects. In consequence, the nature of the distribution (eg normal, log-normal, skewed) will not be known. The data may be available only as mean ± SD, and conversion of such data to a geometric mean, geometric standard deviation and log-normal distribution will introduce errors. However, these errors will be negligible in the range of the data compared with the difference between log-normal and normal distributions when extrapolated to low incidences (see Figure 9).

Advantages

1. Knowledge about human variability in relevant metabolic, toxicokinetic or cytoprotective processes can be incorporated directly into the risk estimation, without the requirement for a sophisticated biologically-based dose-response model.

Table 6 Database-related default uncertainty factors

A minimum database is recognised for any risk assessment, although the requirements may vary depending on the risk assessment scenario. Additional categorical default factors, may be added to allow for deficiencies in the database, for example:-

LOAEL to NOAEL

Sub-chronic to chronic

Database deficiencies

the LOAEL may be divided by a factor (usually 3 or 10) if a real NOAEL has not been defined

an extra factor (usually 3 or 10) may be used if there is no chronic study to match chronic human exposures (Pieters *et al*, 1998)

an extra factor (usually 3 or 10) would be used if there is a part of the human lifecycle during which exposure occurs, which has not been tested in animal studies

See also Figure 7. All of these factors could be removed by appropriate test data.

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10. ANNEX 1 (Examples of quantitative risk assessment for threshold toxicity)

In all cases the quantitative risk assessment relates to an environmental chemical which has a tolerable daily intake (TDI) established by application of a 100-fold uncertainty factor to the NOAEL from a study in rats. The NOAEL was 10mg/kg/day and the only other dose studied (50mg/kg/day) gave a 20% incidence of renal damage. There are no toxicokinetic data in animals to allow modification of the default uncertainty factor and the 10-fold interspecies factor is assumed to be necessary. Adequate data were not available to modify the 10-fold factor for human variability at the time the TDI was determined.

In these "worked examples" the values are given with high precision in order to show the method of calculation, but in reality each value should be given to only 1 significant figure.

Analysis assuming a log-normal population distribution

Data are usually reported as the mean ± standard deviation (SD), but the default assumption for population distribution is a log-normal distribution. A log-normal distribution is assumed because this is a more conservative assumption than a normal distribution. If adequate population distribution data were available these would be modelled to give a better representation of the actual population distribution of the parameter. If the individual data are available these should be analysed for the geometric mean and geometric standard deviation (GSD), and if not then a necessary initial step is the conversion of the normal SD into a GSD. The coefficient of variation is calculated as the SD/mean. The coefficient of variation (CV) can be approximated to the log GSD (geometric standard deviation) by calculation of sigma:-

sigma = $[\ln(CV^{2+1})]^{0.5}$

GSD = EXP (sigma)

The log GSD can then be used to calculate the log Z score associated with a factor of 3.16 ($10^{0.5}$) away from the mean - calculated as 0.5/log GSD. The distribution for this number can then be calculated from the normal distribution of 0.5/log GSD (NORMDIST in Excel) and the proportion exceeding this value as 1- normal distribution of 0.5/log GSD.

Scenario 1

The intake was found to be twice the TDI, and the duration of excessive intake was relevant to the potential generation of toxicity. There are no human toxicokinetic or toxicodynamic data available. What is the increase in risk?

i) Assuming CVs of 50% for kinetics and 50% for dynamics

In this case there are no kinetic or dynamic data on the compound and default coefficients of variation (CVs) have to be used. In consequence, the risk estimate is determined by the assumptions made, that is CVs of 50% for kinetics and 50% for dynamics .

At the allowable exposure (eg the TDI) the numbers of individuals in the population not covered by factors of 3.16 for kinetics and dynamics (for individuals with intakes at the

TDI) would be 7432 per million for each of kinetics and dynamics, giving a product for both factors (the numbers not covered by both defaults) of 55 per million.

If the intake is increased by a factor of 2, this will double the internal dose and reduce the kinetic uncertainty factor to 3.16/2 (1.58 or $10^{0.2}$). This would result in 164,809 subjects per million not covered by the available kinetic factor, 7432 per million for dynamics and the product for both of 1220 per million not covered.

Conversion of numbers not covered into an incidence of actual risk of adverse effects would require combination of the overall population distribution and the dose-response curve (in animals). This could be achieved by Monte-Carlo analysis, or other approaches which would overlap the two incidence distributions. Given the poor characterisation of the dose-response curve, and the need to use the slope from the animal study, it is probably reasonable to assume a simple linear relationship (or log-linear).

Scenario 2

The intake is less than the TDI but it is recognised from toxicokinetic studies that there is a sub-group of the population with impaired metabolism of the compound. The clearance in normal individuals in the general population is 25 ± 15ml/min (mean ± SD) but is only 10 ± 8ml/min in the sub-group, which represents 10% of the general population.

A number of assumptions have to be made, eg that the sub-group may be at greater risk (ie that the parent chemical is active), that the target organ sensitivity is the same in both groups, that the 10-fold factor is applied to the main (normal) group and that the quantitative kinetic data are valid.

i) Assuming a CV of 50% for dynamics

The numbers of the main "normal" group in the population not covered by 3.16 would be 18937 per million (because of the high CV; 15/25 = 60%) for kinetics and 7432 per million for dynamics, giving a product for both factors of 140 per million. The kinetic factor available to the sub-group would be 3.16 x the difference in predicted internal dose, or 3.16 x (10/25), ie 1.264. The higher coefficient of variation in the subgroup (80% or 0.8) would also have to be taken into account. This would result in 369,531 per million of the sub-group not covered by the available kinetic default and 7432 per million not covered for dynamics, giving a product for both factors of 2735 per million not covered.

Thus the 2.5 fold difference in clearance plus greater variability results in a 19.5 fold increase in the numbers not covered in the sub-group. Although the available kinetic factor for the sub-group means that almost one-half are not covered by the kinetic default, this does not result in half the sub-group being "at risk" when both factors are combined.

Analysis of the total population risk would give a combined total of (0.9 x 140) + (0.1 x 2735) per million, ie 400 per million of the general population, most (274) of whom would belong to the sub-group.

Analysis assuming a normal population distribution

Scenario 1 (as above)
The intake was found to be twice the TDI, and the duration of excessive intake was relevant to the potential generation of toxicity. There are no human toxicokinetic or toxicodynamic data available. What is the increase in risk?

i) Assuming CVs of 50% for kinetics and 50% for dynamics

In this case there are no kinetic or dynamic data on the compound and default coefficients of variation (CVs) have to be used. In consequence, the risk estimate is determined by the assumptions made, that is CVs of 50% for kinetics and 50% for dynamics .

At the allowable exposure (eg the TDI) the numbers of individuals in the population not covered by factors of 3.16 for kinetics and dynamics (for individuals with intakes at the TDI) would be 8 per million for each of kinetics and dynamics, giving a product for both factors (the numbers not covered by both defaults) of <1 per million.

If the intake is increased by a factor of 2, this will double the internal dose and reduce the kinetic uncertainty factor to 3.16/2 (1.58 or $10^{0.2}$). This would result in 123024 subjects not covered per million by the available kinetic factor, 8 per million for dynamics and the product for both of about 1 per million not covered.

The main differences between the different population distribution models arise in the tails of the distributions, for example at a factor of 3.16 away from the mean the values for log-normal and normal are 7432 and 8 per million, whereas at a factor of 1.58 away from the mean the values are 166437 and 123024 respectively.

Scenario 2 (as above)
The intake is less than the TDI but it is recognised from toxicokinetic studies that there is a sub-group of the population with impaired metabolism of the compound. The clearance in normal individuals in the general population is 25 ± 15ml/min (mean ± SD) but is only 10 ± 8ml/min in the sub-group, which represents 10% of the general population.

A number of assumptions have to be made, eg that the sub-group may be at greater risk (ie that the parent chemical is active), that the target organ sensitivity is the same in both groups, that the 10-fold factor is applied to the main (normal) group and that the quantitative kinetic data are valid.

i) Assuming a CV of 50% for dynamics
The numbers of the main "normal" group in the population not covered by 3.16 would be 159 per million (because of the high CV; 15/25 = 60%) for kinetics and 8 per million for dynamics, giving a product for both factors of <1 per million. The kinetic factor available to the sub-group would be 3.16 x the difference in predicted internal dose, or 3.16 x (10/25), ie 1.264. The higher coefficient of variation in the subgroup (80% or 0.8) would also have to be taken into account. This would result in 370700 per million of the sub-group not covered by the available kinetic default and 8 per million not covered for dynamics, giving a product for both factors of 3 per million not covered.

Analysis of the total population risk would give a combined total of (0.9 x <1) + (0.1 x 3) per million, ie <1 per million of the general population. Comparison of this analysis with the log-normal analysis given above shows how model dependent the risk estimate is for threshold effects.

APPENDIX 4

REPORT ON

QUANTITATIVE MICROBIOLOGICAL

RISK ASSESSMENT

(FOOD AND OTHER CONTAMINATED PRODUCTS)

Table of contents:

SUMMARY

Microbiological risk assessment is a scientific process. It consists in gathering and analysing information and data with the objective of identifying what pathogens and/or their toxins or metabolites, products, or situations lead to illness, and at determining the magnitude of the impact these have on human health, together with an identification of the factors that influence it.

Most of traditional microbiological risk assessments have been mainly qualitative. Qualitative risk assessment remains the only option when data, time or other resources are limited or as a first evaluation of a microbiological safety issue. The present trend, however, is to encourage the development of a quantitative approach to microbiological risk assessment. Mathematical (quantitative) treatment of information would provide a better insight into the microbiological risk. The mathematical models designed and utilised in this context are in themselves important scientific tools and sources of information. In many present situations, however, the need to provide useful risk conclusions would probably require a broad scientific approach associating an "ordinal", qualitative evaluation, and a "cardinal", quantitative and probabilistic evaluation.

The focus of this report is on the issues that need to be considered when introducing quantitative approaches to the risk assessment of pathogenic microbiological contaminants in food and other contaminated products.

INTRODUCING QUANTITATIVE APPROACHES TO MICROBIOLOGICAL RISK ASSESSMENT

Several classes of products or situations may be subjected to microbiological risk assessment. Microbial contaminants include micro-organisms that are not voluntarily introduced in a product, nor fulfilling a useful purpose. Microbial contamination may involve pathogenic agents of different classes. Quantitative microbiological risk assessment was originally developed to evaluate the safety of drinking water with regard to resistant pathogens such as viruses and protozoa. To date, quantitative microbiological risk assessment is increasingly applied to food safety issues which represent a public concern for both regulatory authorities and consumers. Emerging areas of concern might involve in particular recreational water and tattoos.

Several features are unique to the risk assessment of microbial contaminants. In principle, each exposure to a pathogen or its toxin represents an independent, non cumulative event (except for particular fungal toxins). (Pathogenic) microbial contaminants are not voluntarily added to a food. Their presence results from incidental introduction at any stage of the production, manufacture, distribution, and use continuum. Conditions thereof may vary and influence the initial level of micro-organisms. Pathogen or toxin level may change dramatically over time or due to preparation or handling practices. Micro-organisms are highly variable and have the potential to acquire or loose virulence-associated characteristics. It is likely that the population's response to an infectious pathogen is extremely variable reflecting, in large part, the variability in the immune status of humans. The dynamics of microbial infection may involve many factors such as the infective dose, the rate of infection, the incubation period, whether any resulting disease is acute or chronic, or leads to a carrier

state and secondary transmission. All these factors need to be considered to provide a complete picture of a microbiological risk.

The application of a quantitative approach to microbiological risk assessment requires risk assessors to carefully consider the scientific basis for their estimates, and to explicitly state the assumptions made. This is beneficial to transparency, especially in comparison to what is generally the case in qualitative risk assessments. However, users should avoid a false sense of precision in the application of quantitative risk assessment. When exploiting the results, it should be clear that quantitative risk estimates are not exact values, but rather should be seen as indicative of the order of probability of an adverse event occurring. Also, in many cases mathematics and statistics at an advanced level are used. This can not be circumvented without sacrificing the scientific rigor of the assessment. However, significant efforts must be made to present the results of a risk assessment study in a format that is accessible to the different groups, including the non-scientists, that would use it.

APPROACHES TO QUANTITATIVE MICROBIOLOGICAL RISK ASSESSMENT

Hazard identification

The focus and extent of hazard identification depends on the purpose of the risk assessment.
In the food sector in particular, most risk assessments have been conducted for policy determination, involving a given pathogen/commodity combination. In that case hazard identification is straightforward and involves gathering information on the specified pathogen with regard to a given food or groups of foods. This is rather unique, and other situations may require different approaches.
When hazard identification is developed in the framework of the assessment of the risk from exposure to a defined product, hazard identification is a categorial activity aimed at identifying which pathogens have been, or potentially could be, associated with the product. In that case, reliable hazard identification is dependant on the availability of public or animal health data and information on the occurrence and levels of pathogens in the product of concern. Recently, expert systems have been developed to support this activity.
Microbiological risk assessment may also be applied to understanding a public health problem. There, hazard identification consists in evaluating the weight of the scientific evidence for the association between the pathogen and adverse effects in human or animals, determining the ways in which adverse effects can be expressed, inferring causal relationship between risk factors and the disease, and determining the major sources of exposure. Laboratory, clinical and epidemiological data are crucial, whereas bayesian approaches have been very recently applied to assist in inferring causal relationship.

Hazard characterisation - Dose-response relationship

Hazard characterisation provides a qualitative or quantitative description of the severity and duration of adverse effects. A dose-response assessment should be performed if the data are obtainable. The outcome of exposure to a micro-organism or its toxin depends on the characteristics of the pathogen, the host and the vector matrix (the infectious disease triangle). Therefore, a hazard characterisation should provide information on

these characteristics and their interaction, with regard to the scenario under study. This implies that there is not one single best hazard characterisation or dose-response model, but that the analyst should make the best possible choice. If this requires subjective choices to be made, these should be communicated and agreed with the risk manager, and their implications clearly outlined.

Sources of information and data

Two broad sources of information may be used to elucidate dose-response relationship, each with their strengths and weaknesses.
Data from experimental studies include human volunteer feeding studies, animal models, and *in vitro* studies. Their applicability rests on the extent to which the experimental infection quantitatively reflects a natural infection. Generally, experimental studies reflect a specific combination of factors in the infectious disease triangle and do not reflect all relevant variability. Combination of results from different experimental studies may provide important information in this respect.
Data from observational studies include routinely acquired data and specific studies. They may more accurately reflect actual exposure situations, with a mixed host population and pathogens in a natural physiological status and delivered through actual risk-sources. As such, these data are highly valuable for hazard characterisation. However, other limitations may apply.

Each approach to collecting information and data on dose-response relation has advantages and disadvantages. It is generally recommended to take into account all relevant information. Critical evaluation of how data were generated helps proper applications. It is critical to acknowledge the strengths and weaknesses inherent to the method of collection and to the data utilised, and to formally express any uncertainty that exists. Ways of combining the different forms of quantification of the dose-response relation should be sought in order to minimise that uncertainty.

Dose-response modelling

Dose-response modelling attempts to mathematically describe the probability of adverse health effects following exposure to different doses. The mathematical model is utilised to extrapolate from experimental or epidemiological data the probability of adverse effects at low doses. The variability between individuals and the uncertainty can also be characterised by the dose-response function.

The interaction between a pathogen, the host and the food matrix may be treated as a chain of conditional events (exposure, infection, acute illness, complication and chronic sequelae, death), whereby the completion of any stage is required for the realisation of the next stage. Two biological concepts are of key importance in deriving plausible dose-response models. These are threshold vs. non-threshold events, and independent vs. synergistic action. There has been substantial efforts to define a minimal infectious dose (MID) for various food borne pathogens. These efforts have typically not been successful. To date, the current school of thought is that the dose-response relationship for infectious micro-organisms is non-threshold.
Building on the non-threshold hypothesis, a family of related hit-theory models has been developed, of which the *exponential* and *Beta-Poisson* models are the best known examples. The *exponential model* assumes that each micro-organism has the same

probability *r* of establishing infection (in all possible hosts). The factor *r* is a specific constant in each study, but may be different between studies (e.g. another strain of the pathogen, another host population, another matrix). The *Beta-Poisson model* is presently more widely used, because it fits more experimental datasets. It assumes that the probability *r* is not constant, but instead is different for any organism in any host, and this variability is described by a Beta-distribution [$r \sim \text{Beta}(\alpha, \beta)$]. The Beta-Poisson model provides a flexible description of the dose-response relation for infection. It is currently accepted for describing a variety of microbial pathogens in foods. Variation of the two parameters α and β allows adjustment of the model curve to fit dose response data sets. The Beta-Poisson model estimates the average risk to a population following the ingestion of an average dose. Modified Beta-Poisson models have been proposed (e.g. the Beta-binomial model) where variability for the probability of infection from a particular dose is incorporated within the simulations so that the model estimates the risk of infection for an individual consuming a specific dose. The Beta-Poisson model involves two simplifying assumptions on the parameter values. It is a special case of a more general hypergeometric model, which is computationally less easy to apply. Methods to estimate parameters of the hypergeometric model are being developed.

When fitting models to data, appropriate methods should be used to ensure maximum likelihood, while determination of parameter uncertainty is indispensable. Experimental datasets are usually obtained under carefully controlled conditions, and the available data apply to a specific combination of pathogen, host and matrix. In actual exposure situations, there is more variability in each of these factors, and dose-response data needs to be generalised. Assessing such variability requires the use of multiple datasets that capture the diversity of human populations, pathogen strains and matrices. Failure to take such variation into account may lead to underestimation of the actual uncertainty of risks. When developing dose-response models from multiple datasets, one should use all of the data that is pertinent. There are currently several ways of determining which data source is best. This requires that the risk analyst makes choices. Such choices should be based on scientific arguments to the maximum possible extent, but will inevitably include subjective arguments. Such arguments should be communicated to the risk manager and their significance and impact for the risk management discussed. The credibility of dose-response models increases significantly if dose-response relations derived from different (types of) data sources are consistent. Important information for validation may come from high quality epidemiological studies. Systems for collecting, collating, analysing and disseminating epidemiological information and data should be actively conserved and developed in response to the needs associated with the development of quantitative microbiological risk assessments.

Exposure assessment

Exposure assessment determines the probability and the likely levels of exposure in the human population. In a complete quantitative risk assessment, the final goal is to produce a mathematical expression describing the exposure, which is combined with a dose-response model. For food borne pathogens, the occurrence and levels of the microorganism or toxins in the foods of interest, the dynamics of the micro-organism or toxin, and the consumption pattern and habits of the population under study, need to be taken into account.

Structure of the exposure assessment model

An essential step in the development of an exposure assessment model is to produce a description of the relevant stages of the food pathway in sufficient detail, while having regard to the risk management questions and the endpoint of the risk assessment. During this stage the risk assessor is forced to structure the problem and to identify the key processes to be modelled and the information needed. The conceptual model describing the pathways and processes leading up to the exposure may be divided into discrete model units, or sub modules, that are eventually linked together.

Depending on the emphasis and the perspective of the exposure (risk) assessment different approaches have been used in developing the overall model. For instance, the Event Tree describes a scenario from the initiating event to a defined end-point of the assessment. The Fault Tree begins with the occurrence of a hazard and from there describes the events that must have occurred for the hazard to be present. Additional approaches to modelling used in assessments of microbial food hazards include a Dynamic Flow Tree model which emphasises the dynamic nature of bacterial growth and incorporates predictive microbiology using statistical analysis of data, or a Process Risk Model which focuses on the integration of predictive microbiology and scenario analysis to provide an assessment of the hygienic characteristics of a manufacturing process. Variations on these themes exist. The broad types of models described here operate in only one direction, which does not make the inclusion of feedback mechanisms possible. This may be a limiting factor when modelling complex biological systems. Alternative approaches recently proposed may include dynamic models based on differential equations, or Markow chain, and random-walk models or so-called neural networks. It should be noticed that methods for dealing with uncertainty associated with the choice of the structure of risk models are lacking.

Once the conceptualisation of the problem and the structure of the model is decided upon, estimates of the exposure can be made. In a deterministic approach, a quantitative assessment of the exposure is estimated based on single point estimates of the model parameters. The sensitivity of the deterministic model can be evaluated by selecting different combinations of each input parameter to see how much the outcomes vary. The various combinations are commonly known as what-if scenarios. Obviously this approach has several limitations. In a probabilistic approach, uncertainty and variability are taken into consideration by representing parameters as probability distributions rather than single point values. Accordingly, the outcome of a probabilistic model is a probability distribution. There are a number of techniques to calculate the outcome distribution such as the method of moments, exact algebraic solutions and Monte Carlo simulation. Several applications of Monte Carlo simulation with regard to risk assessment of microbiological foodborne hazards have documented the merit of the method. Despite its increased complexity over the point-estimate approach, the probabilistic approach, incorporating Monte Carlo simulation, is now becoming the preferred approach to quantitative microbiological risk assessment (for foods).

Building the exposure assessment model

For foodborne hazards the exposure depends on the occurrence and the levels of micro-organisms in the food at the time of consumption, and the consumption pattern. A

significant feature of exposure assessment for microbiological hazards is that it should specifically take into account the dynamics of the microbial population. To that aim, exposure assessment employs predictive microbial approaches and models within the larger exposure model. Most probabilistic models of exposure assessment of foodborne pathogens use Monte Carlo simulation techniques. The Monte Carlo simulation model is constructed so as to describe in a systematic and logical way along the production-to-consumption continuum the contamination sources, the likely numbers of a pathogen that might be introduced into the food, the influence of factors that affect the distribution, survival, growth, or inhibition of the micro-organism. This includes: qualitative understanding of the whole process (module, sub-module); identification of variables and parameters that should describe the process, quantitative information; data collection, data evaluation, data analysis; selection of distributions for variables/parameters.

The exposure assessment models are based on experimental data or on assumptions developed through expert opinion when significant data are lacking. The methodological limitations in exposure assessment are generally related to the qualitative and/or quantitative insufficiency of available data needed to estimate the exposure. The exposure assessments are often based on predictive models that were developed using data from broth experiments and their ability to describe growth or inactivation in food need to be validated.

Risk characterisation

Risk characterisation is the integration of hazard identification, hazard characterisation including dose-response assessment, and exposure assessment, to provide an overall probability of a given population being subjected to an adverse health effect. A particular aspect of risk characterisation for microbiological pathogens refers to expressing the severity of the related disease. Severity may be expressed in a variety of ways, most of which include consideration of possible outcomes. Recently, a non-specific approach to measuring the health burden of foodborne illness has been proposed, based on health-related quality of life scales (quality or disability adjusted life years, QALYs or DALYs) which are commonly used in health economics and medical decision making.

The two components, variability and uncertainty, describing the degree of reliability of the risk estimate, should be thoroughly described. The separate effect of variability and uncertainty on the risk estimate should be made clear. Estimating separately variability and uncertainty will provide useful information for further decision making. In any case, because in quantitative microbiological risk assessment the output of risk characterisation is a probability distribution of the risk, it should be clearly stated if this distribution represents variability, uncertainty, or both.

A sensitivity analysis of the result of mathematical modelling should be performed, to provide information on the effect of changes in the mathematical approach on the result of the risk estimate. A sensitivity analysis has two objectives. The first is to identify the elements or factors that most impact on the magnitude of the risk. The second is to "move around" with the uncertainties/assumptions to see how much they affect the results, i.e. to determine the robustness of the model toward these

uncertainties/assumptions. For sensitivity analysis in the context of microbiological risk assessment it could be advisable to examine two aspects: the effect of changes in the estimated parameters and the effect of the choice of input distributions.

Validity of QMRA results can be established at two different levels: verification and validation. Verification is basically a technical exercise, aimed at assuring the precision of parameter estimates and implementation of computer software. It is mainly the responsibility of the analyst, but could involve specialist review. One aspect of validation is the scientific acceptability of model assumptions, model formulations and criteria for data selection and treatment. This involves communication with the scientific community at large. Another aspect is comparison with empirical data. Microbiological risk assessment is unique because often the diseases of concern do actually occur in the population, and model estimates could be compared with observational data from epidemiological studies (e.g. cross sectional surveys, cohort studies, case-control studies, intervention studies) which should be actively developed and strengthened.

The risk characterisation, along with a report of the risk assessment process, is handed over to the risk managers, and serves as the basis on which risk management decisions are made. The basis for the estimate should be fully and systematically documented and all assumptions and constraints indicated to ensure that process is transparent. The report should be made publicly available to give interested parties (stakeholders), the opportunity of comments and suggestions to the process. This also serves the purpose of exposing the report to peer reviewing.

DEFINITIONS

Risk assessment is an evolving field, and several organisations, groups or individuals have proposed definitions for the terms utilised (e.g. Terminology Standardisation and Harmonisation, 1999; ISO/TMB Working Group on Risk Management terminology, 2000; Codex Alimentarius Commission, 1999). These definitions may vary to some extent. For the purpose of this report, the terms related to microbiological risk assessment have been utilised according to the definitions given in the Codex Alimentarius document "*Principles and guidelines for the conduct of microbiological risk assessment*" (ALINORM 99/13A). These definitions are in line with the definitions proposed in Appendix 1.

1 - INTRODUCTION

Microbiological risk assessment is a scientific process.

It consists in gathering and analysing information and data with the objective of identifying what pathogens and/or their toxins or metabolites, foods, or situations lead to food borne illness, and in determining the magnitude of the impact these have on human health, together with an identification of the factors that influence it.

Microbiological risk assessment may be conducted to provide answers to a variety of questions, such as :

- Estimation of the current risk level associated with a pathogen/food or product combination, to determine whether and which action has to be taken.

- Identification of the best points at which to implement controls. This, in turn, requires identifying points and/or factors in production to consumption/use that most significantly influence the human health outcome and are therefore important risk determinants .

- Comparison of control options/mitigation measures, implying comparison of the level of risk and/or effectiveness in risk reduction for different options/scenarios.

- Identification of hazards to be targeted by priority, given limited resources. In such situations, comparative assessments can be conducted to identify hazards of primary concern.

- Need to make a decision about a microbiological hazard, when time is limited.
A crude assessment with simplifying assumptions can provide general information and guidelines for managerial conduct in a short time.

In all these situations, evaluating the microbiological safety of a food or any other potentially contaminated product typically requires consideration of multiple factors that influence the prevalence and numbers of a microbial pathogen (or level of a toxin) in the product, and how this correlates with the probability and severity of adverse human health effects.

The emphasis of this report is on the development of **quantitative risk assessment** for estimating the current risk associated with **pathogenic microbial contaminants** in foods or other contaminated products, i.e. where those micro-organisms that may cause human disease are not voluntarily introduced in food or other products. Nevertheless, it has to be borne in mind that several classes of micro-organisms are presently utilised in the food- and other industries where they serve a useful purpose, for instance as "starters" of a directed fermentation process, as technological aids, or for the production of specific food ingredients (e.g. production of enzymes by micro-organisms, natural or genetically modified). Obviously, such "useful" micro-organisms, and the conditions in which they are utilised, may also be subjected to an assessment of any potential risk.

However, the specific aspects of the assessment to be conducted in these particular situations have not been considered in this report.

Current situation

a) - In the food sector

Assessments of the risk associated with microbial contaminants in foods have been conducted since long, in one form or another, by the scientific community, the food industry and regulatory bodies. Recently, however, the need to adopt more formal principles and approach to microbiological risk assessment for foods has been recognised, with particular regard to the implications of the SPS agreement.

To address this need, the Codex Alimentarius Committee on Food Hygiene fostered discussions on an overall framework for microbiological risk assessment for foods. These discussions resulted in an international consensus embodied in the Codex Alimentarius document "*Principles and Guidelines for the Conduct of Microbiological Risk Assessment*" (Alinorm 99/13 A)

This document defines microbiological risk assessment as

"*a scientifically based process consisting of the following steps:*
(i) hazard identification
(ii) hazard characterisation
(iii) exposure assessment
and (iv) risk characterisation"

It provides an outline of the elements of a Microbiological Risk Assessment, indicating the types of decisions that need to be considered at each step.

This framework is appealing for several reasons. While bearing similarities with the paradigms utilised in other fields of activities and thus ensuring commonalties of approaches, it allows for incorporation of features unique to the attributes and concerns of microbiological food safety. It is flexible enough to handle a variety of applications. It may be used for planning and conducing microbiological risk assessments (MRAs) of varying complexity. It has been applied successfully to a variety of MRAs in different food safety contexts. As a consequence, it is considered of being of primary interest to governments and other organisations, companies and other interested parties who need to prepare a microbiological risk assessment for foods.

In addition to Codex, other groups have been active in developing valuable guidelines for microbiological risk assessment of more general application (e.g. ILSI, 2000). These documents include all the essential steps identified in the Codex approach, provide additional useful information, but slightly differ in the denomination and grouping of the stages involved. For the sake of simplicity, the content of this report is structured to the Codex framework.

Based on the paradigm delineated in the Codex Alimentarius document, two general approaches to microbiological risk assessment may be undertaken. These have been described as qualitative and quantitative.

Qualitative risk assessments are descriptive treatments of information.
Quantitative risk assessments are mathematical analysis of numerical data, either generated or formulated based on expert opinion.

Most of traditional microbiological risk assessments in the food sector have been mainly qualitative. Qualitative risk assessment remains the only option when data, time or other resources are limited. Alternatively, qualitative risk assessment may be undertaken as a first evaluation of a food safety issue to determine if the risk is significant enough to warrant more detailed analysis.
Qualitative microbiological risk assessments should be more than simply a literature review or summary of the available information about an issue.
A qualitative risk assessment should follow the systematic approach delineated in the Codex framework, and include sections dealing with hazard identification, exposure assessment, hazard characterisation and risk characterisation. The structured framework should assist in reducing the possible bias associated with the risk assessor's interpretation of qualitative information, help providing a framework for translating qualitative information into an objective evaluation of the overall risk, and help ensure that descriptive statements are not misinterpreted by risk managers and others that will use the assessment.

The present trend, however, is to encourage the development of a quantitative approach to microbiological risk assessment. Mathematical (quantitative) treatment of information would provide a better insight into the microbiological risk. The mathematical models designed and utilised in this context are in themselves important scientific tools and sources of information: they provide a framework for analysing the available information, aid in identifying knowledge gaps, provide a context for discussing the biological processes involved, and as a whole help in identifying and focusing on critical issues. In addition, a quantitative approach to microbiological risk assessment can support an effective microbiological risk management under the concept of risk tolerability where appropriate, assist in making comparisons, while accounting for variability and uncertainty and their impact.

In many present situations, however, the need to provide useful risk conclusions would probably require a broad scientific approach associating an "ordinal", qualitative evaluation, based on real life experience and expert judgement, and a "cardinal", quantitative and probabilistic evaluation where enough quantitative and reliable data are available.

b) - In other sectors

To date quantitative microbiological risk assessment (QMRA) is primarily applied to food safety issues since health problems associated to food consumption are relatively frequent and there is a public (authorities and consumers) concern.

Even though in the European region drinking water rarely creates health problems, QMRA is applied in this domain. Actually, QMRA was originally developed to evaluate the safety of drinking water with regard to resistant pathogens such as viruses and protozoan (oo)cysts. Several risk assessment studies have been published (e.g. Regli *et al*., 1991; Teunis *et a*l., 1997). For risk management decisions a preliminary definition of acceptable risk of infection of 10^{-4} per person per year has been used in the USA. However, no formal QMRA frameworks for pathogens in drinking water have been published. Note that the ILSI framework for QMRA was originally aimed at application in drinking water (ILSI Risk Science Institute Pathogen Risk Assessment Working Group 1996) and was later updated (ILSI, 2000) to cover both water and food. QMRA has also been applied in risk trade-off problems such as the balance between positive and negative health effects of drinking water disinfection (Havelaar *et al.* 2000). WHO has stated that the new revision of water-related guidelines including the Guidelines for Drinking Water Quality, will be based on a risk assessment/risk management approach, and is actively preparing documents to support this process.
According to the brief description of products and situations amenable to QMRA as detailed in section 2.1, two sectors have priority for QMRA, since emerging problems have already been detected: recreational waters and tattoos. Although any product of section 2.1 is at least in theory amenable of QMRA, recreational waters and tattoos have to have priority in QMRA because their increasing social incidence.

In the context of the above, the **scope of this report** is to discuss some of the issues that need to be considered when introducing quantitative approaches to risk assessment of microbiological contaminants in foods and other contaminated products.
Food will be considered as a case study. Only nuances will be introduced with regard to the assessment of the microbiological risk associated with other contaminated products, where appropriate.

2 - CASES FOR INTRODUCING QUANTITATIVE APPROACHES TO MICROBIOLOGICAL RISK ASSESSMENT

Humans are permanently exposed to infectious agents. This exposure has to be under the best possible control in order to avoid illness, disease and death. Citizens and consumers are more or less regularly exposed to series of products that contain or may contain microbes and infectious agents with the subsequent risk of infection. Risk Analysis is increasingly recognised as the approach to be taken to establish which infectious agents, products and environmental situations need better control and prevention and at what level. Specifically, quantitative microbiological risk assessment (QMRA), is developing at a rapid pace and is increasingly considered as a useful tool to inform decision- and policy-makers when deciding upon Risk Management actions.

Since there is an enormous variability in the products that may transmit infectious agents and in the environmental and ecological situations that may affect such transmission, the first step is a brief description of the potential infectious agents, of the products that may transmit infectious agents, of the potentially affected host and of the environmental situations that may affect the risk of transmission.

There are several methods to quantify risks. When the emphasis is on the adverse effects, epidemiological methods provide the most direct way to quantify risks as well as the produced effects. When the emphasis is on the pathogen, or when effects do not occur, or when their frequency is low or when the effects are of minor incidence, quantitative risk assessment is more appropriate. The best assessment is a stringent combined application of epidemiological and quantitative risk assessment methods.

2.1 Classes of products and situations amenable to Q-MRA.

Food and drinking water are the products associated with major risk of (toxico-) infection in consumers for the following reasons:
- Every person ingest several times per day food and water
- Microbial contamination of foods and microbial growth may take place during production, processing, distribution, storage and preparation.

Medicines, blood products and medical devices are products occasionally used by citizens. These products are intended to be free of harmful micro-organisms. The risk associated to these products is only existing if the appropriate production and quality control procedures fail.

Cosmetics and Tattoos. Cosmetics are products of increasing use in the EU. From babies to old people there is a tendency to increase the number of cosmetics utilised as

well as the frequency of their application. Cosmetics are in general easily biodegradable compounds topically applied. They may enhance microbial infection or transmit pathogens, if contaminated. These situations may be of particular concern when cosmetics are used in the eye area or on mucous membranes or on damaged skin. Children under 3 years, elderly people and people showing compromised immune responses may be particularly affected by contaminated cosmetics. At the present, EU regulations of the microbial content in cosmetics do not exist, although the SCCNFP in their Notes of Guidance recommend microbial limits in cosmetics to ensure the consumer safety. In this section a border line cosmetic-like activity of increasing demand are the tattoos, which are practised today in the absolute absence of regulations addressed to the professionals, locals, tools, products and environmental conditions. Tattoos are administrated by intradermal injection of appropriate inks to adorn the human body and for some cosmetic purposes as lip lining and eyebrow lining. Well-recognised microbial (among others) adverse effects as transmission of infective agents are known. This new situation deserves quantitative microbiological risk assessment and epidemiological assessment.

Household products consist of series of diverse products aiming to clean, disinfect and give better condition, appearance or smelling of the dishes, clothes, textiles, implements, furniture and surfaces. In many instances as consequence of their intrinsic formulation these products are sterile, but in some cases they are biodegradable and may enhance or transmit microbial infection if contaminated.

Toys, textiles and houseware. These types of products do not normally contain micro-organisms, nor facilitate microbial growth. However in some cases they may transmit microbial pathogens if not adequately produced and cleaned.

Pets and other animals. Zoonosis are microbial human infections transmitted by animals. In this context the contact with animals at domestic level (pets) or in animal production activities may induce a recognised risk.

Labour and occupational sources of contamination are hospitals and plants that process wastes and residues .

Environment In the last years, environmental factors as temperature, precipitation, and wind and ocean currents may quite strongly affect the pattern of occurrence (WHO, 1996; US Academy of Medicine, 1997). Typical examples are the higher prevalence of respiratory infections in winter or the enteropathogens spread in summer time. The so-called climate sensitive diseases are:

- Vectorborne diseases (malaria and viral diseases).
- Waterborne diseases (cholera, leptospirosis and parasitic diseases as schistosomiasis, cryptosporidiosis and giardiasis)
- Foodborne diseases (in particular campylobacteriosis and salmonelosis)
- Airbornediseases (meningococcal meningitis, coccidioidomycosis, viral respiratory infections and bacterial infections as legionellosis and pneumonia.
- Plant and fish diseases

Travelling and leisure activities. Modern citizens spend an increasing important time in leisure sport or outdoor activities or travelling to exotic places. There is also an increasing tendency to enjoy exotic cuisine , new foods, pamper our pets or enjoy extreme physical activities. There is a number of infections that may be associated to these activities, including the sexually transmitted diseases if these activities imply higher promiscuity.

2.2 Classes of microbial pathogenic agents - Routes of exposure

Bacteria, fungi, viruses, protozoa and other parasites. Bacteria, fungi and viruses are the basic and most important microbial pathogenic infectious agents responsible of still frequent cases of illness and death. Microbes are ubiquitous in nature and a paramount characteristic of bacteria and fungi with respect the QMRA is that under favourable conditions they may rapidly grow, thus increasing the probability to infect the host. This situation is not shared by virus, which only may grow and spread when appropriate cellular hosts are infected. In addition to the traditional parasites, *Giardia* and *Cryptosporidium* are two protozoa that cause enteric illness transmitted by water that constitute a potential risk to public health. Spores of bacteria and some fungi, cysts for protozoa are resistant forms that may survive conditions that destroy the so-called "vegetative" bacteria, fungi or protozoa.

Prions. Although prions are not microbes they behave as infectious agents. Last years the spread Bovine Spongiform Encephalopathy (BSE) created considerable public concern, which was exacerbated from 1996 when was detected a new variant (nv) of the Creutzfeld-Jakob disease (CJD).

Toxins. Microbial toxins are an important component in the context of all types of toxins. They are considered as toxic chemicals and in consequence treated on the frame of quantitative chemical risk assessment. However, since there are transmitted and produced by microbes, microbial toxins may also be object of QMRA. Toxins of bacterial origin usually lead to acute illness. For toxins of fungal origin, the main concern relates to long term, chronic effects. Risk assessment of microbial toxins should account for these specific differences.

Routes of exposure. For a given pathogen, and at times for a given product also, there might be different routes of exposure such as parenteral or intravenous injection, chirurgical actions, ingestion, inhalation or topical contact. When several routes of exposure may be involved in the transmission of the disease, these have to be taken into account in the microbiological risk assessment.

2.3 Issues specific to microbiological risk assessment

(N.B. in this section only food is taken into consideration, as an example.)

Specific factors need to be considered when assessing a microbiological risk.
With regard to food safety evaluations, these include (but are not limited to) the following:

- Microbial food safety risks are primarily the result of single exposures (even chronic sequellae). In principle, each exposure to a pathogen or its toxin represent an independent, non cumulative event (except for particular fungal toxins). There are however some important nuances to be made because infection by pathogenic agents confers specific immunity in the host. Upon subsequent exposure, immunity may protect the host from infection, from illness or may reduce the severity of illness. The extent to which this needs to be accounted for in QMRA depends mainly on the duration of protective immunity, which may be in the order of only a few months for some enteropathogenic bacteria to lifelong for e.g. hepatitis A virus. Immunity may occasionally also be induced by exposure to non-pathogenic variants of the same species. For example, exposure to *Listeria monocytogenes* with reduced virulence has been shown to protect mice from infection and death after exposure to pathogenic strains of *L. monocytogenes* (Chakraborty *et al.* 1994). There are also some suggestions for cumulative effects of repeated exposure to *L. monocytogenes*. No general statement can be made on the extent to which immunity should be accounted for in quantitative microbiological risk assessment, since this depends on the micro-organism of concern. In all cases, it is important to describe the present knowledge about immunity in hazard characterisation.

- (Pathogenic) microbial contaminants are not voluntarily added to a food. Their presence results from incidental introduction (from the environment, including the producing animal(s), workers and/or materials in contact with the food) at any stage of the production, manufacture, distribution, use continuum. Conditions thereof may vary and influence the initial level of micro-organisms (in a raw material, an incoming material, a ready-to-eat product).

- Potential for change in pathogen or toxin level. Pathogen numbers can decrease as a result of a cooking step. Conversely, pathogenic bacteria capable of growth in foods can increase as a result of abusive storage. The formation of microbiological toxins is linked to cell levels. Therefore, the risk of foodborne microbial disease is influenced by the conditions associated with food storage (including abuse) and handling.

- Microbial variability. Micro-organisms have the potential to acquire or loose virulence-associated characteristics. They have various physiological mechanisms that may allow them to adapt to control measures.
In addition, the virulence can be affected by the food matrix in which micro-organisms are present.

- Variability in host response. It is likely that that the population's response to an infectious pathogen is variable (and possibly rivals the complexity observed with carcinogenic compounds). The variability of response in large part reflects the variability in the immune status of humans. Individuals can range from highly susceptible to resistant depending on their genetics, age, physiological status, and a variety of other biological and socio-economic factors. Where the disease process for infectious agents involves their multiplication in the host, there is not necessarily a correlation between the levels of the pathogen in the food and the severity of the disease response.

- Dynamics of infection. The dynamics can be influenced by many factors such as the infective dose, rate of infection, incubation period, whether any resulting disease is acute or chronic, or leads to a carrier state and secondary transmission. The distinction between infection (the fact that a micro-organism has taken up residence in a host) and disease is an important issue for microbiological risk assessment. There is also a need to consider not only the immediate effects of the infection, but also the longer term secondary consequences.

2.4 Benefits and possible limitations of quantitative microbiological risk assessment

The application of risk assessment to safety issues improves the transparency of the basis for the actions taken to manage risk. The structured approach that is necessary facilitates the stakeholders' understanding of assumptions and data, with its limitations, that the risk assessment is based on. Equally important is that it makes the comparison between different risk management options possible and the gaps in knowledge obvious. Thus, it makes cost/benefit analyses possible prior to selecting different management options. Further, since modelling is quick and cheap in comparison with generating experimental data it can help in optimising the collection of data most needed.

By developing mathematical models, risk assessors are forced to carefully consider the scientific basis for their estimates, and to explicitly state the assumptions made. This is beneficial to transparency, especially in comparison to what is generally the case in qualitative risk assessment. The discussions on quantitative microbiological risk assessment (QMRA) can actually stimulate and focus discussions on the underlying biological basis of the models. Also, QMRA tends to focus the discussions on the most important aspect in a causative chain of events. It creates the need for multidisciplinary communication and co-operation.

However, it should be kept in mind that the results of any risk assessment should be interpreted carefully and are valid only as much as the data and assumptions made in developing the model are valid. Also, in many cases mathematics and statistics at an advanced level are used in QMRA. This can not be circumvented without sacrificing the scientific rigor of the assessment. However, this may be a limitation since this can make the results and understanding of a QMRA inaccessible to non-specialists. Although the final review of a risk assessment requires specialists, significant efforts must be made to present the results of a risk assessment study in a format that is accessible to the different target groups.

3 - APPROACHES TO QUANTITATIVE MICROBIOLOGICAL RISK ASSESSMENT

Quantitative risk assessment applied to microbial safety issues is a scientifically based methodology to estimate the probability and severity of a health disturbance as a consequence of exposure to microbiological hazards (Whiting and Buchanan 1997, Cassin et al., 1998, Marks et al., 1998). The terminology and methodology are not yet definitive, but the process involves four main steps: 1) Hazard identification, 2) Hazard characterisation 3) Exposure assessment, and 4) Risk characterisation (WHO/FAO 1995, EC 1997, Buchanan 1998, CAC 1998). A formal risk assessment requires a structured and scientific approach, and should be transparent, with the assumptions clearly stated.

3.1 Hazard identification

Risk assessment is usually considered to begin with hazard identification. However, it has to be realised that the context and use of the risk assessment determines the focus and extent of microbiological hazard identification.

Microbiological risk assessments may be conducted for policy determination. This is in particular the case in the food sector where most of the formal risk assessments that have been published fall in this category. In such circumstances, the situation of concern is already identified by the risk managers. It usually involves the definition of a pathogen/product or process combination (e.g. assessment of the health risk from *Listeria monocytogenes* in ready to eat foods). There, hazard identification is straightforward and focuses on gathering information on a specified microbial pathogenic contaminant (characteristics of the pathogen that affect its ability to be transmitted by the product and to cause disease in the host) with regard to a given food or groups of foods. This serves as input to the elaboration of a (process) risk model utilised for further analysis.

This situation is rather unique, and microbiological hazard identification may require different approaches when the microbiological risk assessment is conducted for other purposes.

Hazard identification may be developed in the framework of the assessment of the risk from exposure to a defined product. Here, the question of interest is which pathogens may be transmitted by the product (e.g. which pathogens may be transmitted by a given food commodity, or which pathogens may be introduced in an importing country via import of live animals or their products). In this context, hazard identification is a categorisation activity, identifying which microbiological agents may be potential hazards. In such a case, the focus of hazard identification will be to use available microbiological and epidemiological data to determine which pathogens have been, or potentially could be, associated with the product. Reliable hazard identification is dependant on the availability of public (or animal) health data and information on the

occurrence and levels of pathogenic micro-organisms in the product of concern. Expert systems to support hazard identification with respect to food products are being developed. One example is the SIEFE system (Van Gerwen *et al.,* 1999; Van Gerwen *et al*., 2000). This system employs a stepwise approach to identifying and prioritising microbial hazards in food. The system is based on a structured food database and employs (qualitative) knowledge rules on association of pathogens with food products, survival of pathogens, general characteristics of pathogens and growth opportunities of pathogens. In this context, an essential aspect of hazard identification is to differentiate between trivial and non-trivial concerns. More than one hazard may be identified, arising from the same product, but possibly in different circumstances. Usually, the subsequent stages of the risk assessment would be applied to each hazard identified.

Microbiological risk assessment may also be applied to understanding a public health problem, to describe and analyse situations where the focus is primarily on the disease and its potential outcomes. For example, assessments may be applied to circumstances such as recent recognition (or suspicion) of the aetiology of a disease (e.g. *Campylobacter jejuni* and gastro-enteritis), situations involving a recognised pathogen (e.g. long term consequences of infection by *Salmonella*), instances where the aetiological agent is rapidly changing in character (e.g. influenza), or where a recognised organism is found in new situations (e.g. *Staphylococcus aureus* and toxic shock syndrome). In such situations, microbial hazard identification is quite similar to hazard identification for toxic chemicals. It consists in determining the strength of an association and inferring causal relationships between risk factors and disease, i.e. in identifying (or confirming) the inherent capability of a microbial agent to cause adverse effects, the potential harm, and the circumstances in which adverse human health effects may be expected. Causality may be considered when several arguments are met, such as consistency between results of independent studies, biological plausibility, existence of animal models, time sequence from the suspected cause and the effect(s), dose (or duration) effect relationship. Hazard identification is then based on analyses of a variety of data that may range from laboratory analyses to clinical observations and epidemiological information. Recently, Bayesian approaches have been developed to assist in inferring causal relationships. In this regard, traditional pathogens are relatively well documented and the formal requirements for hazard identification are minimal. However, for new, emerging pathogens, or when facing new situations, an essential aspect of hazard identification is to evaluate the weight of the scientific evidence for adverse effects in human (or animals), the ways in which they can be expressed, and the major sources of exposure.

3.2 Hazard characterisation - Dose-response assessment

Hazard characterisation provides a qualitative or quantitative description of the severity and duration of adverse effects that may result from the ingestion of a micro-organism or its toxin in food. A dose-response assessment should be performed if the data are obtainable, with the purpose of converting exposure level estimates into a probability of adverse effects. Hazard characterisation is a constitutive part of risk assessment. However, it has to be acknowledged that hazard characterisation is a general process which may also be developed as a standalone process, where the results may be easily

transferred to other exposure situations to the same pathogen and for which risk assessments are being conducted.

The outcome of exposure to a micro-organism or its toxin depends on the characteristics of the pathogen, the host and the food matrix. Therefore, a hazard characterisation should provide information on these characteristics and their interaction. When applying hazard characteristic information in a specific risk assessment study, the information that is most relevant to the scenario under study should be used. This implies that there is not one single best hazard characterisation or dose-response model, but that the analyst should make the best possible choice. If this requires subjective choices to be made, these should be communicated and agreed with the risk manager, and its implications clearly outlined.

3.2.1 Review of basic characteristics of the micro-organism, the host, and the matrix

Many factors are involved in the balance of the interaction between the host and the pathogen. Their relative importance and impact on the dose-response relationship should be described and preferably quantified. This requires a major, long-term effort to incorporate available information on pathology of gastro-intestinal infection and disease in statistical and dynamic mathematical models. Development of such models would also fuel experimental work.

A useful framework for dose-response modelling is the disease triangle (Coleman and Marks, 1998), stating that the probability of disease depends on the complex interaction between the pathogen, the host and the environment (e.g. the food matrix). Any model of dose-response relations is necessarily a simplification of this complex interaction, yet should strive to incorporate the major factors and the effects of biological variability.

Characteristics of the micro-organism include: general characteristics, factors contributing to the likelihood of producing food-borne illness, factors contributing to the severity of the illness, other factors that may alter infectivity / virulence / pathogenicity, types of illness associated with exposure, types of illness associated with the pathogen. Pathogen related factors include dose, colonisation potential in the host gastro-intestinal tract, stress proteins, growth rate in the intestines, pathogenicity (species, strain and serotype), specific virulence factors, timing of expression.

Characteristics of the host include: demographic and socio-economic factors (age, sex, race, nutritional status, as appropriate), genetic factors, other predisposing factors (health status, concurrent medications, infections, immune status, and previous exposure), risk groups. Host related factors include age, non-specific barriers (mechanical barriers, gastric acid, enzymes, possible interaction with intestinal microflora), specific humoral and cellular immunity, pre-existing illness.

Characteristics of the matrix include: food type and characteristics (e.g. fat content, buffering capacity), conditions of ingestion (meal size; empty or full stomach). Environmental influences include the characteristics of the food vehicle (protection by the food matrix), conditions of consumption, protective effect of dietary factors,

indigenous microbial competitors in the food, the indigenous microbial competitors in the host gastro-intestinal tract.

3.2.2 Sources of data for hazard characterisation

Different sources of data are available for hazard characterisation, each with their strengths and weaknesses. It is generally recommended to take into account all relevant information. Critical evaluation of how data were generated helps proper application in a risk assessment context.
Two broad sources of information may be used to elucidate dose-response relationship:
- Data from experimental studies, including human volunteer feeding studies, animal models, and *in vitro* studies.
- Data from observational studies, including routinely acquired data and specific studies.

Data from experimental studies

Their applicability rests on the extent to which the experimental infection quantitatively reflects a natural infection. Differences between natural and experimental infections may exist because of several reasons:
- Differences in the physiological state of micro-organisms used for experimentation.
Experimental infections often use micro-organisms that have been maintained in the laboratory. Laboratory isolates, and culture conditions may be unintentionally selective and affect the pathogenicity of strains utilised. The magnitude of differences in infectivity (and potential to cause morbidity) between laboratory maintained cultures and the wild-type micro-organisms is currently not clear. Different strains of one pathogenic species may have different infectivity or disease-causing ability. Using data on only one strain may considerably underestimate uncertainty in the dose-response relation.
- Differences between healthy human volunteers and the population at large.
Human volunteer feeding studies provide the most direct measure of human response to pathogens and have been the data of choice for quantitative microbiological risk assessments. However, human infectivity trials tend to be restricted to healthy (male) adults, challenged by a narrow range of micro-organisms that are not considered life threatening for the test subjects. Uncertainty will underlie the extrapolation of these data to the rest of the population (particularly the very young, the elderly, pregnant women and the immuno-compromised). Ethical, economical and logistic restrictions usually lead to using relatively few test subjects per dose. As a consequence, these experimental conditions may produce relatively high rates of infection or morbidity and necessitate low dose extrapolation over several orders of magnitude.
Interpretation of human volunteer studies requires attention and reporting of experimental details. These can also be used as a quality check on the published results. Aspects include definition of biological endpoints (infection, illness), measurement of dose, which unit of dose was used, is this similar to the unit in exposure assessment, did the method effectively quantify viable, infectious organism (specificity, sensitivity), characterisation of the immune status of volunteers etc.
- Differences between animal models and human infection.
The validity of animal studies rests on the extent to which an infection in animals reflects those in humans (similarities of pathogenicity mechanisms, of physiological and immune response, of quantitative relationship between infectivity, morbidity and mortality). This may be a significant challenge for many foodborne pathogens. Animal

studies have many of the same difficulties as human volunteer studies (healthy animals, high doses). Also, most laboratory animals are highly inbred, so that genetic diversity among the animals is minimal. This reduces the variability associated with the testing, but brings into question the data's applicability to the human general population. An additional aspect to be taken into account is the translation of effects in animals to those in humans.

In conclusion, experimental studies generally reflect a specific combination of factors in the infectious disease triangle and do not reflect all relevant variability. Combination of results from different experimental studies may provide important information in this respect.

Data from observational studies

Data from observational studies may more accurately reflect actual exposure situations, with a mixed host population and pathogens in a natural status and delivered through actual food-sources. As such, these data are highly valuable for hazard characterisation. However, other limitations apply. In general, it is more difficult in observational situations to get an accurate estimate of ingested dose. Factors that modify the dose-response relation may not be explicitly known, and this is a serious caveat to extrapolation of the results to other populations. When data are available, stratified analysis would increase the possibility of generalisations.

Epidemiological investigations, as a source for human dose-response information, may employ either routinely collected data or specific studies.
Routine data for foodborne pathogens include reports on the (annual, national) incidence of foodborne disease, outbreak investigations and laboratory reports. They are easily accessed, but crude. To be useful for risk assessments, they must be interpreted with an understanding of the possible reporting bias. Investigations of outbreaks should be expanded beyond their current scope, and provide information not only on the patients, but also on the consumers that did not become ill, on the conditions of consumption by both groups (e.g. the amount of food consumed), on the specific concentration of responsible micro-organisms, on the frequency and extent of food contamination. Only some well-documented outbreak studies currently provide such data. Epidemiological studies may, however, be valuable for validation of the results of quantitative microbiological risk assessment (see 3.4).

Each approach to collecting information and data on dose-response relation has advantages and disadvantages. Therefore, it is critical to acknowledge the strengths and weaknesses inherent to the method of collection and to the data utilised, and to formally express any uncertainty that exists. Ways of combining the different forms of quantification of the dose-response relation should be sought in order to minimise that uncertainty.

3.2.3 Dose-response modelling

Dose-response modelling attempts to mathematically describe the probability of adverse health effects following exposure to different doses.
Foods are usually contaminated by low numbers of micro-organisms. In contrast, experimental or epidemiological data usually refer to high levels of pathogens in foods.

Hence, a mathematical model is necessary to extrapolate from these data the probability of adverse effects at low doses. The variability between individuals and the uncertainty can also be characterised by the dose-response function.
Dose-response modelling for microbial pathogens in foods is presently one of the most debated topics in the context of the development of quantitative microbiological risk assessment.
Considerations in dose-response modelling are specifically addressed in the following section. It has to be borne in mind that models should be mathematically and biologically valid (McNab 1997).

Modelling concepts

The interaction between a pathogen, the host and the food matrix may be treated as a chain of conditional events, whereby the completion of any stage is required for the realisation of the next stage (Teunis *et al.*, 1996).
The subsequently occurring events can be summarised as follows:

- Exposure
The ingestion of a certain amount of food may imply swallowing a number of pathogenic micro-organisms, would the food be contaminated.
Following ingestion, nothing may happen because the ingested pathogen(s) is destroyed in the host's gastro-intestinal system.
To the contrary, exposure may result in infection.

- Infection
The pathogen is able to survive in the host's digestive system. It reaches a location suitable for colonisation, and actively multiplies itself. For gastro-intestinal pathogens, this may be manifested by faecal excretion or by immunological response. Would this happen, infection may be asymptomatic. It may result in an asymptomatic carrier state. In turn, infection may lead to clinically observable illness. Currently, the term infection is used and defined differently by various disciplines. It should be made clear that in the context of hazard characterisation, the term is used to refer to the colonisation of the intestinal tract, and includes both symptomatic patients and asymptomatic carriers (Last, 1995).

- Acute illness
Tissue damage, the action of toxins, inflammation and other factors may lead to developing clinical symptoms, possibly including complications, and depending on a number of host- and pathogen related factors. Illness is not a quantal response (i.e. an individual being in one of two states ill or not ill), but rather a broad set of host responses that vary in type and in intensity. Therefore, the actually measured incidence of disease is strongly dependent on the case-definition. Illness usually leads to complete recovery but complications, eventually leading to mortality may occur.

- Complications and chronic sequelae
These may result from dehydration, septicaemia, toxaemia, autoimmune diseases or chronic infections.

- Death

With a few exceptions, death is a relatively infrequent event after acute gastro-enteritis in immuno-competent persons. However, death may occur more frequently in risk groups (Young, Old, Pregnant, Immuno-compromised including diabetics) or after complications.

Two biological concepts are of key importance in deriving plausible dose-response models. These are threshold vs. non-threshold events, and independent vs. synergistic action.

The traditional theory considers that there is a threshold level of pathogenic bacterial cells that must be ingested in order for the micro-organism to produce an infection or a disease response in the host. This led to the concept of Minimum Infectious Dose (MID), i.e. the minimum number of bacteria needed to cause disease. In its most extreme form, this concept postulates that if a group of persons is exposed to a level in excess of the MID, infection and/or disease is a deterministic process and will occur in every individual. An alternative concept is to assume that a threshold exists if there is no effect below some average dose, regardless of the size of the population administered a dose (Haas, personal communication).
There has been substantial efforts to define the MID for various foodborne pathogens. These efforts have typically not been successful, and the underlying assumption that a threshold exists for infectious and toxico-infectious agents has been debated and challenged. To date, the current school of thought is that the dose-response relationship for infectious micro-organisms is non-threshold. In contrast, whether the effects of toxins produced *in vitro* (toxigenic organisms) or *in vivo* (toxico-infectious micro-organisms), or other host damage will lead to disease is generally considered to be a threshold effect.

Building on the non-threshold hypothesis, the basic assumptions to derive the currently favoured family of hit-theory models for dose-infection modelling are that:

i) the pathogenic micro-organisms are distributed randomly within the consumed medium, and that the probability of ingesting *n* pathogens (the dose) follows a Poisson distribution;
ii) infection involves independent action of micro-organisms (the probability of one micro-organism infecting the gastro-intestinal tract is independent of others) and;
iii) any single surviving micro-organism can start infection if it arrives at an appropriate site. That is, even if the probability of infection from a single micro-organism is extremely low, it is not zero.

Model functions

It has been cautioned that unless one is extremely careful, it is dangerously easy to generate models that violate core mathematical assumptions of the distributions used (Vose, 1996). Many proposed models can fit appropriately the observable data. However, when extrapolating outside the region of observable data, equally good models can predict drastically different results (Coleman and Marks, 1998; Holcomb *et al*., 1999). This implies that the selected model should represent a concept that is biologically valid. Epidemiological and biological considerations should influence the choice of the final model. Additional data are needed to adapt the model(s) to sub-

populations (e.g. children, the elderly, and the immuno-compromised) that might possess dose-response characteristics different from those of adults.

The above described hypothesis lead to the derivation of a family of related hit-theory models, of which the *exponential* and *Beta-Poisson* models are the best known examples. These are based on a mathematical model originally designed to estimate the infectivity of tobacco mosaic virus (Furumoto and Mickey, 1967a,b). They have been used by several investigators to describe dose-response relations for different classes of biological agents, including extrapolating to the ingestion of low levels similar to what would be expected in food and water (Haas, 1983; Rose and Gerba, 1991; Crockett et al., 1996; Medema et al., 1996; Teunis et al., 1996; Coleman and Marks, 1998; Fazil et al., 1999).

For infection to succeed, at least one organism in the ingested dose has to survive and reach a target site within the host. The *exponential model* assumes that each micro-organism has the same probability *r* of establishing infection (in all possible hosts). The factor *r* is a specific constant in each study, but may be different between studies (e.g. another strain of the pathogen, another host population, another matrix).

The *Beta-Poisson model* is presently more widely used, because it fits more experimental datasets. It assumes that the probability *r* is not constant, but instead is different for any organism in any host, and this variability is described by a Beta-distribution [$r \sim \text{Beta}(\alpha, \beta)$]. The Beta-Poisson model provides a flexible description of the dose-response relation for infection. It is currently accepted for describing a variety of microbial pathogens in foods. Variation of the two parameters α and β allows adjustment of the model curve to fit dose response data sets.

The Beta-Poisson model estimates the average risk to a population following the ingestion of an average dose. Modified Beta-Poisson models have been proposed (e.g. the Beta-binomial model, Cassin *et al*., 1998) that reflect the same assumptions as in the original beta-Poisson model, but where variability for the probability of infection from a particular dose is incorporated within the simulations so that the model estimates the risk of infection for an individual consuming a specific dose.

It is less known that the derivation of the Beta-Poisson model involves two simplifying assumptions on the parameter values. It is a special case of a more general hypergeometric model, which is computationally less easy to apply. However, because the parameter values in actual datasets are frequently in a range where the simplifying assumptions do not hold, erroneous results may result from application of the beta-Poisson model. Methods to estimate parameters of the hypergeometric model have been developed, and will be published shortly (Teunis and Havelaar, 2000).

Other models have been proposed for use such as the *Log-Probit model*, the *logistic model*, the *Weibull-Gamma model* and the *Gompertz model*. The *Log-Probit model* and the *logistic model* describe the hypothesis of minimal infectious dose. They give less conservative risk estimates in the low-dose region that other models based on the single-hit hypothesis. The *Weibull-Gamma model* has begun to be used for dose-response modelling (Farber *et al*., 1996). The model is based on the Weibull model with the assumption that the probability that any individual cell can cause an infection is distributed as a gamma function (the gamma distribution describes the host/pathogen heterogeneity). The model provides flexibility in that it can take on several different shapes depending on the parameter values selected. Several other models (such as the exponential or beta-Poisson models) are considered as special cases of the Weibull-

gamma model. The *Gompertz model* has been extensively used in predictive microbiology. It has been proposed for describing dose-response data (Coleman and Marks, 1998). The present trend is to consider that these models do not represent a valid biological concept.

Fitting models to data

1. Fitting method
The method of maximum likelihood is recommended. (Comparability of estimates is an advantage of using a single method).

3. Selection of the best fitting model(s)
Use the same method for parameter estimation and model ranking.
Start with likelihood tests (for acceptability of fit) and absence of systematic deviations from the model.
Then perform model ranking by means of likelihood ratios (preferred, but only applicable with hierarchically nested models), or by an information criterion (e.g. Akaikes Information Criterion, or the Bayesian Information Criterion). Do not use more parameters than necessary, i.e. parsimony.

2. Uncertainty analysis: determination of parameter uncertainty is indispensable.
Categories of methods that can be applied:
-likelihood-based methods
-bootstrapping
-Markov chain Monte Carlo methods (MCMC)
At least one of these method from these three categories should be used (cross-validation with a different method may improve confidence in the results, e.g. overlaying results from bootstrapping of MCMC on likelihood based confidence intervals).
Note that some methods have restrictions, e.g. the need to be careful with small samples with likelihood-based techniques.

Extrapolation

Low-dose extrapolation

Dose-response information is usually obtained in the range where the probability of observable effects is relatively high. In experimental studies using human or animals subjects, this is related to financial, ethical and logistical restrictions on group size, whereas in observational studies, only major effects can be distinguished from background variation. Because risk assessment models often include scenarios with low dose exposures, it is usually necessary to extrapolate beyond the range of observed data. Mathematical models are indispensable tools for such extrapolations, and many different functional forms have been used for this purpose. Selection of models for extrapolation should primarily be driven by biological considerations and only then by the available data and their quality. The above described working hypotheses of no-threshold and independent action lead to a family of models that is characterised by linear low dose extrapolations. That is, in the low dose range, the probability of infection or disease increases linearly with the dose. Some examples:

exponential model $P = r.D$
Beta-Poisson model $P = (\alpha/\beta).D$
Hypergeometric model $P = \{\alpha/(\alpha+\beta)\}.D$
where D = effective dose and r, α, and β are model parameters.

Extrapolation in the pathogen-host-matrix triangle

Experimental datasets are usually obtained under carefully controlled conditions, and the available data apply to a specific combination of pathogen, host and matrix. In actual exposure situations, there is more variability in each of these factors, and dose-response data needs to be generalised. Assessing such variability requires the use of multiple datasets that capture the diversity of human populations, pathogen strains and matrices. Failure to take such variation into account may lead to underestimation of the actual uncertainty of risks.
When developing dose-response models from multiple datasets, one should use all of the data that is pertinent. There are currently several ways of determining which data source is best. This requires that the risk analyst make choices. Such choices should be based on scientific arguments to the maximum possible extent, but will inevitably include subjective arguments. Such arguments should be communicated to the risk manager and their significance and impact for the risk management discussed. The credibility of dose-response models increases significantly if dose-response relations derived from different (types of) data sources are consistent.
When combining data from different sources, we need to have a common metric on both axes. This often requires adjusting the reported data to make them comparable. For dose, we need to take into account test sensitivity, test specificity, sample size, etc. For response, we need a consistent case definition or adjust reported response to a common denominator (e.g., infection x conditional probability of illness given infection).
The limited data available suggest that the functional form of the dose-response curve for sub-populations at increased risk remains the same as the general population, though the curve will be shifted or the slope changed. However, this may depend on the biological end-point being measured and requires further investigation.
Dose-response relations where an agent only affects a portion of the population may require that sub-population to be separated from the general population in order to generate meaningful results. Using such stratified dose-response models in actual risk assessment studies requires that the percentage of the population that is actually susceptible can be estimated. Consideration of such sub-populations appears to be particularly important when attempting to develop dose-response relations for serious infections or mortality. However, it would also be pertinent when considering an agent for which only a portion of the population can become infected (e.g. Norwalk virus).
Stratified analysis can also be useful when dealing with seemingly outlying results, that may actually indicate a sub-population with a different response. Removal one or more outliers corresponds to removing (or separately analysing) the complete group from which the outlying results originated. Where a specific reason for the separation cannot be identified, there should be a bias toward being inclusive in relation to the data considered. Any elimination of the data should be clearly communicated to ensure the transparency of the assessment.

Credibility of dose-response models

At present, validation of dose-response mathematical models is problematic, mainly because of the limited options for quantitative information and data.
Important information for validation may come from high quality epidemiological studies. Systems for collecting, collating, analysing and disseminating epidemiological information and data should be actively conserved and developed in response to particular needs, and specifically those associated with the development of quantitative microbiological risk assessments. In this regard, targeted epidemiological studies (e.g. case control studies) represent the best quality information and should be developed as far as is reasonably practicable.
Finally, users should avoid a false sense of precision and of security in the application of mathematical modelling. When exploiting the results of a probabilistic approach, it should be clear that the risk estimates are not to be considered as exact values, but rather should be seen as indicative of the order of probability of a risk level occurring.

Future trends

Attempts are currently made to develop dose-response models based on advances in our understanding of the pathogen/host relationship (e.g. Buchanan *et al*., 1999).
A simple three-compartment dose-response model has been proposed, including :
(1) gastro acidity barrier [calculation of the number of viable cells surviving passage through the stomach **,** e.g. Takumi, K., De Jonge, R. and Havelaar, A. Modelling inactivation of *Escherichia. coli* by low pH: application to passage through the stomach of young and elderly people, *J. Appl. Microbiol*, accepted for publication], (2) attachment/infectivity [examining the ability of the bacterial cells that have survived passage through the stomach to attach to and colonise the intestinal epithelium],
(3) morbidity/mortality [likelihood that an infection progresses to overt symptoms or even death].
Such model implies that the rate of infection is primarily dependant on the rate of acid inactivation and the attachment characteristics of the pathogenic micro-organism. Once an infection has been established, the extent and severity of disease (i.e. morbidity/mortality) are not necessarily dose-dependant, but instead a function of the virulence characteristics of the pathogen and the immune/health status of the population.

3.3 Exposure assessment

The exposure assessment part of a quantitative risk assessment determines the probability and the likely levels of exposure in the human population. It is done to estimate the quantities of hazardous organisms in contact with individuals or populations. In a complete risk assessment, the final goal is to produce a mathematical expression describing the exposure, which is combined with a dose-response model. Thus, the exposure assessment is designed to characterise the source(s) of exposure, the magnitude of exposure and the frequency of exposure. The details of how to describe the processes determining the exposure depends on many factors such as the transport vehicle (food, aerosol, water, dust etc) and the route of exposure (oral, through skin, etc.). However, more important are the purpose and the scope of the risk assessment –

the risk management question. In the context of a quantitative exposure assessment of a foodborne hazard the following factors need to be taken in account (Figure 1):
- The occurrence and levels of the micro-organism or toxins in the foods of interest
- The dynamics of the micro-organism or toxin, (e.g. growth, survival, and death, in the relevant stages in the farm to fork chain)
- The consumption pattern and habits of the population under study, i.e. the amount of food vehicle(s) consumed and the frequency of eating.

3.3.1 Structure of the exposure assessment model

An essential step in the development of an exposure assessment model is to produce a description of the relevant stages of the food pathway in sufficient detail. What constitute the relevant stages and level of detail in an exposure assessment, are determined by the purpose and the scope of the risk assessment, since the risk management question may relate to a single link of the food chain or it may involve two or more links. Since it is not possible to model every conceivable event in a system that may have an impact on the exposure the first step is usually to outline or define a conceptual model of the problem. The structure of the conceptual model is based on the risk management question and the endpoint of the risk assessment. During this stage the risk assessor is forced to structure the problem and to identify the key processes to be modelled and the information needed. The result of this process, i.e. the key processes and steps that should be addressed in the assessment can be summarised in a graphical outline of the model structure. This may help in getting the stakeholders/ risk managers acceptance of the model structure and assumptions by improving the transparency of the risk assessment.

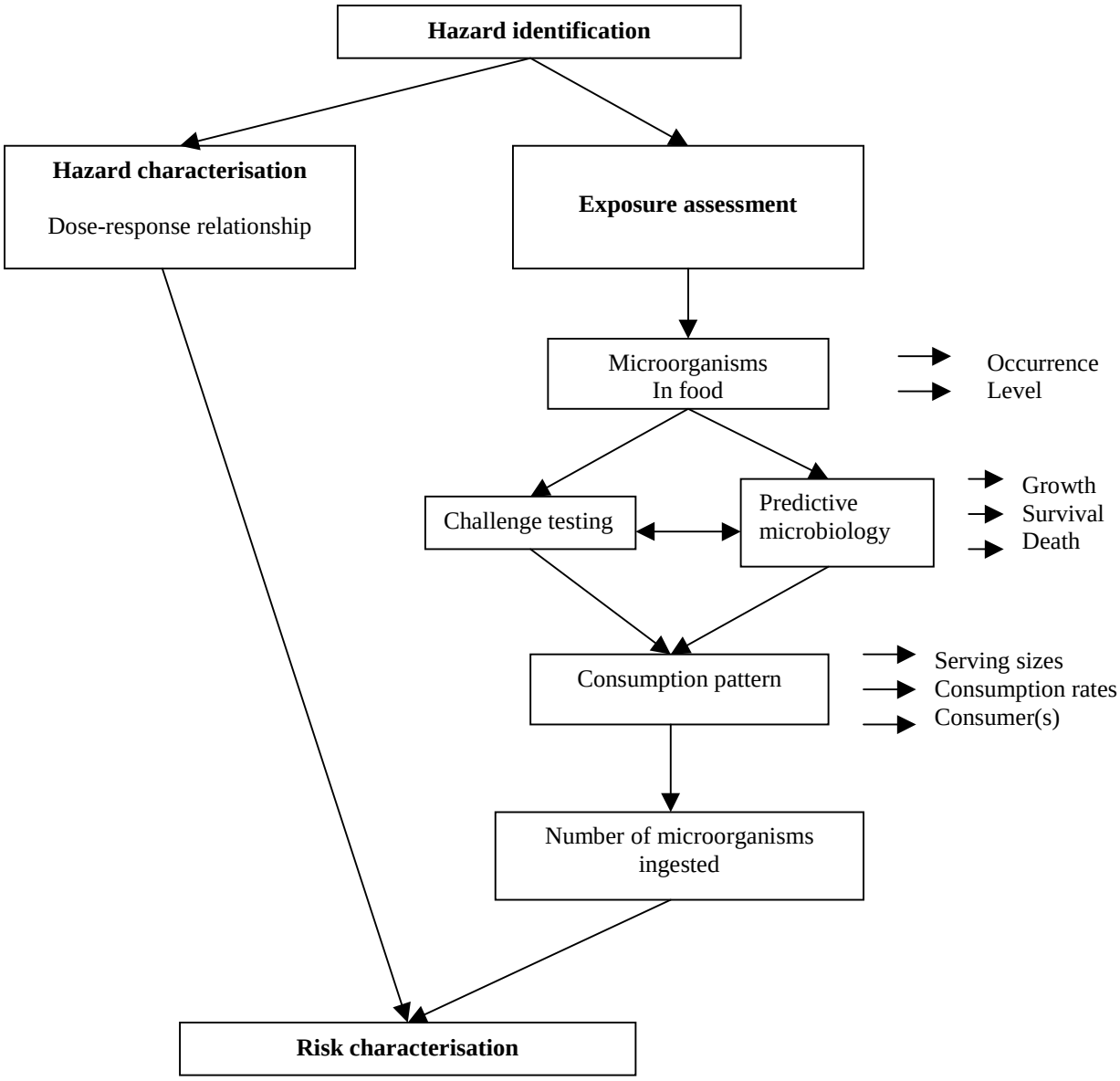

Figure 1. The four steps of risk assessment and the main factors to take into account when assessing the exposure of a foodborne hazard.

The conceptual model describing the pathways and processes leading up to the exposure may be divided into discrete model units, or sub modules, that are eventually linked together. This improves the overview of the model so that quick reference to data and assumptions can be made. In an attempt to provide a general framework for a farm-to-fork exposure assessment, Nauta (2000 c) identified six basic processes that influence the prevalence and/or the number of micro-organisms in a food, and suggested that any microbial hazard can be modelled as a series of these consecutive basic processes. The processes identified were two biological processes (growth and inactivation) and four product handling processes (mixing, partitioning, removal and cross contamination). Depending on the emphasis and the perspective of the exposure (risk) assessment different approaches have been used in developing the overall model. For instance, the Event Tree describes a scenario from the initiating event to a defined end-point of the

assessment (Roberts *et al.*, 1995). This approach serves to describe the high-risk pathways that lead to contamination and subsequent disease and may identify risk variables in need of further data or modelling. In contrast to the Event Tree, the Fault Tree begins with the occurrence of a hazard and from there describes the events that must have occurred for the hazard to be present (Roberts *et al*., 1995). This approach can provide a framework to analyse the likelihood of an event by determining the complete set of underlying conditions or events that allow the given event to occur (Jaykus, 1996). Additional approaches to modelling used in assessments of microbial food hazards include a Dynamic Flow Tree model, (Marks *et al*., 1998) and a Process Risk Model (Cassin *et al*., 1998). The former emphasises the dynamic nature of bacterial growth and incorporates predictive microbiology using statistical analysis of data, whereas the latter focuses on the integration of predictive microbiology and scenario analysis to provide an assessment of the hygienic characteristics of a manufacturing process. Variations on these themes exist. It should be emphasised that the type of final quantitative model being used depends on the focus and perspective of the developer and on the problem being modelled. Also, more elaborate and sophisticated classifications and distinctions between approaches and types of models can be done than in the present work (see e.g. Hurd and Kanneene, 1993). The broad types of models described here operate in only one direction, which does not make the inclusion of feedback mechanisms possible. This may be a limiting factor when modelling complex biological systems. Alternative approaches may include dynamic models based on differential equations, or Markow chain, and random-walk models or so-called neural networks (Skjerve, 1999). It should be noticed that methods for dealing with uncertainty associated with the choice of the structure of risk models are lacking (Morgan and Henrion, 1990).

Once the conceptualisation of the problem and the structure of the model is decided upon, estimates of the exposure can be made, and in the case of a complete risk model, risk can be calculated. In cases when time and resources are short a qualitative or semi-quantitative risk assessment may be carried out. This may be appropriate to compare or rank problems. However, it must be recognised that there is no formal mathematical system for combining these descriptive or ordinal evaluations (Roberts *et al*., 1995). The same model structure may be the basis for a deterministic or a probabilistic model depending on how the model variables are represented.

In the deterministic approach, a quantitative assessment of the exposure is estimated based on single point estimates of the model parameters. The sensitivity of the deterministic model can be evaluated by selecting different combinations of each input parameter to see how much the outcomes vary. The various combinations are commonly known as what-if scenarios. Obviously this approach has several limitations.

In the probabilistic approach, uncertainty and variability are taken into consideration by representing parameters as probability distributions rather than single point values.
In the probabilistic approach it is considered good practice, as a first step, to estimate exposure (or risk) using conservative point estimates, e.g. 95^{th} percentiles or worst case (Burmaster and Anderson, 1994; EPA 1997). For instance, if the worst case scenario still represents an exposure below levels of concern a further analysis taking variability and uncertainty into consideration is not necessary.
Often it is not sufficient to use point estimates to assess the exposure (risk), and a probabilistic approach taking variability and uncertainty into consideration is necessary.

Uncertainty refers to lack of knowledge about specific factors, parameters or models, and variability refers to the true heterogeneity in a population or exposure parameter. Variability can not be reduced through further measurement or study but it can be better characterised. Uncertainty includes parameter uncertainty (measurement errors, sampling errors, systematic errors), model uncertainty (uncertainty due to necessary simplification of real-world processes, mis-specification of the model structure, model misuse, use of inappropriate surrogate variables) and scenario uncertainty (descriptive errors, aggregation errors, errors in professional judgement, incomplete analysis, EPA 1997).

Thus, in the probabilistic approach each uncertain model input parameter is described by probability distributions rather than by single-point values. Accordingly, the outcome of a probabilistic model is a probability distribution. There are a number of techniques to calculate the outcome distribution such as the method of moments, exact algebraic solutions and Monte Carlo simulation (see Vose 1996 for a discussion of these techniques). Using the Monte Carlo approach the model is simulated a number of times to calculate the outcome distribution. Each time (iteration) the model is simulated the values for each parameter are selected at random from the probability distribution defined for each parameter. The number of iterations is set sufficiently high to allow also rare combinations of parameters to occur, or are carried out until the outcome distribution is stable, so a complete evaluation of the exposure (or risk) is possible. The result represents a distribution of exposure (or risk) experienced by an individual or a population based on the combinations of input probability values that could occur. From the distribution not only extreme values but also the most likely outcome based on the selected input distributions is provided.

Several applications of Monte Carlo simulation with regard to risk assessment of microbiological food borne hazards have documented the merit of the method [e.g. Cassin *et al*, 1998 (*E. coli* O157:H7 in hamburgers), Fazil *et al*, 1999 (*C. jejuni* in fresh poultry), SSC, 2000 (BSE: use of vertebral column for the production of gelatine and tallow**)**]. Despite its increased complexity over the point-estimate approach, the probabilistic approach is now becoming the preferred approach to quantitative microbiological risk assessment (for foods). The development of user-friendly software packages, or add-ins, enables risk assessors to use spreadsheet programs as the modelling environment for the Monte Carlo simulations. These are fairly easy to use but may not be flexible enough for some applications and models.
Thus, in the framework evolving in risk assessment of food borne hazards the tendency is to build and use models that integrate uncertainty and variability, and time dependent effects on the stages being modelled.

3.3.2 Building the exposure assessment model

For foodborne hazards the exposure depends on the occurrence and the levels of micro-organisms in the food at the time of consumption, and the consumption pattern. Consequently, the model outputs of the exposure assessment is the probability an individual or a population will be exposed, and the numbers of the pathogen that are likely to be ingested.

A significant feature of exposure assessment for microbiological hazards is that it should specifically take into account the dynamics of the microbial population (growth and/or inactivation of the micro-organism within the food, effects of processing steps and/or storage, handling, preparation practices). To that aim, exposure assessment employs predictive microbial approaches and models within the larger exposure model. Predictive microbial models have been developed to characterise the growth of the pathogen of interest under various extrinsic (environmental variables, such as temperature) and intrinsic (food specific variables, such as pH) conditions. Predictive models also exist that characterise the inactivation of micro-organisms under various conditions. Significant advances have been made in this field in recent years, which have resulted in increasingly sophisticated models and applications. Predictive microbial models have been categorised as primary, describing how microbial numbers change with time in a specified environment, or as secondary level models, which indicate how parameters of primary models change with respect to one or more environmental or cultural factors. A third category encompasses tertiary level models, where primary and secondary models are integrated with software packages and expert systems. The degree of complexity that is required for an exposure assessment is dependent on the degree of precision needed to appropriately describe the behaviour of the micro-organism. [Extensive documentation on predictive microbial modelling, e.g. Ross and McMeekin, 1994; Buchanan and Whiting, 1996; van Gerwen and Zwitering, 1998 etc.]. Very recently, it has been stressed that available predictive models produce point estimates of population size, and mix or even ignore variability and uncertainty. For quantitative microbiological risk assessment, bacterial growth needs to be expressed in terms of probability (e.g. probability that a critical concentration is reached within a certain amount of time). Thus, a new type of predictive models needs to be developed that characterise variability and uncertainty, and integrate these in the evaluations provided (Nauta, 2000 a).

As mentioned previously, most probabilistic models of exposure assessment of foodborne pathogens use Monte Carlo simulation techniques. The Monte Carlo simulation model is constructed so as to describe in a systematic and logical way along the production-to-consumption continuum

- the contamination sources
- the likely numbers of a pathogen that might be introduced into the food
- the influence of factors that affect the distribution, survival, growth, or inhibition of the micro-organism.

This includes

- a qualitative understanding of the whole process (module, sub-module)
- identification of variables and parameters that should describe the process
- quantitative information; data collection, data evaluation, data analysis
- selection of distributions for variables/parameters

When developing exposure assessment sub-models, the assessors should consider the influence of factors such as:

- the characteristics of the pathogenic agent and the expression of pathogenic treats
- the microbial ecology of the food
- the initial contamination of raw materials (including seasonality of production and regional differences)

- the level of sanitation and process controls
- the methods of processing, packaging, distribution and storage of the foods, as well as any preparation steps such as cooking and holding
- patterns of food consumption. These may include typical serving sizes, weekly or annual consumption rates, (extreme consumption modes as appropriate), circumstances under which the food is prepared and consumed, socio-economic and cultural backgrounds (such as ethnicity, seasonality, regional differences, consumer preferences and behaviour that may influence consumption patterns)
- consumption by specific groups (such as infants, children, pregnant women, elderly, or immuno-compromised populations)
- distribution of micro-organisms in the food (e.g. clustering, micro-colonies)

To date, a few quantitative exposure models for microbial food contaminants have been published. Examples include models about *E. coli* O157:H7 in home-cooked ground hamburgers (Cassin et al., 1998; Marks et al., 1998), *S. Enteritidis* in shell eggs (Baker et al, 1998) and liquid pasteurised eggs (Whiting and Buchanan, 1997), *L. monocytogenes* in smoked or gravad salmon and rainbow trout (Lindqvist and Westöö, 2000), *L. monocytogenes* in soft cheese made from raw milk (Bemrah et al, 1998), contamination of milk by *L. monocytogenes* (Peeler and Bunning, 1994), *Bacillus cereus* (Notermans et al., 1997, Zwietering et al., 1996), *Mycobacterium paratuberculosis* (Nauta and van der Giessen, 1998), and the contamination of animal carcasses during processing (Berends et al., 1997).

3.3.3 Limitations in exposure assessment modelling

The exposure assessment models are based on experimental data or on assumptions developed through expert opinion when significant data are lacking. The methodological limitations in exposure assessment are generally related to the qualitative and/or quantitative insufficiency of available data needed to estimate the exposure. Firstly, this relates to data describing the occurrence and levels of the micro-organisms in the specific food type. These data are often insufficient, or hard to compare since they are based on methods with different sensitivity and specificity and on unknown sample sizes. Secondly, there is a need for data on the consumption pattern and handling of specific food types and by different consumer groups. Thirdly, the exposure assessment is dependent on the ability to describe the dynamics of microbiological populations. The exposure assessments are often based on predictive models that were developed using data from broth experiments and their ability to describe growth or inactivation in food need to be validated. Also, exposure assessments are commonly based on microbiological methods that cannot detect viable but non-cultivable organisms. Independent of whether this physiological stage is part of a survival strategy or a step towards deterioration and death, the public health significance of these micro-organisms is difficult to predict and may vary between different pathogenic micro-organisms. The lack of appropriate data noted discussed here adds to the uncertainty of the exposure assessment and thus to the risk assessment.

3.4 Risk characterisation

Risk characterisation is the integration of hazard identification, hazard characterisation including a dose-response assessment and exposure assessment, to provide an overall **probability** of a given population being subjected to infection, morbidity, mortality, or whatever biological response is being considered.

The units utilised to express this probability may be different, such as the probability of illness per serving, the annual cumulative probability of illness based on weekly or monthly exposure, or the annual number of predicted cases within a country. The risk characterisation may include the probability of illness for different segments of the population. The output of the risk characterisation – of the probabilistic modelling – is a distribution of risk. An example is given by Lindqvist and Westöö (2000).

A particular aspect of risk characterisation for microbiological pathogens refers to expressing the **severity** of the related disease. Taking food as a case study for discussion, it is recognised that foodborne pathogens may cause a great diversity of illnesses, with widely different impact on public health. Even one agent is usually related to different illnesses, possibly in different populations. The health impact may vary from mild gastrointestinal disturbances to life-long sequelae and even death. A public health based standard for acceptable risk from micro-organisms in food should therefore not only be based on the probability of disease but also on its severity. Notwithstanding the unit utilised to express the risk (e.g. probability of infection, or of illness), this calls for a non-specific approach to measuring the health burden of foodborne illness. Health-related quality of life scales (quality or disability adjusted life years, QALYs or DALYs) are commonly used for this purpose in health economics and medical decision making, and are increasingly being used in the domain of public health. The basis of these scales is the concept of loss of (healthy) life years, comprising and integrating the effects of mortality and morbidity. Mortality is accounted for by the number of life years lost (LYL), defined as the difference between the actual age at death, and the life expectancy at that age. Morbidity is considered to reduce the value of life during the period of disease and possibly chronic sequelae. A severity weight, expressed as a factor between 0 and 1, accounts for the different levels of impact that specific diseases may have on individual or population health. Thus, the loss of health life years due to morbidity (years lived with disability - YLD) is expressed as the time lived with disease, multiplied by the matching severity weight. The loss of DALYs in a population is then computed by summation of LYL and YLD.

Variability and uncertainty

The two components, variability and uncertainty, describing the degree of reliability of the risk estimate, should be clearly and distinctly described. The variability is the effect of chance and is a function of the system, whereas uncertainty is the assessors lack of knowledge about the parameter (Vose, 2000). The uncertainty may include parameter uncertainty, model uncertainty and scenario uncertainty (see section 3.3.1).

(*Note*: in some risk assessment frameworks, the terms "total uncertainty" or "undeterminability" have been proposed to denote the combination of variability and uncertainty).
The separate effect of variability and uncertainty on the risk estimate should be made clear (Nauta, 2000 b). Estimating separately variability and uncertainty will provide useful information, in particular for some decisions that could follow from the risk assessment. If a large part of the "undeterminability" is due to uncertainty, collecting further samples, and/or additional research, will contribute improving the knowledge about a given factor, thereby increasing the reliability of future, revised, risk assessments. If on the other hand, the "undeterminability" is largely due to variability, collecting more samples is often a waste of time, as more samples will only contribute to describe the heterogeneity of the factor considered, but not to reduce the variability component. There, with specific regard to improving the reliability of the risk assessments, assessors and managers may consider reducing variability by changing the system, i.e. by controlling a manufacturing process, which may narrow down the number of possible scenarios.
In any case, because in quantitative microbiological risk assessment the output of risk characterisation is a probability distribution of the risk, it should be clearly stated if this distribution represents variability, uncertainty, or both.

Sensitivity analysis

A sensitivity analysis of the result of probabilistic modelling should be performed. This will provide information on how a given model depends upon the information fed into it. A sensitivity analysis will provide knowledge on how the effect of changes in the mathematical approach on the result of the risk estimate (Which parameter(s) matter most in the model ? What is the influence of the choice of a certain distribution compared to an alternative choice of distribution ?). Therefore, a sensitivity analysis has two objectives. The first is to identify the elements or factors that most impact on the magnitude of the risk. The second is to “move around” with the uncertainties/assumptions to see how much they affect the results, i.e. to determine the robustness of the model toward these uncertainties/assumptions.

For the sensitivity analysis in context with risk assessment it could be advisable to examine two aspects:
- the effect of changes in the estimated parameters (such as the mean and the variance for an input distribution) and the comparing of which parameters have the largest effect on the output.
- the effect of the choice of input distributions (triangle, normal, poisson, etc..) or other assumptions/specifications

a) The sensitivity analysis for the parameters could be carried out in different ways giving more or less different results depending on how well the data fulfil the belonging assumptions. Carefully thoughts should be given upon which method to employ for the sensitivity analysis depending on e.g. the linearity between the input and the output distribution, the multicollinearity (correlation between input parameters), the unit in which it is carried out etc. Also different methods have different uses and applications, and a universal recipe for measuring sensitivity does not exist.

One very simple way of carrying out a sensitivity analysis is to carry out a relative sensitivity analysis, where a small change in a given parameter is compared with the percentage change in the output parameters. The change could be, say 10 % of the mean, or it could be a fixed fraction of the standard deviation belonging to the parameter or an absolute value. Depending on what is chosen different results of the sensitivity analysis could be seen – the question is what the investigator is interested in examining. The drawback with this method is that if the relationship between the changes in the input parameter and the output parameters are not linear then the results of the sensitivity analysis will depend on the choice of how much the input parameter is changed (10 %, 20 %, etc.).

If carrying out a proper linear regression analysis, where multiple input data sets is used, the R-squared value would indicate whether the assumption of linearity has been violated. (A multiple input data set is e.g. changing the parameter by 5 %, 10 %, 15 %… up and down). If the R-squared value is less than 0.60 then the linear regression does not sufficiently explain the relationship between the inputs and outputs and another method of analysis should be employed.

In such a case Rank Order Correlation may be a better solution. Ranks can cope with non-linear relationships between the input – output distributions, allowing the use of linear regression techniques. Rank-transformed statistics are more robust, and provide a useful solution in the present of long-tailed input and output distributions. However, care must be employed when interpreting the results of analyses based on rank transformation, since any conclusion drawn using ranks does not translate easily to the original model (Saltelli *et al*., 2000).

If multicollinearity occurs among the input parameters incorrect results are often seen, and with different sensitivity analysis directly opposite results may occur. The influence of these multicollinear parameters that influence the output may be overlooked in an analysis based on the ranks and may lead to failure of the sensitivity analysis. If the linear regression is not adjusted for any effect due to correlation between input parameters the results of a sensitivity analysis may also fail. Reducing the impact of multicollinearity is a complicated problem to deal with, but removing the variable that causes the multicollinearity from the sensitivity analysis may be considered.

Other sensitivity analysis than the linear regression and the rank-based method exist, (see e.g. Saltelli *et al*., 2000).

The identification of the most influence parameters (which for the risk assessment would be the main objective) is based on comparing the results of the sensitivity index for each parameter, which again depend on the method employed. For example, if the sensitivity index measures the effect on the output by a fixed fraction of the standard deviation, the parameter with large standard deviation is likely to be judged more important. On the other hand, if the sensitivity index measures the effect on the output by an absolute value a different result may be seen. The latter example may give raise to problems if ‘apples and pears’ is compared - when the units of the input parameters are not the same. In such a case it may be advisable to convert the change in input into a common unit, e.g. the cost of carrying out the change in the given parameter.

b) The sensitivity analysis for the input distributions is not so well defined. A suggestion could be to replace each input distribution at a time with a quite different but still realistic input distribution. The mean and/or the shape of the output distribution may be effected by the replacement. The effect could be described by the change of the output distribution of e.g. the mean, the variance and/or the 5 % and 95 % quantiles.

The scenario analysis determines which input parameters contribute significantly towards reaching a goal. For example, which parameters contribute to exceptionally high risk or which parameters contribute to exposure below a certain value? The scenario analysis is related to sensitivity analysis, and is also referred to as 'two sample tests' in context with sensitivity analysis or 'reliability analysis'.

Separating variability and uncertainty and performing a sensitivity analysis may easily become a complicated problem to deal with and may need help from a statistician or a well consolidated risk analysis expert.

Establishing validity of QMRA results

Validity of QMRA results can be established at two different levels often identified as verification and validation.

Verification. This is basically a technical exercise, aimed at assuring the precision of parameter estimates and implementation of computer software. It is mainly the responsibility of the analyst, but could involve specialist review.

Validation. One aspect of validation is the scientific acceptability of model assumptions, model formulations and criteria for data selection and treatment. This involves communication with the scientific community at large. If different assumptions or approaches are deemed feasible, the effects of alternative assumptions or scenario's should be carefully evaluated and the results should be communicated to the risk manager. Another aspect is comparison with empirical data. Microbiological risk assessment is unique because often the diseases of concern do actually occur in the population, and model estimates could be compared with observational data from epidemiological studies.
Such studies include:
- cross sectional surveys, to acquire predetermined information from a population or population sample (e.g. questioning and examining selected individuals; looking for evidence of an immune response by immunological testing)
- cohort studies, examining, over a period of time, subsets of a defined population who have or do not have a particular attribute. These are usually expensive, difficult and require long term commitment. When electronic records are available, historical cohorts may be useful.
- case control studies, comparing people with the disease (cases) with people who are not suffering from the disease (controls). The choice of cases and controls must be made carefully to avoid problems of bias. Case control studies are relatively quick and not expensive to perform. They should be more widely developed to strengthen the information available from outbreaks investigations.

- intervention studies, where a possible causative factors is reduced or totally prevented and comparing the results with those in a reference population with unmodified conditions. Ideally, the exposure situation is reversed halfway through the study (cross-over trial).
It is critical to recognise the strengths and weaknesses of each of these study types when comparing quantitative microbiological risk assessment information.

Reporting

The risk characterisation, along with a report of the risk assessment process, is handed over to the risk managers, and serves as the basis on which risk management decisions are made.

As decisions are made on the risk characterisation, often with awesome impact on governments, consumers and food producers, it is crucial that the basis for the estimate is fully and systematically documented and that all assumptions and constraints are indicated to ensure that process is transparent.

The report should be made publicly available to allow interested parties (stakeholders), the opportunity of comments and suggestions to the process. This also serves the purpose of exposing the report to peer reviewing, analogous to the process of acceptance of scientific papers for publication. This will help to ensure that the data and the assumptions made during the process are reasonable, that the risk analysis includes the relevant elements, i.e. the appropriate risk units (segments of the population), and that the outcome is reasonable.

4 - CONCLUDING REMARKS -RECOMMENDATIONS - ORIENTATIONS FOR FUTURE WORK

Concluding remarks

Microbiological risk assessment is an evolving discipline. Whereas traditional assessments have been mainly qualitative, there is a requirement for the continued development of a quantitative approach. When developing a quantitative approach and mathematical models, assessors are forced to carefully consider the scientific basis for their estimates, to explicitly state the assumptions made, and to clearly explain the strengths and limitations of the assessment. This is beneficial to transparency, in comparison to what is generally the case in qualitative risk assessments. Moreover, the structured approach to be taken and the mathematical models to be developed can actually stimulate and focus discussions aimed at a better scientific understanding of the underlying biological phenomena and at determining the most important aspects in a causative chain of events. The wide application of quantitative microbiological risk assessment would thus ensure that resources are targeted on measures that, in the light of the best available scientific evidence, would be most effective and efficient in reducing microbiological health risks from foods and other potentially contaminated products.

The quantitative assessment of microbiological risk, whilst sharing many principles common to the assessment of other types of risks, brings different challenges due to the

intrinsic nature of micro-organisms, and to the complex nature of the host pathogen relationship. As developments in genomics and proteomics continue to provide new insights into pathogen-host interactions, it can be anticipated that the relevance of specific complex microbial behavioural patterns, which are currently not fully understood, will be elucidated. For example, aspects including the proposed viable but non-cultivable (VBNC) state and the interplay of signal dependent quorum sensing in the expression of pathogenic traits in pathogen-host interactions will be further understood. This new information will facilitate the practical relevance and significance of these complex processes for effective quantitative microbiological risk assessment procedures.

Common crucial factors are variability and uncertainty, as is the insufficiency of data. The present trend is to take variability and uncertainty into consideration by developing probabilistic risk models. However, variability, which reflect the true heterogeneity in microbial or human populations or in model parameters, needs to be better characterised. Uncertainty refers to the lack of knowledge. In every assessment its sources should be thoroughly identified, together with a discussion on how uncertainty impacts on the risk assessment and its use. When exploiting the results of a quantitative risk assessment, it should be made clear that quantitative risk estimates are not exact values, but rather an indication of the order of probability of an adverse event occurring. In spite of the considerable amount of literature on microbiological contaminants in food and other contaminated products, risk assessment suffers from insufficient data. This does not undermine the validity nor the usefulness of the assessments, provided the strengths and limitations in the data-bases are recognised and that the risk assessment process is internally consistent. However, substantial efforts need to be made to improve the present situation, to maximise the benefits quantitative microbiological risk assessment offers.

Quantitative microbiological risk assessment is already being applied (e.g. in the area of food and water microbiology) and is of great potential value. However, it has to be acknowledged that there is a crucial need for capacity building in Europe, with particular regard to modelling activities. At present, there are very few groups that have the necessary mathematical/statistical skill and it is urgent to enhance the European capacity in that respect. Moreover, to make the best use of the information available, and to plan for the collection of missing data, there is a need to promote interdisciplinary co-operation and interaction between risk assessors, microbiologists, epidemiologists, technologists and other resource persons and to have a good working relationship between risk managers, risk assessors and resource people. Creating a network of European quantitative microbiological risk assessment groups would be an essential step towards that aim.

Finally, to benefit from the full potential of risk assessment in the framework of risk analysis, it is crucial to communicate to risk managers and other stakeholders what types of information can result from quantitative risk assessment and in what situations it is useful. While setting the expectations at a realistic level, this would ensure that the applications of quantitative microbiological risk assessment are taken forward and developed pro-actively, so that the benefits it offers are maximised.

Recommendations - Orientations for future work

This section identifies the variety of actions that need to be taken forward by priority to develop and improve quantitative microbiological risk assessment. The recommendations and orientations for future work have been grouped according to the four stages of risk assessment, i.e. hazard identification, hazard characterisation, exposure assessment and risk characterisation.

Hazard identification :

The confident identification of hazards, and of risk assessment in general, depends upon the availability of high quality medical research, public health data, and epidemiological studies. At a research level, priorities for future work would include i) - investigations on the factors governing the emergence of novel pathogens or the re-emergence of established pathogens, and ii) - investigations on the mechanisms governing the expression of pathogenic and virulence traits in pathogen-host interactions. Also, systems for generating, collecting, collating , analysing and disseminating public health and epidemiological information should be actively conserved and developed.

With specific regard to the particular needs of developing quantitative approaches to microbiological risk assessments, future work should focus in three main directions:
- development of research studies to better identify the types of strains responsible for foodborne diseases, to determine the elements/factors influencing pathogenicity / virulence, and the transmission of the strains responsible for diseases;
- development of analytical methods ensuring that pathogens of concern are detected and characterised in a rapid and quantitative manner all along the production (food) chain;
- and, more importantly, development of the etiological studies (outbreak investigations, case control studies) that are needed to identify causal relationships and the fraction of illness attributable to specific (groups of) (food) products, in order to facilitate a quantitative approach to the problem at stake.

Hazard characterisation and dose-response assessment :

For most micro-organisms of concern, there is a large body of literature describing the associated health effects. However, papers are principally based on clinical observations and are mainly qualitative. With particular regard to the development of quantitative approaches and dose-response modelling:

- There is a need to overcome the limitations of human volunteer / animal models experiments by innovative approaches.

- High quality epidemiological studies should be strengthened and developed, in particular case-control studies of outbreaks. These can be used to better identify and quantify specific risk groups. They are crucial for appropriate validation of quantitative dose-response models.

- Host, pathogen, and environmental factors that affect the survival and multiplication of pathogenic agents and the transmission mechanisms should be identified, and quantified to the extent possible, and available information on pathology of gastro-intestinal infection and disease incorporated in dynamic mathematical models.

- Interaction between micro-organisms, interaction between microbial infection, immunological status, susceptibility of the host, potential between microbial infection and allergic reactions should be evaluated through a fundamental biological approach, with a view to be used for microbiological risk assessment at a later stage.

Exposure assessment :

Development of exposure assessment modelling offers considerable potential benefits to the process of risk assessment. Such development should be better achieved by the construction (at the conceptual level and then in mathematical equations) of a unified theoretical framework utilised to integrate all available data and, once constructed, to govern appropriate missing data collection. This requires a major shift in attitudes and should be actively encouraged.

While having regard to the above recommendation, more appropriate data are needed to reduce the uncertainty associated with exposure assessments. Throughout Europe, national/regional differences exist in how data is collected. Some degree of harmonisation at the European level is needed. At the present stage most of the information will be used in stochastic models and therefore an estimate of the uncertainty and variability is needed and this should be addressed already when planning the data collection.

Priority areas related to data needs are the following:
- Collection of data on prevalence and levels of pathogens in the food chain and its components, sources of contamination, sanitation measures, regional differences, seasonal variation. Possible sources of information include industry, retailers, local authorities etc. A common structure or clearinghouse for posting of relevant data as far as practicable should be instituted to facilitate networking and the exchange of data and information. Such a clearinghouse or network may also work as a forum for facilitating the development of common methodologies to address the general processes and problems encountered when modelling exposure.
- Microbiological analyses which provide the essential information needed for exposure assessment are to a high degree method sensitive. An important goal is therefore to develop and use equivalent analytical methods and sampling plans (e.g. size of the analytical portion, number of samples-detection limit of the survey, awareness of what the results represent).
- Collection of information on the consumption patterns and food handling practices. This should be done in regard to the different segments of the population and include information on what the different groups eat, how much, purchasing habits, preferences, storage time and temperature, mishandling practices, preparation and cooking habits.

Risk characterisation :

- A common framework for the presentation of the results of the risk assessment is needed. The presentation should clearly present the uncertainties of the result as well as the constraints and the assumptions upon which the risk assessment is made.

- The parameters describing the degree of reliability of the risk estimate, variability and uncertainty should be clearly described.

- There is a need to perform sensitivity analysis to demonstrate the influence of assumptions used in the risk assessment on the final risk estimate. An agreement should be sought on the way to perform sensitivity analyses and to standardise the approach. This, however, is very complicated as it depends on the purpose of the sensitivity analysis as well as the structure of the data.

- There is a need to further consider a common logic to evaluate/validate the models.

- Risk assessment studies should be subject to quality assurance practices and should be amenable to auditing and review by the stakeholders

- Risk assessment results are one important aspect of decision making in the microbiological risk management process. However, not all information necessary is included in the risk assessment framework. Therefore, risk assessment results should be integrated into the science of decision analysis, including consideration of public health or economic aspects.

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APPENDIX 5

QUANTITATIVE MICROBIOLOGICAL RISK ASSESSMENT OF INFECTIOUS DISEASES

Table of Contents

QUANTITATIVE MICROBIOLOGICAL RISK ASSESSMENT OF INFECTIOUS DISEASES

Executive Summary

Livestock production, animal disease and disease transmission, as well as spread of infection throughout the food production chain refer to different levels of consideration. These levels represent individual herds, regions, national herd and international (trade) level, respectively.
For a proper understanding of strengths, weaknesses, threats and opportunities, it is necessary that each respective issue be considered. This approach is addressed in this report.

Risk assessment (RA) in livestock production refers to both qualitative and quantitative methodologies. For these two lines of approach sufficient and reliable data is needed. This data is currently lacking at all levels.

RA is not only relevant to policy makers, it is equally important for the farming sector because this has the responsibility for providing high quality food (commodities) including safeguards and confidence for the consumer with regard to public health issues. RA at farm level, represented by e.g. good farming practice codes and the application of HACCP principles, may largely improve livestock production conditions.

There is no uniform philosophy for the application of Quantitative Risk Assessment (QRA)
for livestock production. Certain questions raised by decision-makers require specific methods. Furthermore, researchers in the EU do not utilise the same methods for addressing the same issue. Therefore, an overview of different fields of attention in RA for livestock production and transmissible diseases is presented. Examples of application are provided for enhancing insight into the highly variable situations occurring from individual herd to international trade.

It can be concluded that – next to the reported lack of sufficient and reliable data – decision-making about livestock disease transmission by using currently available QRA methods means that

- further research input into this field of RA is needed within the EU;
- more harmonisation among researchers in this area in the EU is necessary e.g. through the formation of a taskforce and better co-ordination of activities;
- one has to be aware of the fact that QRA is time-consuming and costly; it therefore
  requires adequate priority setting;

- apart from scientific arguments, risk perception of the general public may influence the process of decision-making. Hence risk communication is of paramount importance.

1. INTRODUCTION

Within the framework of quantitative risk assessment the application of risk analysis to infectious agents and transmissible diseases requires special attention. This applies to human diseases as well as to animal and plant diseases. This document is dealing in particular with animal transmissible diseases which play an essential role in livestock production at herd, region and country level, and in international trade with live animals and products derived from them.

The adoption of the WTO agreement on the application of sanitary and phytosanitary measures (SPS Agreement) in 1994 has markedly modified the rules governing trade in animals and animal products (Marabelli et al., 1999). Countries are allowed to apply import restrictions based on the health status of the national herds to ensure animal health and food production. On the other hand, export restrictions can be avoided by a good health status relative to other countries. In the European Union (EU) it was decided to set high standards for animal health and to establish a strategy of non-vaccination for the most important contagious animal diseases (Horst, 1999; van Schaik, 2000).

Based on the fact that within the EU disease control by vaccination is limited, emphasis has to be paid on risk management of transmissible diseases should they emerge. For that purpose, knowledge should be made available about the potential risk factors that play a role in the introduction of a disease, the possible way of spread of the infectious agent on a farm, the spread from farm to farm and, further on in the food chain with possible effects on the quality of animal products including potential consequences for public health.

A small series of studies has been conducted to identify and quantify risk factors related to the introduction and spread of infectious diseases in animals. For review see Barkema et al. (1998), Frankena et al. (1992; 1993), Horst et al. (1999), Martineau et a. (1982), Sorensen et al. (1995), van Schaik (2000) and Vonk-Nordegraaf et al. (1998). Such epidemiological studies have been focussed on either highly contagious diseases, like foot-and-mouth disease, or endemic diseases, like infectious bovine rhinotracheitis (IBR) or mastitis. In many cases knowledge about quantitative risk data related to disease occurrence is still lacking. In such a case it is nonetheless worthwhile to make use of information that is “qualitative” in nature. Among those are “critical management points” which play a role in disease prevalence and spread without being quantified. As an example, paratuberculosis in cattle is mentioned here where such critical management points are of paramount importance for the management and control of the disease. Other examples of qualitative approaches refer to a Good Farming Practice and Hygiene Code as part of a general hazard analysis critical control point (HACCP) concept at the farm level (Noordhuizen and Welpelo, 1996).

It is obvious that any programme for prevention of animal transmissible diseases has a direct impact on the quality of the products and hence on the marketing at, both the national and international level. It is mainly for this reason that countries or the EU interfere in animal health control by establishing eradication and prevention programmes.

In addition to economic arguments, public health and consumer protection aspects lead countries to observe and improve animal health in order to avoid diseases that may affect humans.

At the international level, the OIE in its Animal Health Code (1999) has introduced procedures to assess the animal health status of a country and to estimate the risks associated with trade by providing methods to identify and to analyse certain hazards. For the purpose of international and intra-Community trade in animals and animal products, quantitative risk analysis offers a tool to evaluate and to demonstrate in a standardised and comparable manner the health situation in a country. As a prerequisite, the methods applied have to be formalised and standardised on a scientific background, based on epidemiology, animal health economics and bio-statistics.

This report is dealing with the specific aspects of quantitative risk analysis of livestock diseases associated with livestock production (farm, region, country) and movement of or trade in live animals and their products.

Various methodologies, as applied in QRA of livestock diseases are reviewed, and examples of such applications presented. Finally, some reflections are made regarding decision making under lack of information and problem dynamics and uncertainty. This report does not pretend to provide a complete review of the QRA in livestock production; only major issues are raised.

2. HEALTH AND DISEASE IN LIVESTOCK PRODUCTION

2.1. Different levels of livestock production

In order to have sufficient understanding of the objectives, opportunities and constraints of livestock production in relation to risk assessment, we first address the different levels of livestock production operation: herd; region; sector/national level; international level.

Level and/or status	Emphasis put on operational goals related to	Needs in animal health	Tools for optimising demonstrating health
Herd	Farm economics !!!	Management support	Herd health programmes
	Public health !	Risk factor profiles	Good Farming Practice Code
Region	Farm economics !!!	Management support	Herd health programmes
	Public health !!	Risk factor profiles	Good Farming Practice Code
		Disease control	Disease control programmes
Sector/natl.	Economics !!!	Disease control	Disease control programmes
	Public health !!!	Evidence of actions	Quality control (e.g. HACCP)
		Risk factor profiles	Certificates; lab results
			Good Farming Practice Code
			Risk management systems
Internatl.	Economics !!!	Evidence	Certificates; lab results
	Public health !!!	More evidence	QRA

! means minor emphasis, !!! means high emphasis

It should be borne in mind that the above named distinction is for clarity reasons alone; in some places there is a certain overlap between levels. On the other hand there is no pretension to be complete. Point is that it should be clear that the different operational and strategic objectives may largely differ from level to level. Hence, the demands with regard to health status (either improvement, optimising or maximizing, or just demonstrating) per level are also different. This will explain later-on why different applications with regard to risk assessment and risk management are applied at the different levels of livestock production.

2.2. The basic problems in livestock production regarding decision-making

By and large, the major difference between herd, region and sector/national level on the one hand and the international level on the other hand refers to the operational decision-making in the former and the evidence-based rationale in the latter. This has quite an impact on the data that are currently collected, as well as on the data that should (ideally) be collected for each respective purpose.

The individual farmer, for example, can be quite happy if his veterinarian provides him with qualitative information about disease risks on his farm during the execution of a veterinary herd health advisory programme. Accuracy and reliability of the data collected on the farm are continuously issue for debate. Much could be improved in that respect, and should be improved if individual farmers are linked up in a chain quality assurance programme, either on a voluntary or a compulsory basis. Good Farming Practice codes will not be sufficient to demonstrate to third parties what the individual farmer has done to optimise animal or public health. Currently, pilot projects are running to test the feasibility of applying HACCP concepts at farm level.

At the sector level it is clear that farmers associations and industry are looking for ways to optimise productivity, e.g. to improve the health status by implementing disease control programmes (such as for Aujeszky disease in pigs and Infectious Bovine Rhinotracheitis in cattle). Activities are market driven, while consumers may have additional demands (welfare; environment; food quality).

At the international level the call for formal QRA becomes stronger. Health certificate and lab testing based animal health status is no longer sufficient to gain or retain market access. However, if the data needed are not available, the infrastructure to collect such data not operational and the resources not in a position to handle the gathered data, then a formal QRA procedure becomes very difficult to perform. QRA needs data from all levels mentioned in the Table on the previous page. It can be concluded that the overall availability of data for the purpose of QRA in livestock production is poor.

2.3. Health and Infectious disease at the different levels

Herd; region; sector/national level

In order to provide the means for a better understanding of the production system at these levels, its different purposes, different intervention activities and the data that usually are handled for that purposes, we introduce here the ***chain of risk events***.

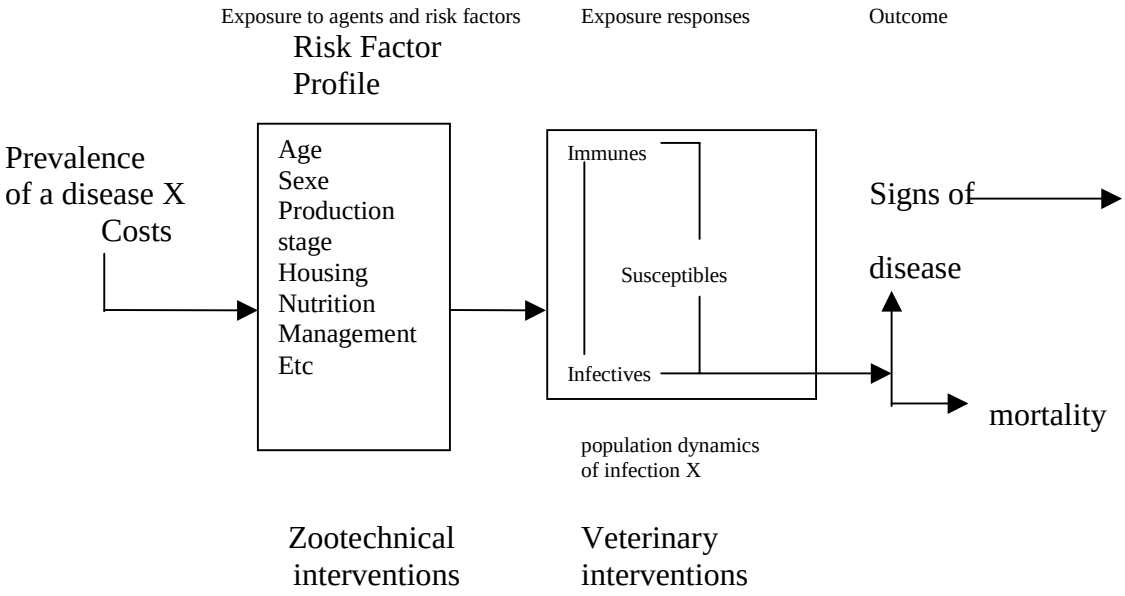

Fig. 1: The chain of risk events, exposure and outcome

Disease prevalence may vary over time due to changes in risk factors or their impact, but also because the proportion of susceptible, immune and infective animals in a population changes over time. The outcome of such dynamics may be that overt disease signs occur. On the basis of such signs the economist may estimate the disease related losses.

Interventions are classically taken by the veterinarian at the point where the proportions of immune, infective and susceptible animals are to be taken into account; the elementary example here is vaccination of the herd (yes or no). Risk management interventions however are commonly taken at an earlier stage of disease development in a population: this is part of preventive action. Knowledge about disease risks therefore is highly welcomed by e.g. local and regional veterinarians. This principle applies to both the individual herd, the regional population and the national herd. Not only proportions differ but also the characteristics will differ with each level.

International level

It is no longer accepted that laboratory testing of animals for freedom of certain diseases and animal health certificates are sufficient for facilitating live animal trade. Formal Quantitative Risk Assessment (QRA) is now warranted to demonstrate to third parties what the scientific basis of and rationale is behind such health certificates. It has been shown above that for performing formal QRA several hurdles (e.g. data; infrastructure; resources) have to be taken. These are addressed in later paragraphs.

2.4. The current situation regarding risk assessment in livestock production

In this paragraph, the respective activities related to risk assessment and risk management as related to infectious diseases are addressed for the respective operational levels: herd, region, sector/national level and international level. Fig.1 provides an overall view over all these levels in an integrated manner. It is related to ***the risk chain concept***.

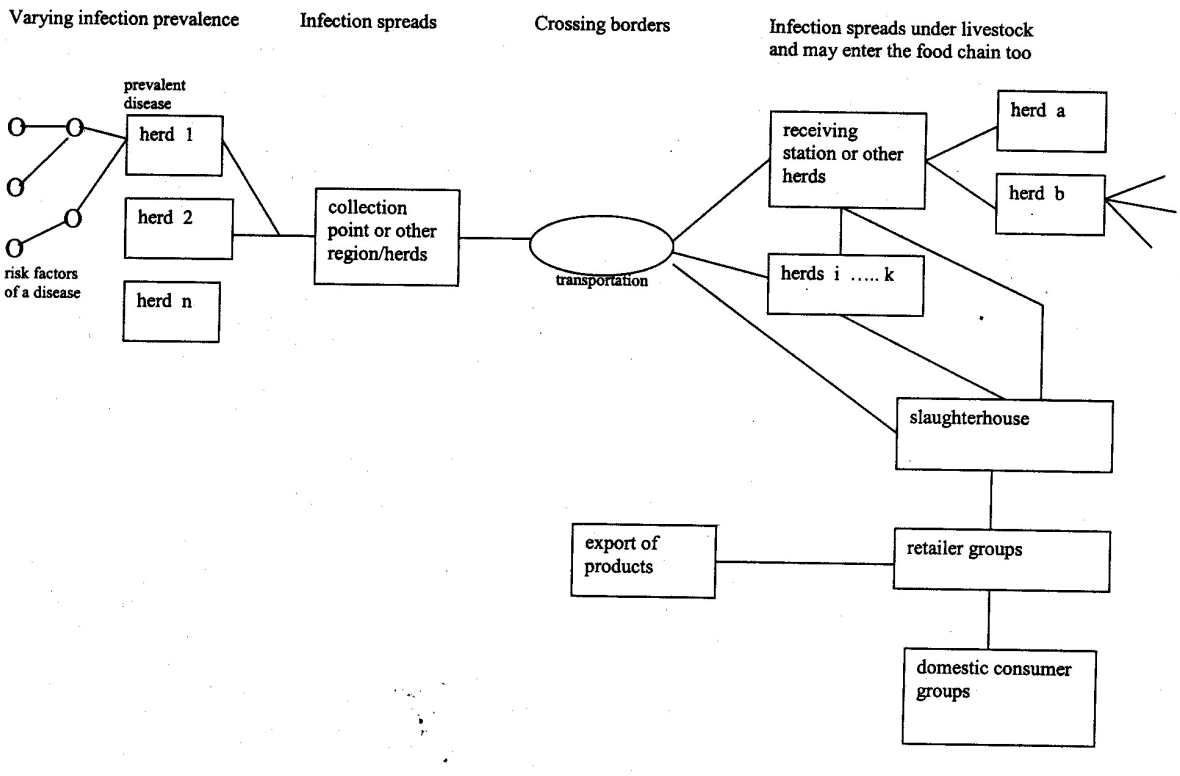

Fig. 2: Diagram of spread of transmissible diseases through livestock populations and into the food chain , crossing borders

When this concept is adapted to the situation of livestock production as a whole, including national or international trade, the differences between risk assessment approaches, either qualitative or quantitative, to transmissible diseases in livestock on the one hand and to contaminants or quality of food on the other hand may become more visualized, and drawbacks as well as opportunities can be shown.

At herd level, different risk conditions related to e.g. animals (breed, production stage, age etc) and the environment (e.g. housing, micro-climate, feeding, management) lead to a variability in disease prevalence over time (see also Fig.1). This is especially true for endemic disease situations.

With regard to the introduction of infectious disease agents into the herd, much depends on the number of infectious animals, the proportion of susceptible animals versus

immune animals, as well as on the nature of the agent and transmission routes whether or not an infection will become established. Such introduction and establishment of an infection is yes/no facilitated by general hygiene procedures on the farm and the extent to which a farm is "closed" (e.g. no visitors allowed; no purchase of animals from unknown sources; concentrates from a GMP feed mill). Once an infection is introduced on the farm, further spread can occur through e.g. airborne or direct contact transmission, unless measures have been taken to prevent this (van Schaik, 2000). For both the introduction and the spread of infections as well as for prevention, the risk factors play a paramount role. There are two entries for dealing with such infections: (1) endemic diseases which have only a farm-economic impact and which, hence, the farmer has to deal with by himself (e.g. bovine mastitis; E.coli diarrhoea problems), and (2) endemic diseases with an (economic) impact also at sector level because for example the market requires freedom of disease (e.g. bovine Herpesvirus type I virus infections, salmonellosis, Aujeszky's disease), and the sector may start a control programme to eliminate the disease from the sector.

A problem at farm level is currently that little is known about the farm-specific risk factors, and about the herd prevalence and incidence of certain diseases, and that monitoring at farm level is not commonly executed or, if executed, often without a formal protocol. Hence data is missing and, if data is available, it is often not representative while reliability and accuracy is at least doubtful. In herd health programmes a qualitative risk assessment and following risk management procedure will often be successful, but only for direct farm-operational matters. Additionally, there is an increasing tendency to implement Good Farming Practice codes to change attitudes and mentality towards risk awareness.

Risk factor identification and quantification of risk factor contribution to infection occurrence at herd level has only a short young history and has mainly been addressed at infections that are of direct interest to farmers (e.g. bovine lameness; mastitis). The same is true for animal health economics which, originally, was applied to estimate disease losses on the farm, but currently focuses more on disease (risk) modelling.

The population dynamics of infections have only recently become an issue for (applied) research, for example for studying infection patterns in populations and the effects of certain intervention policies (e.g. yes/no vaccination of a herd, how many times to vaccinate, evaluation of test and culling strategies).

At regional level or national level, an infection, once introduced in that region, may spread between herds. Such spread largely depends on the animal population density in that region/country, on the nature of the infectious agent and its transmission routes, on trade structures and animal movement densities, and on other risk factors that contribute to this spread (see also Figs. 1 and 2). The same applies as in the previous case: risk factor identification and quantification of their contribution has not widely been applied, although some nice examples can be given.

Specifically, animal health economics modelling (see paragraph 3.3 and 3.4) and infection transmission modelling (by using the basic reproduction ratio R_0 concept, see paragraph 3.5) have lately been applied to this level, for example when studying population dynamics of classical swine fever or bovine Herpes virus type I infections in livestock at large scale.

These applications are usually performed to answer specific questions of national animal health policy makers or of the livestock production sector with regard to the prevention of diseases, the reduction of prevalence and the implementation of intervention measures. The relevant disease categories are the endemic diseases and the highly contagious epidemic diseases; the latter as far as the impact at national or sector level is concerned.

With regard to the trade of live food animals (including semen and embryo's) within a country, a whole variety of risk reducing measures can be applied, ranging from compulsory washing and disinfection facilities for animal transportation vehicles, to the maximum number of animals per m^2 of truck loading surface, to the routing of trucks from high health status to low health status farms and not vice versa, to health certificates listing freedom of herds/animals from specific diseases. Again, this is regulated at national and or sector level. The risk analysis situation is highly comparable to the one at sector level because of joint interests.

With regard to the international trade of live animals it can be stated that formal risk assessment procedures are not widely applied. Usually, animals are screened for health status at the site of shipment, which can be depicted in a health report or certificate. Importation of live animals from outside the EU means the provision of such reports or certificates, while at the entry ports another check is made, either at the individual animal level or at a sample of a group. Principally, the border is now positioned around the receiving farm; farmers may ask for additional testing on specific diseases.

For exportation the same procedure is carried out, from animal testing to health certification. The specific diseases from which an importing country desires to be safeguarded are listed. They refer not only to the highly contagious diseases (e.g. foot and mouth disease; classical swine fever; brucellosis; tuberculosis) but also –variable per country- to named endemic diseases like bovine Herpes virus type I infections, and Aujeszky's disease. If health certificates of either individual animals or samples from groups of animals are not regarded as reliable or not reliable enough, or should at least be supplemented by a transparent formal risk assessment procedure, then there is large room for improvement in this respect.
Risk assessment studies following formal QRA procedures such as laid down by the OIE (1999) have rarely or not at all been carried out in Europe. In New Zealand such formal procedures for live animal importations have been initiated by the government some years ago for safeguarding the national herd (McDiarmid, 1993).

Several large scale studies have been carried out for assessing the risk on introducing foot and mouth disease in a European Union member state when the imported animals would come from different countries from within and outside the EU (Horst, 1998). Each country was given a "qualitative risk score" (from high to moderate or low risk) based on e.g. previous outbreaks, animal population densities, transport network, speed of diagnostics and reliability of diagnostics, functionality of a monitoring and surveillance system, if available at all, expert opinion etc. A comparable epidemiological and economic study has been done on classical swine fever in Belgium (Saatkamp, 1996)

Concerning the animal collection sites one can state in general that these sites are often a collection point of infectious agents as well, because animals of different origin are gathered, and cross-infection can easily occur due to contact or airborne transmission, high animal density, and lowered general disease resistance due to preceding transport stress. When hygiene and disinfection measures for people, trucks and buildings on that site do not achieve optimal standards, the risk of cross-infection further increases. Quantitative studies in that respect have not been carried out at large scale.

During transportation of live animals there is always the probability that cross-infections may occur, because usually animals come from different herds, certainly when larger groups are involved. Different herds of origin will often mean different health status. In addition to the national regulations for transportation of animals (like duration, drenching, stocking density and other welfare issues) little has been done about identifying the risks of introduction and spread of infectious agents from one region to another, or from one country to another in a quantitative sense. The screening studies that have been carried out are rather qualitative in nature and often based on microbiological testing (e.g. culturing of dirt and faeces on and in trucks returning from abroad).

At the receiving station or herd (that is: after national or international transportation) the animals may proceed to other herds or to slaughterhouse. Prevalent infections which have not been detected before may hence be spread to other herds; overt disease may then be a consequence for the receiving farmer. This overt disease will be a smaller problem if only endemic diseases are involved which cause a relatively small economic impact (the disease can be treated or the animal culled or –at the worst case - the whole herd will loose its health certificate until further actions have been taken). The problem will be much more dramatic if a highly contagious disease is involved and the infection will spread from the receiving farm to other herds. Even if clinical and laboratory diagnostics are of high standards, a true early warning system in the respective livestock sector is not yet operational. Much depends on veterinarians' and farmers' skills, knowledge, reliability and responsibility. Formal risk assessment procedures involving these receiving stations have not been carried out. High standard hygiene and disinfection measures together with (additional) testing are common procedures to safeguard the receiving stations or herds from introducing infections, at least sample-wise.

Animals directly being transported to slaughterhouses represent a limited risk when they carry infections. There is hardly any risk that such infections are transmitted to other livestock in production units if appropriate hygiene measures are taken. The remaining risk refers to zoonotic infections and infections which may turn into food borne infections which should then be detected at the slaughterhouse.

In conclusion:
When addressing Risk Assessment in livestock production one should distinguish the different operational levels (individual herd; sector; country; international) before pointing to any relevance of formal Quantitative Risk Assessment (QRA).
At individual herd level the formal QRA procedures are not warranted for serving the individual farmer's goals.
For purposes at national level and for answering specific questions at sector level, the current methodologies are suitable (see chapter 3).

At sector level, particularly in exporting countries, QRA provides an additional tool to **demonstrate** to third parties that a certain animal health status based on laboratory screening and health certificates has a sound basis. Whether QRA is specifically needed for that purpose is questionable, but the market dictates. For importing countries the availability of formal QRA data will strongly help to attain a certain reliability and gain confidence, possibly better than with health certificates and lab testing alone.
However, the above named issues reveal many gaps and deficiencies in data collection and handling, specifically at farm level. Implementation of monitoring & surveillance at farm level in order to facilitate tracking and tracing, as well as early warning would represent major break-through in the general RA approaches. Additionally, infrastructure and resources are needed.

3. METHODOLOGIES AS APPLIED IN RISK ASSESSMENT IN LIVESTOCK PRODUCTION

3.1. General introductory remarks

Risk assessment by and large can be executed in either a qualitative or quantitative sense. Both approaches consider the probability of occurrence of the risk and the estimation of the consequences. In qualitative or informal RA respective steps are made in a general manner using terms such as “unlikely” or “quite likely” to describe probabilities of occurrence and terms like “serious” or “catastrophic” for describing consequences. The objective of such an approach is to divide risks into low-probability and low-impact events which can be excluded from further study, and high-risk and high-impact events needing more careful consideration.
At e.g. the herd level, examples of qualitative methodologies are veterinary herd health programmes and disease control programmes. The application of the HACCP concept at farm level for controlling disease introduction and disease spread is currently under study.
Risk Assessment and risk management are both related to the systematic application of management policies and practices of identifying, analysing, assessing, treating and monitoring risks. Basically, they can be applied to every level, from individual herds to international policy making. It refers to a way to avoid losses and to maximize opportunities.

Quantitative Risk Assessment comprises several phases (see OIE Code, 1999). Based on Chapter 2 where it was stated that QRA is best applied at the level of international trade and movement of live animals, the elementary assumption is that the QRA model is the function of two probabilities:

- the probability that a particular infectious agent may enter a country or region, and
- the probability of a domestic exposure.

The former probability mainly depends on four different factor clusters, namely (1) biological factors, (2) the country factor, (3) the commodity factor and (4) the number of animal importation units.

Biological factors are influenced by species, breed, age of the animals, agent prediction sites, vaccination and medication status, etc. The country factor is determined by the disease incidence/prevalence figures of the exporting country. Note that disease monitoring and surveillance systems are needed, as well as evaluation data of disease control programmes and zoning systems to provide such information. The commodity factor is a probability estimate based on the presence and tenacity of an infectious agent in a commodity. This general model leads to an unrestricted risk estimate. Taking risk reduction measures into account, this unrestricted risk estimate will be specified to a restricted risk estimate.

Considering the exposure assessment part of the chain of risk events model (see also Fig.1) leads to describing the pathways related to exposure of animals and humans in the importing country to the hazards released from a given source, and estimating the probability of the exposures occurring, either qualitatively or quantitatively (OIE Code, 1999, Appendix VI).

Risk Assessment procedures should involve risk management and risk communication strategies at all times. Of these two, risk communication is often undervalued. Risk management follows the outcome of the formal risk assessment procedure. It addresses the range of options for treating a particular risk, then evaluating these options for selecting the most suitable one, and implementing it. Selection of an option is based on scientific arguments, technical, economic and ethical feasibilities, public acceptance and politics.
Once risk management has been implemented, it should be maintained. Since risk management involves choices made with imperfect information, it is likely that risk management should be revised from time to time.

Risk communication is an open process and is directed in two ways of exchanging information, opinions and perceptions about risks. It leads directly to better understanding and better risk management decisions, and is a valuable tool to provide a forum for interchange with all parties concerned – in one way or another – about the nature of the hazards, the risk assessment procedure and how the risks should be managed. Often it is the case that perceived risks ranking does not match with actual or calculated risks ranking. Therefore, communication is a necessity.

3.2. Data and their relevance to risk assessment

Completely relevant data are seldom available to provide a sound and firm basis for assessing probabilities needed in decision-making. Usually there is doubt about the relevance of historic data due to differences in time and space between the data themselves and the outcome of interest. It is necessary to consider the reliability of any historical data. Who has recorded the data, what observation and recording method has been used, what diagnostic method was applied, who has done the processing of data and how, etc.? Many items can be subject to bias, of which the extent is not known, and more errors may have slipped in during data processing and summarizing the information. In other words, extreme caution and common sense are needed when handling data, especially from the field, hence implying also the livestock production sectors.

On-farm data recording according to a formal protocol (consistency of observation, consistency in recording, reliability of information, representativeness, accuracy etc.) is paramount for QRA. Such data is commonly not available at the sector or national level; sparsely some data is available from smaller field trials and in-station experiments.

The relevance of a given data set is often issue for debate. There are largely three ways of summarizing such data:

1. the data can be treated as a sample and estimates of moments of the distribution can be calculated;
2. the data can be arranged as empirical cumulative distribution functions (CDF) and allowed to "tell their own story";
3. if appropriate, some standard distribution function such as the normal or the beta distribution may be fitted to the data.

Provided the data are not forced to fit some inappropriate distribution, the choice between the three options can depend on convenience in the subsequent analysis. When data are really sparse, maximum use can be made of the few observations on some continuous uncertain quantity by using the simple rule that whatever the underlying form of probability distribution is, the *k*-th observation from a set of *n* random and independent observations, when the observations are arranged in ascending order, is an unbiased estimate of the $k/(n+1)$ fractile. Thus, the fractile estimates can be plotted and a CDF drawn subjectively.

As mentioned in chapter 3.1 "Hazard identification" of the final report "Quantitative Microbiological Risk Assessment (Food and other, contaminated products)" dated September 25th, 2000, the first steps in the formal Risk Assessment procedure should be the hazard identification, followed by hazard categorization. A prerequisite for hazard identification would be the availability of animal health and disease data. For that purpose, monitoring and surveillance systems should be implemented at farm level and sector level. Tracking and tracing procedures cannot be implemented without these. In livestock production at the national level, hazards are usually defined on the basis of market access threats (required freedom of named diseases) representing an economic drive and or on the basis of both public health and food safety requirements (indirect economic drive, public image related issue). Other issues related to data sources and data reliability have been addressed in the afore named report.
Another issue related to data collection and data processing refer to the infrastructure (number of mandatory and voluntarily notifiable animal diseases, animal disease reporting systems, infrastructure of veterinary services, data processing units, etc). This is one of the major questions in identifying and categorizing hazards in many countries: *"Infections do not know any border, diseases do"*.

The animal health status of wildlife (possibly threatening food animals) and the question whether an infection is present in a certain region is often underestimated or remains unclear due to lack of monitoring and surveillance.

3.3. Components of risky decision problems

There are six components of a risky decision problem:

1. Decisions or alternative actions between which the decision maker must choose, denoted by a_j.
2. Events or uncertain 'states of nature' over which the decision maker has no control, denoted by S_i.
3. Probabilities measuring the decision maker's beliefs about the chances of occurrence of uncertain events, denoted by $P(S_j)$.
4. Consequences or outcomes, sometimes called payoffs, indicating what might happen if a particular action or sequence of actions is chosen, and given that a particular event or sequence of events occurs. These consequences may be expressed in terms of a single attribute, such as profit. Consequences which each action and event combination may have can also be expressed in terms of a number of attributes, such as cash for consumption, equity and debt level, denoted by X_{ij}.
5. The decision maker's preferences for risky consequences.
6. A choice criterion or objective function.

Rational choice under risk may be defined as choice consistent with the decision maker's beliefs about the chances of occurrence of alternative uncertain consequences and with his or her relative preferences for those consequences. The decision maker's beliefs are reflected in probabilities he or she assigns (implicitly or explicitly) to uncertain events, while his or her preferences for consequences are captured in the way by which risky payoffs with their associated probabilities are converted to some index that can be used as the criterion for choice.

Example:

An outbreak of foot-and-mouth disease (FMD) occurs in a certain region of a country. FMD is feared because it spreads rapidly among cattle, sheep and pigs and causes high losses (example taken from Hardaker et al., 1997).These losses (payoffs) result from the need to destroy affected animals to reduce further spread of the disease (events), and from other disease-control measures such as slaughter of contact herds and preventive vaccination.

The national government, which is responsible for controlling highly contagious diseases, has to decide on an effective policy (i.e. the decisions). As the size of the losses is small relative to the overall wealth of the society, risks can be widely spread and risk aversion will not be significant. Consequently, the problem can be solved using expected money values (EMVs) as the choice criterion. Policies are compared on the basis of discounted losses, and the policy with the lowest expected national economic loss is chosen.

At the beginning of an outbreak, the government has for example two options to choose. The first is to attack the disease with an 'area policy', which includes tracing and killing all animals from diseased herds and contact herds.
The second option is the more risky but less expensive one called 'farm policy'. In this policy only herds which are diagnosed with FMD are slaughtered. Some 6 weeks after the start of an outbreak, the government will review the success of its policy. With the

area policy, there is a probability of, say, 0.75 that the FMD outbreak will have been eradicated. In that case, the total (discounted) losses are assumed to be € 40 million.

However, there is a 0.25 chance that the disease will still not be under control and that new herds are being infected. In such a situation, the government has another set of options: either to continue the area policy or to start a 'vaccination policy'. The latter includes preventative vaccination of all susceptible animals in that region such that the animals are protected against contracting the disease. Vaccination is relatively costly: it involves not only vaccines but also labour to vaccinate the animals. If the government continues the area policy, then uncertainty about when the disease will be eradicated might be represented by two possibilities: either the outbreak will be cleared up in about 10 weeks (incurring assumed total losses of € 60 million) or in about 14 weeks (with assumed losses totalling € 80 million). The two possibilities might be judged to be equally likely, implying probabilities of 0.5. On the other hand, a vaccination policy is assumed to result in eradication within 8 weeks with a probability of, say, 0.8, or within 10 weeks with a probability of 0.2. The total discounted losses involved are taken to be € 55 and € 83 million, respectively.

Initially the government could also opt for a farm policy. This policy is presumed to eradicate the outbreak in 35 per cent of the cases, and then only causes a loss of € 15 million. But there is a probability of 0.65 that the disease will not be under control after 6 weeks. Then there is only one alternative left: vaccination. This is presumed to eradicate the disease in 9 weeks (p = 0.9) or in 12 weeks (p = 0.1), with € 90 and € 130 million as total discounted losses, respectively.

The example is summarized in form of a decision tree, which is shown belowin Fig. 3. More realistic examples can be found in Houben (1995), Saatkamp (1996), Buytels (1997), and Horst (1998).

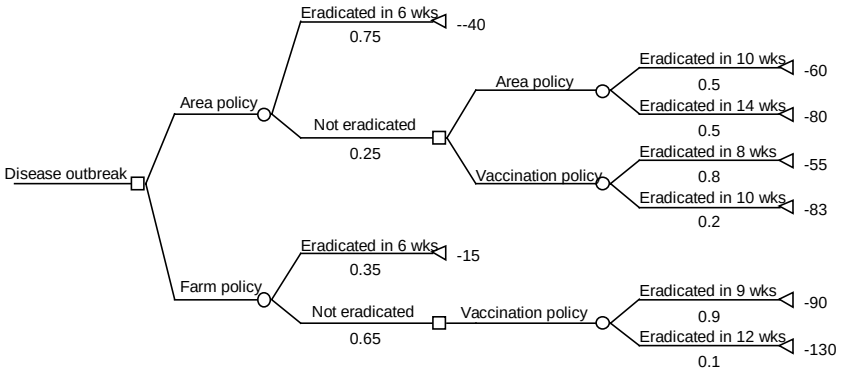

Figure 3: Decision tree for foot-and-mouth disease problem

3.4 Stochastic simulation as a quantitative tool in risk analysis

Simulation can be described as a method of problem analysis in which a (computer) model is created of the situation that can then be manipulated by input modification until the problem is solved. Any model is an approximation to the real situation and certainly the closer the approximation becomes, the more difficult and time-consuming the model will be to analyse. The skill of the analyst lies in the way he balances the reality of his model with the effort it will take to find an answer to his problem.

The complicating factor in most mathematical models arises from chance or stochastic elements. As mentioned above, it is usually possible to fit a standard probability distribution to the available data. The @RISK computer package can be used for quantitative modelling. It brings advanced modelling and risk analysis to Excel worksheets. If a decision maker or analyst quantified the risk, i.e. determined outcomes and probabilities of occurrence, he can use @RISK to describe uncertain values in Excel worksheets and to present the stochastic results. There are many forms and types of probability distributions, each of which describes a range of possible values and their likelihood of occurrence.

In @RISK, all distribution types use a set of arguments to specify a range of actual values and distribution of probabilities. The normal distribution, for example, uses a mean and standard deviation as its arguments. The mean defines the value around which the bell curve will be centred and the standard deviation defines the range of values around the mean. Over thirty types of distributions are available in @RISK for describing distributions for uncertain values.
Sampling is used in @RISK simulation to generate possible values from probability functions. These sets of possible values are then used to evaluate the Excel worksheet. Sampling is the process by which values are randomly drawn from input probability distributions. Because of this, sampling is the basis for the hundreds or thousands of "what-if" scenarios @RISK calculates for the worksheet. Each set of samples represents a possible combination of input values which could occur. Sampling in a simulation is done repetitively - with one sample drawn every iteration from each input probability distribution. With enough iterations, the sampled values for a probability distribution will become distributed in a manner which approximates the known input probability distribution. The statistics of the sampled distribution - mean, standard deviation and higher moments - will approximate the true statistics that were input for the distribution.

A major sampling technique in @RISK is Monte Carlo sampling. Monte Carlo sampling refers to the traditional technique for using random numbers to sample from a probability distribution. The term "Monte Carlo" was introduced during World War II as a code name for simulation of problems associated with development of the atomic bomb. Monte Carlo sampling techniques are entirely random. That means, any given sample may fall anywhere within the range of the input distribution. Samples, of course, are more likely to be drawn in areas of the distribution which have higher probabilities of occurrence. With enough iterations, Monte Carlo sampling will "recreate" the input distributions. A problem arises, however, when a small number of iterations are performed.

To summarize, with many model inputs being in the form of probability distributions, a method of retaining these distributions and propagating them through the model is required to give outputs (i.e. the risk estimates wanted), also in the form of frequency or probability distributions. There may also be a model pathway (from risk source to consequence) for uncertainties and these can be incorporated by the inclusion of each potential pathway into the integrated model as well, and if appropriate, weighted by the likely probability assigned to that pathway (see Figure 4).

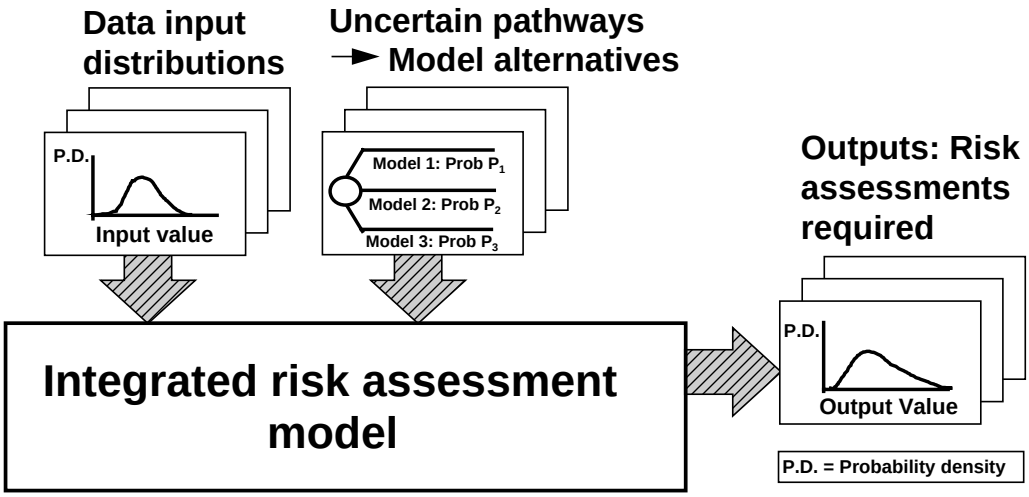

Figure 4: Propagation of distributions through the model (Wooldridge, M.M., 1997)

Example I:

This example is based on Huirne & Hardaker (1998). As a result of specialization and concentration, the production and marketing of fresh pig meat are distributed over several, usually independent farm and agribusiness firms. Together, these farms and firms act as a supply chain. Because the several farm and firm stages of the chain are linked vertically, they influence each other's technical and economic performance. Usually the optimisation of each individual stage results in suboptimal overall chain results. To prevent this, vertical chain coordination is needed. Chain coordination is even more necessary because of rapidly growing concerns for total quality management and food safety.

A key-issue in the relationship between successive chain participants ('supplier' - such as pig breeder - and its 'customer' - pig fattener) is product quality. A stochastic simulation model was developed to examine the effect of (on) food quality level on (of) the relationship between pig breeder and fattener when risk is recognized. We have assumed that cooperation enables joint cost minimization and have derived the conditions for cost minimization under both adversarial and cooperative structures. A stochastic model was developed on the PC using Excel and @Risk. The model explicitly considers the four major (food) quality costs: prevention costs, internal failure, external failure, and appraisal. In most adversarial relationships, prevention costs and internal failure costs are borne by the supplier and appraisal and external failure costs are

borne by the customer. The model recognizes that the food quality and inspection standards are not always perfect (i.e., they are stochastic).
The primary finding is that restructuring an adversarial relationship as a cooperative relationship will lead to an improvement in product quality (i.e. food quality). Many if not most chain coordinating activities/contracts are really risk-sharing arrangements. Because of asymmetric information in adversarial relationships, all such arrangements are potentially vulnerable to adverse selection and moral hazard, and therefore causes of market failure and potential inefficiency. In some adversarial cases, the risk problems may cause markets to operate perversely.

The stochastic model provides insight into the usually slow adoption rate of untried improved chain technology by risk-averse participants. Such risk-induced friction also means that the aggregate chain output is less than it would be if there were less risk. This in turn means that cost prices for chain products tend to be higher than would otherwise be the case.
For other examples on stochastic simulation, reference is made to Horst (1998), Meuwissen and Huirne (1998), and Meuwissen (2000).

Example II:

Gallagher et al. 2000 carried out a QRA for the transmission of bovine tuberculosis from badgers to cattle within localised areas in GB. In this paper, the development of stochastic Quantitative Risk Assessment (QRA) models is considered. An overall framework to describe such models is presented and an estimation procedure for the first module of this framework is outlined in more detail.

An initial model framework to describe the various stages necessary for badger to cattle transmission on a particular farm is demonstrated. The outputs from each of the five modules will be distributions for the probability of badger infection with M. bovis (P1), excretion of the bacteria (P2), its survival in the environment (P3), cattle exposure to the organism (P4), and cattle infection (P5). In this paper the idea of developing a stochastic QRA procedure for estimating P1 has been proposed and the results from two farms have been presented for illustrative purposes.

3.5. Applications of the basic reproduction ratio R_0 in risk assessment: some examples

The basic reproduction ratio, $R_{0,}$ is a threshold value describing the infection dynamics in a population. This R_0 is defined as the average number of secondary cases generated by one primary case in a fully susceptible population of defined density (Anderson and May, 1982, 1990; de Jong et al. 1991). A disease will most likely sustain in a population when the R_0 is greater than or equal to unity (one). Infections which can be characterised by high R_0 values will be more difficult to control than diseases with low R_0 values. In order to eradicate a disease the R_0 value should be below unity. Lowering of R_0 can be achieved by, for example, vaccination, or test and cull.

R_0 can be displayed as $(ß/\alpha)* N_0$, where $(ß * N_0)$ represents the average number of animals infected by one infectious animal per time unit, and $(1/\alpha)$ represents the

average number of time units during which an infected animal is infectious. Usually these parameters are used in so-called SIR-models, where S = susceptible to infection, I = infectious and R = removed.

Application examples at regional and herd level are given by Hage et al. (1996) for the eradication of bovine herpesvirus type I from dairy herds. After introduction of this virus into a dairy herd and the rapid spread within 5 weeks, the R_0 within the herd was estimated as at least 7, in other cattle 4. The R_0 between herds has also been estimated by Hage (1997); it can be an important parameter when for example disease control or eradication is to be considered. Eradication may occur when both the R_0 within and R_0 between herds are below unity. Bosch (1997) estimated the efficacy of different vaccines against bovine herpesvirus type I in dairy cattle by studying their potential to lower the R_0 value and, hence, to reduce virus spread and transmission in a population. For acceptable efficacy, the R_0 value should be well below unity. This author found that when the virus is introduced into vaccinated herds, major outbreaks still could occur because the R_0 value was significantly higher than unity.

Other examples are given by Stegeman (1995) regarding Aujeszky's disease and van der Poel et al. (1993) and van der Poel (1995) regarding BRSV.

3.6. Quantitative risk assessment in case of importation or exportation (live animals, food, animal products)

Examples to illustrate the methodology of import risk analysis are given by Morley (1993). Using mathematical models, the disease risks associated with the importation of animals and animal products were calculated. The basic question is the probability that a disease outbreak occurs following the importation of one animal import unit (AIU, a live animal or a specific weight of a product). This probability depends on several other probabilities, like the probability that an animal import unit is infected with a disease agent, the probability of survivability of the agent (depending on the prevalence of the disease in the exporting country), the probability of exposure of the commodity to susceptible animals or humans of the importing country, and the probability that the agent is transmissible via the mode of transmission, given the animal import unit is infected, the agent survives in the commodity. The calculation of the probability that infectious agents may be introduced into an importing country is shown in the following example for Classical Swine Fever (Morley, 1993):

Example I

Probability of classical swine fever agent entry associated with the importation of 500,000 kg of 400-day-aged boneless pork ham weighing 7-9 kg, prepared according to the Parma ham process

Classical swine fever (CSF)

Country factor

(86 outbreaks during 1991 x 371 average herd size x 0.05 average duration of infection in years) / 26,850,250 swine population = 5.9 x 10^{-5}

Commodity factor

Classical swine fever (CSF) virus inactivated in less than the 400-days aging process; consider a very low value, e.g. 1 x 10^{-8}

Number of animal import units (n AIUs)
500,000 kg / 7 kg minimum weight per ham x 2 per pig = 35,714 AIUs

Probability of agent entry
1-(1-country factor x commodity factor)^{nAIUs}
= 1-(1-[5.9 x 10^{-5} x 1 x 10^{-8}])^{35,714}=2.1 x 10^{-8}
(probability that at least on animal import unit of the importation is infected)
Of course, this very low risk on such a large annual importation applies only to this specific product.

Following the above mentioned example, a scenario for the probability of domestic exposure (PDE) involving the feeding of meat scraps to swine can be described as follows (Morley 1993):

The scenario is based on the assumption that uncooked meat scraps are discarded from households and fed to swine. A probability could be based on the division of the total number of farms reporting the presence of swine by the total number of households in the country, and multiplying this by the proportion of producers which could be expected to feed household scraps to swine. A farm is assumed to represent a household. The probability that smaller farms practice swill feeding is higher than in farms of higher pig concentrations. The probability that rural households keep pigs is usually higher than that of urban households.

Scenario: Feeding meat scraps to swine in Canada:

- No. of households in the country	*=*	*10.018.265*
- No. of rural households (< 1000 persons)	*=*	*2.129.365*
- No. of pig holding farms	*=*	*29.592*
- Proportion of households rearing swine	*=*	*0,003*
- No. small farms rearing swine (1-77 swine)	*=*	*14.907*
- Proportion small farms / total farms	*=*	*0,500*

- PDE for this scenario (0,003 x0,50) = 1,5 x 10^{-3}.

Example II

Another example for the methodology of quantitative risk assessment in particular with live animals is given by Kelly, Leslie and Wooldridge (2000) for Bluetongue infections.

A QRA was made for the import of cattle infected with blue tongue virus into Great Britain (GB) from Canada.
Consider any bovine animal intended for export to GB. Such an animal will be in the BT Group with probability PInf and not in the BT Group with probability 1-PInf. Animals in the BT Group may or may not be detected by the pre-export procedure. This

procedure involves on-farm isolation, testing for BTV/EHDV at the time of isolation using the Agar Gel Immuno-Diffusion (AGID) test, quarantine following a negative test result and a final test in quarantine, again using the AGID test. Animals with a negative test result are exported. Overall, animals in the BT Group and intended for export to GB will not be detected with probability PNDet and detected with probability 1-PNDet. The probability that any animal in the BT Group which has not been detected by the pre-export procedure is viraemic at the time of entry into GB is given by PVir. It follows that the probability that such an animal is not viraemic is given by 1-Pvir. The overall probability of any animal entering GB being viraemic (P) is given by

$$P = \frac{PInf \times PNDet \times PVir}{1 - PInf\left(1 - PNDet\right)}$$

By assuming that each animal entering GB is independent and has the same probability P of being viraemic, the risk per year of introducing BTV/EHD into GB (R) is given by

$R = 1 - \left(1 + P\right)^N$ *N = number of imports per year.*

By this study, it could be demonstrated that the risk per year of introducing bluetongue into GB is between a 0,004% and a 0,473% chance with 90% certainty.

Example III

Disney (2000) described a method of quantitatively modelling the risk of undetected animal disease transmission in poultry meat exports. This paper describes a quantitative risk analysis with a simulation model developed to address the issue of low pathogenic avian influenza risk to importing countries in fresh and frozen broiler meat exports. Similar methodologies could also be used for almost any issue of animal product imports into the United States.

The model uses Monte Carlo Simulation techniques to simulate an uncertain and variable number of shipments from commercial broiler firms in an exporting country over a period of 6000 years. The model is programmed in Microsoft Excel, using Palisade Corporation's @Risk software. A combination of standard and 'not-so' standard statistical tools are utilized in the determination of probabilities for undetected infected poultry meat progressing through five major nodes. One of the more interesting applications involves the pragmatic quantitative application of the Central Limit Theorem in calculating the probability of a single piece of contaminated poultry meat reaching a susceptible bird in the importing country.

A baseline scenario is developed assuming that a minimal level of commercial surveillance is taking place in the relevant commercial broiler flocks - the results of which are all negative. Alternative scenarios explore the reduction in expected risk associated with varying increases in the current level of commercial broiler surveillance -again, the results of which are all negative. Interestingly, available statistical techniques for estimating undetected disease prevalence never assure disease freedom. This is also addressed. Finally, a scenario is developed to measure the reduction in risk associated with individual flock testing for every flock destined for an export shipment.

4. OTHER CONSIDERATIONS

4.1. When formal risk analysis is needed

Formal risk analysis obviously has costs, at least including the costs of the time to do the required thinking and figuring. Not many decisions will warrant this input of effort. There are two cases where formal analysis may be thought worthwhile.

The first is for repeated risky decisions for which a sensible strategy might be devised that could be applied time and again. The benefit from better individual decisions may be small, but the accumulated benefit over many decisions may justify the initial and continuing investment of time and effort in analysis.

The second case for formal risk analysis arises when a decision is very important, in the sense that there is a considerable gap between the best and the worst outcomes. A case in point is a major investment decision in controlling animal disease.

The fact that a decision or a set of decisions is sufficiently important to justify efforts to reach a better choice is not the only consideration in deciding whether to undertake a formal analysis. Many real choices in agriculture are complex, and may not be well represented using the formal methods of analysis. Some common characteristics of complex decision problems are:

1. The available information about the problem is incomplete.
2. The problem involves multiple and conflicting objectives.
3. More than one person may be involved in the choice or may be affected by the consequences.
4. Several complex decision problems may be linked.
5. The environment in which the decision problems arise may be dynamic and turbulent.
6. The resolution of the problem may involve costly commitments that may be wholly or largely irreversible.

The psychological response of people to such complexity varies and may be more or less rational because it is related to risk perception. Some simply defer choice, even when to do so is to court disaster. For example, in hard financial times, it has been observed that some governments may cut off communications at the very time when they should be discussing how to resolve the emerging crisis.

The fundamental question in considering the role of formal methods of risk analysis is whether, in a particular case, the need to sweep aside much of the complexity of the real decision problem will leave a representation of the problem that is (a) sufficiently simple to be capable of systematic analysis, yet (b) sufficiently like the real situation that an analysis will aid choice. Obviously, it is our contention that the answer to these questions will be in the affirmative sufficiently often to make it worthwhile for

(political) decision makers to familiarize themselves with the formal methods of risk analysis.

4.2 Stochastic dependency and joint probability distributions

Most risky decision problems involve more than one uncertain quantity. The one-variable methods of probability elicitation can be applied validly to several variables relevant to some risk analysis only if the variables are stochastically independent. Two variables are stochastically independent if the probability distribution of one does not depend on the value experienced of the other. In practice, complete stochastic independence may be the exception rather than the rule. However, because accounting for stochastic dependence is difficult, it may often be judged to be 'near enough' to assume it when the degree of association between variables is thought to be fairly low.

If it is judged that the assumption of independence for two or more uncertain quantities is unrealistic, there is usually no alternative but to confront the inherently difficult task of joint specification. Here the options include (1) elicitation of joint distributions, (2) use of historical data, alone or in combination with elicitation, and (3) a 'hierarchy of variables' approach. These methods are discussed in detail in Hardaker *et al.* (1997).

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APPENDIX 6

REPORT ON PRESENTATION OF RISK ASSESSMENT FINDINGS

The "Committee Guidelines" working sub-group decided to make a review of a sample of opinions presented by the Scientific Committees, their framework and formulation, with the aim of issuing guidelines for an harmonised opinion presentation by the various Committees.

Some of the elements included in the review were:

- terms of reference - questions asked to the Scientific Committee
- sources and type of information used
- references to the assessment process (regulations, guidelines)
- uncertainties expressed
- wording and expressions used
- editorial format
- integrity and transparency
- values given -refusal -impossibility to answer

These elements were listed in a form to be used as the basis for reviewing each selected opinion (Annex 1).

Criteria for selection of the opinions.

The opinions taken into consideration were those available on-line on the 8th February 2000. 3 opinions were examined if the total number of opinions of a Committee was < 30 and 6 opinions if total number was ≥ 30. The opinions to be assessed were selected in a random way.
Table 1 summarises the number of opinions available on 8 February 2000 and the number of opinions selected for each Committee. Annex 2 contains the full database of the review.

Table 1 Opinions (including reports, evalutions etc.) available as 'outcome of discussions' on 08/02/00.

Committee	*From*	*To*	*Total*	*Selected*
Scientific Committee on Toxicity, Ecotoxicity and the Environment	09/02/98	25/11/99	25	3
Scientific Committee on Medical Products and Medical Devices	16/09/98	02/06/99	15	3
Scientific Committee on Cosmetic Products and Non-Food Products int.	24/06/97	23/06/99	87	6
Scientific Committee on Plants	10/02/98	24/09/99	39	6
Scientific Committee on Veterinary Measures relating to Public Health	17/02/98	23/09/99	11	3
Scientific Committee on Animal Health and Animal Welfare	24/03/98	08/12/99	15	3
Scientific Committee on Animal Nutrition	05/11/97	03/12/99	12	3
Scientific Committee on Food	15/01/98	02/12/99	40	6
Scientific Steering Committee	23/01/98	10/12/99	34	6
			278	39 (14%)

Results of the review of opinion according to the list of elements and attributes and general comments.

The list of elements did not fit equally well to all the different opinions, and some important characteristics of the opinions may not have been recognised.

There were major differences in size, degree of detail, format and scope among the reviewed opinions. They ranged for one page short comments to full detailed reports consisting of more than 100 pages. Thus it seems to be unavoidable that some differences in format may remain even after a process of format harmonisation.

The Commission requested nearly all of the opinions; only very few of them were prompted at the Committee's initiative.

The source of information was stated in most opinions, often in a reference list. An issue to be examined for the future is whether the quoted documents or literature will always have to be fully referenced.

Existing guidelines were often used as reference, naturally depending on the scope of the opinion. In some cases no official EC documents are available while in other cases they do exist. The reader is not always systematically informed about this point.

Numerical calculations done by the Committee were seen only in a limited number of cases, but values and calculations from references were often presented. In general, the transparency of the calculation process adopted was sufficient.

The uncertainty in the assessment of risk was generally not expressed in a single concluding sentence, but given more generally during the discussion or including adverbs or modal verbs in the conclusions. The variety of solutions on this matter adopted in the examined opinions probably reflects the difficulty in standardising the uncertainty concept in a single way of expression.

The editorial format among the opinions from the different Committees was far from homogenous. In particular, in several cases the reader finds difficult to identify the main messages and the conclusions without an extensive reading of all the text.

Most of the opinion did have a chapter with final conclusions, but named in different ways. Some Committees have already standardised the question of the editorial format in their interior, as all of their opinions conform to a uniform format.

The wording used for expression of risk varied as varied the scope of the opinions and the context in which the expressions were given. Quantitative risk expressions were few and only occasionally specific values were recommended. The importance of this aspect and the possibility of confusion for the reader, is demonstrated by the following examples of risk statements taken from the reviewed opinions:

'..is acceptable because of the non-toxicity…'

' the risk of transmission of BSE via embryo transfer is low to negligible'

'.. are regarded to be safe..'

'.. as carrying a negligible BSE-risk..'

'..suggest an extremely low risk of transmission..'

'.. no evidence to indicate…is likely to cause adverse effect..'

'.. may result in unacceptable risk..'

'..no significant risk..'

'.. risk is considered to be remote, low, extremely low..'

'..that there is a risk of phytotoxic effects..'

'..will not raise any particular risk..'

'..does not pose a hazard..'

'..not be harmful to consumer..'

'..products present a potential risk to public health..'

' poses no significant risk for consumers..'

'..can be used safely..'.

Request for further information/data was done in a few cases, and in some cases the opinion included a statement of the actual impossibility to answer specific questions.

- **RECOMMENDATIONS REGARDING THE PRESENTATION OF OPINIONS.**

Harmonisation and preparation of a Guideline Document

It is recommended that a Guideline Document be developed by the Steereing Committee to harmonise some aspects related to the presentation of opinions by the Scientific Committees.
The pronounced diversity in the questions asked to the different Committees naturally limits the extent to which harmonisation can be achieved. These limits will have to be considered in the preparation of a Guideline Document on presenting opinions.

Editorial format

More consistency in the format of the opinions would facilitate the use of opinions, at least for non-professional readers who wish to quickly understand the answers and are sometimes less interested in (or less able to understand) the technical reasons motivating the answers.

To this aim, it would be beneficial to use the same format and titles across the Committees for 'identical' chapters. At least for the opinions released to answer a question posed by the Commission, a recommended structure can be:

1. Title
2. Terms of reference (where the questions are reported)

3. Background (where the context of the question is detailed and reference is made to the source of documents and to the normative framework)
4. Opinion (where the essence of the opinion is summarised)
5. Scientific arguments supporting the opinion (where the topic is discussed in details, with subdivision in chapters, each one with a title, when appropriate and a final mandatory chapter named: Conclusions. These conclusions frequently are an expanded text from which the essence of the opinion is extracted.
6. References (where the quoted literature should be reported; as to the documents specifically made available by the Commission to answer the question, they should be mentioned in the Background section and not here).

Wording of the risk assessment evaluations.

The Scientific Committees should agree among themselves on a glossary for the words and expressions to be used regarding risk assessment. Such an agreed glossary would also serve as a 'reference glossary' for the client of the opinion and others too.

In developing such a glossary, the Scientific Committee should be aware that adjectives such as minimal, negligible, etc. and expressions as 'no risk', 'acceptable risk', etc. may sound to have a different meaning for scientists, experts and the layman. The glossary could explain the exact meaning attributed to these expressions or, alternatively, each opinion should explain the exact context in which such expressions are used. In general, judgements about 'acceptability' ought to be used only when clear legislative terms of reference are available (f.i. the limit of 0.1 μg/L for ground water for pesticides); otherwise the criterium of acceptability should be explained in detail. In every case, it seems to be very important that the reader is informed about existence or non-existence of official EU legislation of reference within the frame of which the risk assessment judgement is formulated.

When the opinion of a Committee contains specific reference to risk management decisions or consists of advise on risk management, the Committees should be aware that this may be beyond the mandate of a "scientific" group and carefully consider the appropriateness of releasing such opinions. While, in fact, the contents of an opinion should be defendable in scientific terms with the arguments detailed in the opinion, such a documented scientific justification may not be possible with regards to managerial aspects.

Summarised presentation of opinions

Taking into consideration the large amount of opinions to come, it may be useful if a sort of supplementary ultra short general tabular list could be developed for past and future opinions. This summary would particularly help the consultation of the web site list in a quick way.

Expression of uncertainty in the opinions

It is recommended to draw the attention of the Committees on this subject. Although a simple and uniform way of expressing uncertainty is probably not achievable, it should

be agreed that such an issue should be clearly addressed in the opinions, informing the reader about the solidity of the statements made and, when appropriate, the sources of uncertainty in the judgement. To avoid possible misunderstanding by the reader, the Committees should also make clear whether this issue is of relevance to the final use of the opinions or it turns out to be practically non-influent.

Adequacy of the opinions to the final purposes of the requesters.

It is also recommended to ascertain to which extent the main client (The Commission) is satisfied with the opinions so far delivered and whether problems were encountered regarding the interpretation and appropriateness of the opinion.

Annex 1 : LIST OF GENERAL REQUIREMENTS OF SCIENTIFIC OPINION PRESENTATION

Committee:
Opinion:

Terms of reference of the opionion.					
requested by EC		specific		adressing specific agents	
		detailed		- complex media	
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	
				- complex media	
				- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
Source of information used					
not specified					
specified		public			
		grey or proprietary			
		both			
		others			
Existing guidelines or regulations used as reference for the opinion					
not specified					
specified		European			
		International			
Transparency of numerical calculations presented					
Not applicable					
no					
yes					
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed					
no					
yes		form of expression			
Editorial format of the opinion					
title of main chapters					
paragraph conclusion(s)		no			
		yes			
Wording used for expression of risk					
key wording or expressions					
risk expression		qualitative			
		quantitative			
recommended value (unit)		no			
		yes			
request for further information/data		no			
		yes			
refusal / impossibility to answer		no			
		yes			

Annex 2. General database of the examined opinions

Committee: CSTEE 1

Opinion: on Cadmium - The Final Report by WS Atkins International Ltdbbased on : The Final Report (September 1998) & Additional Assessment (September 1998): "Assessment of the risks to health and to the environment of Cadmium contained in certain products and of the effects of further restrictions on their marketing and use".

<table>
<tr><td colspan="6">Terms of reference of the opionion. ? NOT TITLED The CSTEE has been asked to express its opinion on the adequacy of the above named reports: (1) Whether the degree of risk to the environment and man, as assessed by the WS Atkins Reports, is sufficiently justified? (2) To comment on the general quality of the Reports.</td></tr>
<tr><td rowspan="3">requested by EC</td><td rowspan="3">X</td><td>specific</td><td></td><td>adressing specific agents</td><td></td></tr>
<tr><td>detailed</td><td>X</td><td>- complex media</td><td>X</td></tr>
<tr><td>generic</td><td></td><td>- commercial, industrial process, procedures or sites</td><td></td></tr>
<tr><td colspan="2"></td><td colspan="2"></td><td>- guidelines for assessment or regulation</td><td></td></tr>
<tr><td rowspan="4">spontaneously by SC</td><td rowspan="4"></td><td colspan="2" rowspan="4"></td><td>adressing specific agents</td><td></td></tr>
<tr><td>- complex media</td><td></td></tr>
<tr><td>- commercial, industrial process, procedures or sites</td><td></td></tr>
<tr><td>- guidelines for assessment or regulation</td><td></td></tr>
<tr><td colspan="6">Source of information used</td></tr>
<tr><td>not specified</td><td></td><td colspan="3"></td></tr>
<tr><td rowspan="4">specified</td><td rowspan="4">X</td><td>public</td><td colspan="2">X (reference list)</td></tr>
<tr><td>grey or proprietary</td><td colspan="2"></td></tr>
<tr><td>both</td><td colspan="2"></td></tr>
<tr><td>others</td><td colspan="2"></td></tr>
<tr><td colspan="6">Existing guidelines or regulations used as reference for the opinion</td></tr>
<tr><td>not specified</td><td>X</td><td colspan="2"></td></tr>
<tr><td>specified</td><td></td><td>European</td><td colspan="2"></td></tr>
<tr><td colspan="2"></td><td>International</td><td colspan="2"></td></tr>
<tr><td colspan="6">Transparency of numerical calculations presented</td></tr>
<tr><td>Not applicable</td><td>X</td><td colspan="4"></td></tr>
</table>

no				
yes				
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed				
no				
yes	X	form of expression		
Editorial format of the opinion				
title of main chapters		Title of Opinion	Executive Summary	Conclusions of the WS Atkins Reports, September 1998
		Opinion of the Scientific Committee for Toxicity, Ecotoxicity and the Environment	References	
paragraph conclusion(s)		no		
		yes		
Wording used for expression of risk				
key wording or expressions		none		
risk expression		qualitative		
		quantitative		
recommended value (unit)		no	X	
		yes		
request for further information/data		no	X	
		yes		
refusal / impossibility to answer		no	X	
		yes		

Committee: CSTEE 2
Opinion: on Risk of cancer caused by textiles and leather goods coloured with azo-dyes

<table>
<tr><td colspan="6">Terms of reference of the opionion. NOT TITLED. The CSTEE has been asked to comment on a) the assessment of the risk of cancer caused by textiles and leather goods coloured with azo dyes as described in the corresponding Report by the Laboratory of the Government Chemist (LGC) and b) the general quality of the above Report.</td></tr>
<tr><td rowspan="3">requested by EC</td><td rowspan="3">X</td><td>specific</td><td>X</td><td>adressing specific agents</td><td>X</td></tr>
<tr><td>detailed</td><td></td><td>- complex media</td><td></td></tr>
<tr><td>generic</td><td></td><td>- commercial, industrial process, procedures or sites</td><td></td></tr>
<tr><td colspan="3"></td><td>- guidelines for assessment or regulation</td><td></td></tr>
<tr><td rowspan="4">spontaneously by SC</td><td rowspan="4"></td><td colspan="2" rowspan="4"></td><td>adressing specific agents</td><td></td></tr>
<tr><td>- complex media</td><td></td></tr>
<tr><td>- commercial, industrial process, procedures or sites</td><td></td></tr>
<tr><td>- guidelines for assessment or regulation</td><td></td></tr>
<tr><td colspan="6">Source of information used</td></tr>
<tr><td>not specified</td><td></td><td colspan="4"></td></tr>
<tr><td rowspan="4">specified</td><td rowspan="4">X</td><td>public</td><td colspan="3"></td></tr>
<tr><td>grey or proprietary</td><td colspan="3">X</td></tr>
<tr><td>both</td><td colspan="3"></td></tr>
<tr><td>others</td><td colspan="3"></td></tr>
<tr><td colspan="6">Existing guidelines or regulations used as reference for the opinion</td></tr>
<tr><td>not specified</td><td></td><td></td><td colspan="3"></td></tr>
<tr><td>specified</td><td>X</td><td>European</td><td colspan="3">X</td></tr>
<tr><td colspan="2"></td><td>International</td><td colspan="3"></td></tr>
<tr><td colspan="6">Transparency of numerical calculations presented</td></tr>
<tr><td>Not applicable</td><td>X</td><td colspan="4"></td></tr>
<tr><td>no</td><td></td><td colspan="4"></td></tr>
<tr><td>yes</td><td></td><td colspan="4"></td></tr>
<tr><td colspan="6">Uncertainty in the assessment or risk evaluation specifically mentioned or discussed</td></tr>
<tr><td>no</td><td></td><td colspan="4"></td></tr>
<tr><td>yes</td><td>X</td><td>form of expression</td><td colspan="3"></td></tr>
<tr><td colspan="6">Editorial format of the opinion</td></tr>
</table>

title of main chapters	Opinion		Opinion	Justification of the Opinion
paragraph conclusion(s)	no X		in the Opinion	
	yes			
Wording used for expression of risk				
key wording or expressions	none			
risk expression	qualitative			
	quantitative			
recommended value (unit)	no	X		
	yes			
request for further information/data	no	X		
	yes			
refusal / impossibility to answer	no	X		
	yes			

Committee: CSTEE 3

Opinion: on the results of the Risk Assessment of : Alkanes, C10-13, chloro {SCCP} carried out in the framework of Council Regulation (EEC)793/93 on the evaluation and control of the risks of existing substances

Terms of reference of the opionion. TITLED INTRODUCTION The CSTEE has been asked to give its opinion on the risk assessment on short chain length chlorinated paraffins produced within the EU Programme for Existing Chemicals. Chlorinated paraffin products are based on polychlorinated alkanes and they are divided into three categories depending on the carbon chain length, short (C10-C13), medium (C14-C17) and long (C20-C30), and the reviewed document deals with the first of these categories. A working group within CSTEE was established and it has reviewed the Final draft (dated May 1998) of the risk assessment.

requested by EC	X	specific	X	adressing specific agents	X
		detailed		- complex media	
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	
				- complex media	
				- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	

Source of information used			
not specified			
specified	X	public	
		grey or proprietary	X
		both	
		others	

Existing guidelines or regulations used as reference for the opinion			
not specified			
specified	X	European	X (Thenical Guidance Document)
		International	

Transparency of numerical calculations presented		
Not applicable	X	
no		
yes		

Uncertainty in the assessment or risk evaluation specifically mentioned or discussed		
no		

yes	X	form of expression	'…many assumptions..large uncertainty…' '… risk assessment…is a dificult task…'

Editorial format of the opinion				
title of main chapters		Introduction	General substance information	General information on exposure
		Environmental exposure assessment	Environmental effects assessment	Environmental risk characterisation
		Human exposure assessment	Human health effects assessment	Human risk characterisation
		CSTEE conclusions		
paragraph conclusion(s)		no		
		yes	X	
Wording used for expression of risk				
key wording or expressions		'…poses no significant risk for consumers..'		
risk expression		qualitative		
		quantitative		
recommended value (unit)		no	X	
		yes		
request for further information/data		no	X (generation of additional information is essetial to increase the scientific..)	
		yes		
refusal / impossibility to answer		no	X	
		yes		

Committee: SCAHAW 1
Opinion: Strategy for Emergency Vaccination against Foot and Mouth Disease (FMD)

Terms of reference of the opionion. The Scientific Committee on Animal Health and Animal Welfare has been requested to:* establish the criteria leading to a decision to implement emergency vaccination against foot and mouth disease;* establish guidelines for a vaccination programme; * prepare guidelines for the movement of animals and animal products within and out of the vaccination zone(s).

requested by EC	X	specific		adressing specific agents	
		detailed		- complex media	
		generic	X	- commercial, industrial process, procedures or sites	X
				- guidelines for assessment or regulation	X
spontaneously by SC				adressing specific agents	

			- complex media	
			- commercial, industrial process, procedures or sites	
			- guidelines for assessment or regulation	
Source of information used				
not specified				
specified	X	public	X (reference list)	
		grey or proprietary		
		both		
		others		
Existing guidelines or regulations used as reference for the opinion				
not specified				
specified	X	European	X	
		International		
Transparency of numerical calculations presented				
Not applicable	X			
no				
yes				
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed				
no	X	not applicable		
yes		form of expression		
Editorial format of the opinion				
title of main chapters		1. Background	2. Terms of reference	3. Rationale for the possible use of emergency vaccination
		4. Vaccines and tests	5. Criteria and factors affecting the decision to implement emergency vaccination	6. Guidelines for the emergency vaccination programme
		7. Guidelines for the movement of animals and animal products within and out of an area which has been subjected to emergency vaccination.	8. Conclusion and recommendations	9. References
		10. Minority opinion professor, dr. Soren alexandersen	11. Acknowledgements	

paragraph conclusion(s)	no	
	yes X	
Wording used for expression of risk		
key wording or expressions	none	
risk expression	qualitative	
	quantitative	
recommended value (unit)	no	X
	yes	
request for further information/data	no	X
	yes	
refusal / impossibility to answer	no	X
	yes	

Committee: SCAHAW 2
Opinion: Welfare Aspects of the Production of Foie Gras in Ducks and Geese

<table>
<tr><td colspan="6">Terms of reference of the opionion. NOT TITLED The Scientific Committee on Animal Health and Animal Welfare is asked to report on the animal welfare aspects of the production of foie gras using ducks and geese.</td></tr>
<tr><td rowspan="3">requested by EC</td><td rowspan="3">X</td><td>specific</td><td></td><td>adressing specific agents</td><td></td></tr>
<tr><td>detailed</td><td>X</td><td>- complex media</td><td></td></tr>
<tr><td>generic</td><td></td><td>- commercial, industrial process, procedures or sites</td><td>X</td></tr>
<tr><td colspan="2"></td><td colspan="2"></td><td>- guidelines for assessment or regulation</td><td></td></tr>
<tr><td rowspan="4">spontaneously by SC</td><td rowspan="4"></td><td colspan="2" rowspan="4"></td><td>adressing specific agents</td><td></td></tr>
<tr><td>- complex media</td><td></td></tr>
<tr><td>- commercial, industrial process, procedures or sites</td><td></td></tr>
<tr><td>- guidelines for assessment or regulation</td><td></td></tr>
<tr><td colspan="6">Source of information used</td></tr>
<tr><td>not specified</td><td></td><td colspan="4"></td></tr>
<tr><td rowspan="4">specified</td><td rowspan="4">X</td><td>public</td><td colspan="3">X (reference list)</td></tr>
<tr><td>grey or proprietary</td><td colspan="3"></td></tr>
<tr><td>both</td><td colspan="3"></td></tr>
<tr><td>others</td><td colspan="3"></td></tr>
<tr><td colspan="6">Existing guidelines or regulations used as reference for the opinion</td></tr>
<tr><td>not specified</td><td></td><td colspan="3"></td></tr>
<tr><td>specified</td><td>X</td><td>European</td><td colspan="3">X</td></tr>
<tr><td colspan="2"></td><td>International</td><td colspan="3"></td></tr>
<tr><td colspan="6">Transparency of numerical calculations presented</td></tr>
<tr><td>Not applicable</td><td>X</td><td colspan="4"></td></tr>
<tr><td>no</td><td></td><td colspan="4"></td></tr>
<tr><td>yes</td><td></td><td colspan="4"></td></tr>
<tr><td colspan="6">Uncertainty in the assessment or risk evaluation specifically mentioned or discussed</td></tr>
<tr><td>no</td><td></td><td colspan="4"></td></tr>
<tr><td>yes</td><td>X</td><td>form of expression</td><td colspan="3"></td></tr>
<tr><td colspan="6">Editorial format of the opinion</td></tr>
<tr><td colspan="2">title of main chapters</td><td>Introduction</td><td colspan="2">7 subjects specific chapters</td><td>Summary, conclusion and recommendations</td></tr>
<tr><td colspan="2"></td><td>References</td><td colspan="2">Acknowledgements</td><td></td></tr>
</table>

paragraph conclusion(s)	no		
	yes X		
Wording used for expression of risk			
key wording or expressions			
risk expression	qualitative		'..mortality can be very high,..' '..is detrimental to the welfare of the birds…'
	quantitative		
recommended value (unit)	no	X	
	yes		
request for further information/data	no	X	
	yes		
refusal / impossibility to answer	no	X	
	yes		

Committee: SCAHAW 3
Opinion: The use of Mixtures of the Gases CO2, O2, and N2 for Stunning or Killing Poultry

Terms of reference of the opionion.TITLED REQUEST FOR OPINION The Scientific Committee on Animal Health and Animal Welfare is asked to report on the suitability, from an animal welfare point of view, of the use of mixtures of the gases carbon dioxide, oxygen, and nitrogen for the stunning and killing of poultry					
requested by EC	X	specific	X	adressing specific agents	X
		detailed		- complex media	
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	
				- complex media	
				- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
Source of information used					
not specified					
specified	X	public		X (reference list)	
		grey or proprietary			
		both			
		others			
Existing guidelines or regulations used as reference for the opinion					
not specified	X				
specified		European			
		International			
Transparency of numerical calculations presented					
Not applicable	X				
no					
yes					
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed					
no	X				
yes		form of expression			
Editorial format of the opinion					
title of main chapters		Background		Request for Opinion	Methods examined

	7 subjects specific chapters		Research Needs	Summary and Conclusions
paragraph conclusion(s)	no			
	yes X			
Wording used for expression of risk				
key wording or expressions	none			
risk expression	qualitative			
	quantitative			
recommended value (unit)	no	X		
	yes			
request for further information/data	no	X		
	yes			
refusal / impossibility to answer	no	X		
	yes			

Committee: SCAN 1
Opinion: report on the use of certain micro-organisms As additives in feedingstuffs

Terms of reference of the opionion. The Scientific Committee for Animal Nutrition is requested to give an opinion on the following questions: 1. Is the use of the micro-organisms shown in the annexed list 1 safe to corresponding animal species under the conditions proposed? 2. Can their use result in development of resistance in bacteria to prophylactic or therapeutic preparations or exert an effect on the persistence of bacteria in the digestive tract of corresponding animal? Is or can the micro-organism become resistant to antibiotics? 3. Do the products indicated in the annexed list contain or consist of genetically modified organisms within the meaning of Article 2-1 and 2-2 of Council Directive 90/220/EEC 2 ? If it is the case, was a specific environmental risk assessment carried out, similar to that laid down in the above-mentioned Directive, is the outcome satisfactory in view of the requirements of this Directive? 4. Do the toxicology studies allow to conclude that the proposed use does not present risks to the consumers, to the users ? 5. In the light of the answer to the above-mentioned questions, are the proposed conditions of use acceptable?					
requested by EC	X	specific		adressing specific agents	
		detailed	X	- complex media	X
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	
				- complex media	
				- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
Source of information used					
not specified					
specified	X	public			
		grey or proprietary		X	
		both			
		others			
Existing guidelines or regulations used as reference for the opinion					
not specified					
specified	X	European	X		
		International			
Transparency of numerical calculations presented					
Not applicable	X				
no					

yes					
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed					
no					
yes	X	form of expression		lack of information	
Editorial format of the opinion					
title of main chapters		Terms of reference		Background	Opinion of the committee
		Annex			
paragraph conclusion(s)		no X		under Opinion	
		yes			
Wording used for expression of risk					
key wording or expressions					
risk expression		qualitative		'.. will not raise any particular risk,..' '.. does not pose a hazard..'	
		quantitative			
recommended value (unit)		no	X		
		yes			
request for further information/data		no	X		
		yes			
refusal / impossibility to answer		no	X		
		yes			

Committee: SCAN 2
Opinion: Assessment by the Scientific Committee on Animal Nutrition (SCAN) of a micro-organisms product : Neoferm BS-10 ® 1

Terms of reference of the opionion. none					
requested by EC	?	specific	X	adressing specific agents	X
		detailed		- complex media	
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	
				- complex media	
				- commercial, industrial process, procedures or sites	

			- guidelines for assessment or regulation	
Source of information used				
not specified	X			
specified		public		
		grey or proprietary		
		both		
		others		
Existing guidelines or regulations used as reference for the opinion				
not specified	X			
specified		European		
		International		
Transparency of numerical calculations presented				
Not applicable	X			
no				
yes				
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed				
no	X			
yes		form of expression		
Editorial format of the opinion				
title of main chapters		Executive summary		
paragraph conclusion(s)		no X		
		yes		
Wording used for expression of risk				
key wording or expressions				
risk expression		qualitative	'..was considered by SCAN to be of particular concern.' '..a feed additive would be unsafe.'	
		quantitative		
recommended value (unit)		no	X	
		yes		
request for further information/data		no	X	
		yes		
refusal / impossibility to answer		no	X	
		yes		

Committee: SCAN 3
Opinion: on possible risks for the consumer, the animal and the users (operators) from the use of Carbadox and Olaquindox as Feed Additives

<table>
<tr><td colspan="6">Terms of reference of the opionion. The Scientific Committee for animal nutrition is requested to re-evaluate the authorisations of carbadox and olaquindox, and to answer the following question: In view of the information provided to the Commission is there a risk for the consumers, the animal and the users (operators) by the use of quinoxaline-N-dioxides carbadox and olaquindox?</td></tr>
<tr><td rowspan="3">requested by EC</td><td rowspan="3">X</td><td>specific</td><td>X</td><td>adressing specific agents</td><td>X</td></tr>
<tr><td>detailed</td><td></td><td>- complex media</td><td></td></tr>
<tr><td>generic</td><td></td><td>- commercial, industrial process, procedures or sites</td><td></td></tr>
<tr><td colspan="3"></td><td>- guidelines for assessment or regulation</td><td></td></tr>
<tr><td rowspan="4">spontaneously by SC</td><td rowspan="4"></td><td colspan="2" rowspan="4"></td><td>adressing specific agents</td><td></td></tr>
<tr><td>- complex media</td><td></td></tr>
<tr><td>- commercial, industrial process, procedures or sites</td><td></td></tr>
<tr><td>- guidelines for assessment or regulation</td><td></td></tr>
<tr><td colspan="6">Source of information used</td></tr>
<tr><td>not specified</td><td></td><td colspan="3"></td></tr>
<tr><td rowspan="4">specified</td><td rowspan="4">X</td><td>public</td><td colspan="2"></td></tr>
<tr><td>grey or proprietary</td><td colspan="2"></td></tr>
<tr><td>both</td><td colspan="2">X (reference list)</td></tr>
<tr><td>others</td><td colspan="2"></td></tr>
<tr><td colspan="6">Existing guidelines or regulations used as reference for the opinion</td></tr>
<tr><td>not specified</td><td></td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td>specified</td><td>X</td><td colspan="2">European</td><td colspan="2">X</td></tr>
<tr><td colspan="2"></td><td colspan="2">International</td><td colspan="2"></td></tr>
<tr><td colspan="6">Transparency of numerical calculations presented</td></tr>
<tr><td>Not applicable</td><td>X</td><td colspan="4"></td></tr>
<tr><td>no</td><td></td><td colspan="4"></td></tr>
<tr><td>yes</td><td></td><td colspan="4"></td></tr>
<tr><td colspan="6">Uncertainty in the assessment or risk evaluation specifically mentioned or discussed</td></tr>
<tr><td>no</td><td></td><td colspan="4"></td></tr>
<tr><td>yes</td><td>X</td><td colspan="2">form of expression</td><td colspan="2">detailed comments to studies</td></tr>
<tr><td colspan="6">Editorial format of the opinion</td></tr>
</table>

title of main chapters	Terms of reference		Background	Opinion of the committee
	References			
paragraph conclusion(s)	no X		in the Opinion of the committee (6. conclusions)	
	yes			
Wording used for expression of risk				
key wording or expressions				
risk expression	qualitative		'..should provide for the consumer freedom from concern..' '..not be harmful to the consumer.'	
	quantitative			
recommended value (unit)	no	X		
	yes			
request for further information/data	no	X		
	yes			
refusal / impossibility to answer	no	X		
	yes			

Committee: SCCNFP 1
Opinion: concerning Ketoconazole adopted by the Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers during the plenary of 23 June 1999

Terms of reference of the opionion. The adaptation to technical progress of the Annexes to Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products. Technical adaptation to Annex III of Directive 76/768/EEC, List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down.					
requested by EC	X	specific	X	adressing specific agents	X
		detailed		- complex media	
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	
				- complex media	
				- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
Source of information used					
not specified					
specified	X	public			
		grey or proprietary			
		both			
		others X		result from a range of (not specified) tests	
Existing guidelines or regulations used as reference for the opinion					
not specified					
specified	X	European		X	
		International			
Transparency of numerical calculations presented					
Not applicable	X				
no					
yes					
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed					
no	X				
yes		form of expression			

Editorial format of the opinion				
title of main chapters	1. General data		2. Terms of reference	3. Safety Assessment & Classification
	4. Opinion		5. Statement on the toxicological evaluation	
paragraph conclusion(s)	no X		(the conclusion is in the chapter Opinion)	
	yes			
Wording used for expression of risk				
key wording or expressions	'… can be used safely..'			
risk expression	qualitative		'… can be used safely..'	
	quantitative			
recommended value (unit)	no	X		
	yes			
request for further information/data	no	X		
	yes			
refusal / impossibility to answer	no	X		
	yes			

Committee: SCCNFP 2
Opinion: concerning 2-Methyl-5-hydroxyethylaminophenol (Colipa n° A31) - adopted by the Scientific Committee on Cosmetic Products and Non-food Products intended for Consumers during the plenary of 23 June 1999

Terms of reference of the opionion. 2.1 Context of the question: The adaptation to technical progress of the Annexes to Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products. 2.2 Request to the SCCNFP: The SCCNFP is requested to answer the following questions :* Is 1-Methyl-2-hydroxy-4(b -hydroxyethyl)amino-benzene safe for use in cosmetic products? * Does the SCCNFP propose any restrictions or conditions for its use in cosmetic products?					
requested by EC	X	specific	X	adressing specific agents	X
		detailed		- complex media	
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	
				- complex media	

			- commercial, industrial process, procedures or sites	
			- guidelines for assessment or regulation	
Source of information used				
not specified				
specified	X	public		
		grey or proprietary		
		both		
		others X	result from a range of (not specified) tests	
Existing guidelines or regulations used as reference for the opinion				
not specified				
specified	X	European	X	
		International		
Transparency of numerical calculations presented				
Not applicable	X			
no				
yes				
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed				
no	X			
yes		form of expression		
Editorial format of the opinion				
title of main chapters		6. General data	7. Terms of reference	8. Safety Assessment & Classification
		9. Opinion	10. Statement on the toxicological evaluation	
paragraph conclusion(s)		no X	(the conclusion is in the chapter Opinion)	
		yes		
Wording used for expression of risk				
key wording or expressions		'… can be used safely..'		
risk expression		qualitative	'… can be used safely..'	
		quantitative		
recommended value (unit)		no	X	
		yes		
request for further information/data		no	X	
		yes		
refusal / impossibility to answer		no	X	
		yes		

Committee: SCCNFP 3
Opinion: on in vitro methods to assess percutaneous absorption of cosmetic ingredients adopted by the plenary session of the SCCNFP of 20 January 1999

Terms of reference of the opionion. No					
requested by EC		specific		adressing specific agents	
		detailed		- complex media	
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC	X			adressing specific agents	
				- complex media	X
				- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
Source of information used					
not specified					
specified	X	public			
		grey or proprietary		X	
		both			
		others			
Existing guidelines or regulations used as reference for the opinion					
not specified					
specified	X	European		X	
		International			
Transparency of numerical calculations presented					
Not applicable	X				
no					
yes					
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed					
no	X				
yes		form of expression			
Editorial format of the opinion					

title of main chapters	1. Background	2. Position of the Scientific Committee on Cosmetics (SCC)/Scientific Committee on Cosmetic and Non-Food products (SCCNFP)	3. Submission of COLIPA data on in vitro/in vivo dermal absorption/percutaneous penetration (SCCNFP/0073/98)
	4. Opinion of the SCCNFP		
paragraph conclusion(s)	no X	(in the chapter Opinion..)	
	yes		

Wording used for expression of risk		
key wording or expressions	none	
risk expression	qualitative	
	quantitative	
recommended value (unit)	no	X
	yes	
request for further information/data	no	X
	yes	
refusal / impossibility to answer	no	
	yes	X (data not sufficient to formulate a scientific opinion on how…)

Committee: SCCNFP 4
Opinion: concerning 2,6-Dimethoxy-3,5-Pyridinediamine HCL (Colipa n° A101)

Terms of reference of the opionion. The SCCNFP is requested to answer the following questions : * Is 3,5-Diamino-2,6-dimethoxy-pyridine, dihydrochloride safe for use in cosmetic products? * Does the SCCNFP propose any restrictions or conditions for its use in cosmetic products?

requested by EC	X	specific	X	adressing specific agents	X
		detailed		- complex media	
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	
				- complex media	

			- commercial, industrial process, procedures or sites	
			- guidelines for assessment or regulation	
Source of information used				
not specified	X			
specified		public		
		grey or proprietary		
		both		
		others		
Existing guidelines or regulations used as reference for the opinion				
not specified				
specified	X	European X		
		International		
Transparency of numerical calculations presented				
Not applicable	X			
no				
yes				
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed				
no	X			
yes		form of expression		
Editorial format of the opinion				
title of main chapters		1. General data	2. Terms of reference	3. Safety assessment & classification
		4. Opinion	5. Statement on the toxicological evaluation	
paragraph conclusion(s)		no		
		yes X	under Opinion	
Wording used for expression of risk				
key wording or expressions		'.. can be used safely in ..'		
risk expression		qualitative		
		quantitative	' at a max concentration of 5%'	
recommended value (unit)		no		
		yes	X (%)	
request for further information/data		no	X	
		yes		
refusal / impossibility to answer		no	X	
		yes		

Committee: SCCNFP op 5
Opinion: concerning the interim position on fragrance allergy

Not an opinion

Terms of reference of the opionion. Does the SCCNFP agree to the inclusion of all IFRA restricted materials into Annex III (List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down)? Are the permitted usage levels recommended by IFRA suitable for use in the Cosmetics Directive 76/768/EEC? * Does the SCCNFP agree that all materials that IFRA recommend should not be used as fragrance compounds are included in Annex II (List of substances which must not form part of the composition of cosmetic products)? * It is proposed that all known fragrance allergens are labelled on cosmetics if used in the product. Does the SCCNFP agree to this proposal? If so ….					
requested by EC Member state, parliament	X	specific		adressing specific agents	
		detailed		- complex media	X
		generic	X	- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	
				- complex media	
				- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
Source of information used					
not specified					
specified		public			
		grey or proprietary			
		both			
		others			
Existing guidelines or regulations used as reference for the opinion					
not specified					
specified		European			
		International			
Transparency of numerical calculations presented					
Not applicable					
no					
yes					
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed					
no					

yes		form of expression			
Editorial format of the opinion					
title of main chapters					
paragraph conclusion(s)		no			
		yes			
Wording used for expression of risk					
key wording or expressions					
risk expression		qualitative			
		quantitative			
recommended value (unit)		no			
		yes			
request for further information/data		no			
		yes			
refusal / impossibility to answer		no			
		yes			

Committee: SCCNFP op 6
Opinion: concerning 1-amino-3-methyl-4-(2-hydroxyethyl)-amino-6-nitrobenzene

Terms of reference of the opionion. ?					
requested by EC	?	specific		adressing specific agents	
		detailed		- complex media	
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	
				- complex media	
				- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
Source of information used					
not specified	X				
specified		public			

		grey or proprietary	
		both	
		others	
Existing guidelines or regulations used as reference for the opinion			
not specified	X		
specified		European	
		International	
Transparency of numerical calculations presented			
Not applicable	X		
no			
yes			
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed			
no	X		
yes		form of expression	

Editorial format of the opinion			
title of main chapters	Summary sheet on Commission Review	Classification	Statement on the toxicological evaluation
paragraph conclusion(s)	no X		
	yes		
Wording used for expression of risk			
key wording or expressions			
risk expression	qualitative	'oral toxicity low.' 'no signs of maternal toxicity' '..leading to an appropriate "safety margin"' etc	
	quantitative		

recommended value (unit)	no	
	yes	X (classification group)
request for further information/data	no	X
	yes	
refusal / impossibility to answer	no	X
	yes	

Committee: SCF 1
Opinion: on imazalil for incorporation in cheese coatings

<table>
<tr><td colspan="6">Terms of reference of the opionion. To give an opinion on the safety in use of imazalil as a food additive for use in coatings for hard and semi-hard cheeses.</td></tr>
<tr><td rowspan="3">requested by EC</td><td rowspan="3">X</td><td>specific</td><td>X</td><td>adressing specific agents</td><td>X</td></tr>
<tr><td>detailed</td><td></td><td>- complex media</td><td></td></tr>
<tr><td>generic</td><td></td><td>- commercial, industrial process, procedures or sites</td><td></td></tr>
<tr><td colspan="3"></td><td>- guidelines for assessment or regulation</td><td></td></tr>
<tr><td rowspan="4">spontaneously by SC</td><td rowspan="4"></td><td colspan="2" rowspan="4"></td><td>adressing specific agents</td><td></td></tr>
<tr><td>- complex media</td><td></td></tr>
<tr><td>- commercial, industrial process, procedures or sites</td><td></td></tr>
<tr><td>- guidelines for assessment or regulation</td><td></td></tr>
<tr><td colspan="6">Source of information used</td></tr>
<tr><td>not specified</td><td></td><td colspan="3"></td></tr>
<tr><td rowspan="4">specified</td><td rowspan="4"></td><td>public</td><td colspan="2"></td></tr>
<tr><td>grey or proprietary</td><td colspan="2"></td></tr>
<tr><td>both</td><td colspan="2"></td></tr>
<tr><td>others</td><td colspan="2"></td></tr>
<tr><td colspan="6">Existing guidelines or regulations used as reference for the opinion</td></tr>
<tr><td>not specified</td><td></td><td></td><td colspan="2"></td></tr>
<tr><td>specified</td><td>X</td><td>European</td><td colspan="2">X</td></tr>
<tr><td colspan="2"></td><td>International</td><td colspan="2"></td></tr>
<tr><td colspan="6">Transparency of numerical calculations presented</td></tr>
<tr><td>Not applicable</td><td></td><td colspan="4"></td></tr>
<tr><td>no</td><td></td><td colspan="4"></td></tr>
<tr><td>yes</td><td></td><td colspan="4"></td></tr>
<tr><td colspan="6">Uncertainty in the assessment or risk evaluation specifically mentioned or discussed</td></tr>
<tr><td>no</td><td></td><td colspan="4"></td></tr>
<tr><td>yes</td><td></td><td>form of expression</td><td colspan="3"></td></tr>
<tr><td colspan="6">Editorial format of the opinion</td></tr>
<tr><td colspan="2">title of main chapters</td><td colspan="2"></td><td></td><td></td></tr>
<tr><td colspan="2"></td><td colspan="2"></td><td></td><td></td></tr>
<tr><td colspan="2"></td><td colspan="2"></td><td></td><td></td></tr>
</table>

paragraph conclusion(s)	no	
	yes	
Wording used for expression of risk		
key wording or expressions		
risk expression	qualitative	
	quantitative	
recommended value (unit)	no	
	yes	
request for further information/data	no	
	yes	
refusal / impossibility to answer	no	
	yes	

Committee: SCF op 2
Opinion: on an additional list of monomers and additives for food contact materials

Not applicable for this opinion

Terms of reference of the opionion.					
requested by EC		specific		adressing specific agents	
		detailed		- complex media	
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	
				- complex media	
				- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
Source of information used					
not specified					
specified		public			
		grey or proprietary			
		both			
		others			
Existing guidelines or regulations used as reference for the opinion					
not specified					
specified		European			
		International			
Transparency of numerical calculations presented					
Not applicable					
no					
yes					
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed					
no					
yes		form of expression			
Editorial format of the opinion					
title of main chapters					

paragraph conclusion(s)	no	
	yes	
Wording used for expression of risk		
key wording or expressions		
risk expression	qualitative	
	quantitative	
recommended value (unit)	no	
	yes	
request for further information/data	no	
	yes	
refusal / impossibility to answer	no	
	yes	

Committee: SCF op 3
Opinion: on the scientific background of the spanish notification on a regulation on broths, consommés, soups and creams

Terms of reference of the opionion. To assess whether the informations provided by the notification of the Spanish Decree on soups and broths form a scientific basis for risk assessment of the organisms enlisted and to consider the risk to consumer's health from the soups and broths covered by the document.					
requested by EC	X	specific		adressing specific agents	
		detailed	X	- complex media	X
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	
				- complex media	
				- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
Source of information used					
not specified					
specified	X	public			
		grey or proprietary			
		both		X	
		others			
Existing guidelines or regulations used as reference for the opinion					
not specified					
specified	X	European X			
		International			
Transparency of numerical calculations presented					
Not applicable	X				
no					
yes					
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed					
no	X				
yes		form of expression			
Editorial format of the opinion					

title of main chapters	Terms of reference		Background	An evaluation of the information provided
	Conclusion		References	
paragraph conclusion(s)	no			
	yes X			
Wording used for expression of risk				
key wording or expressions	'..that it is unlikely, that the introduction of ..will change the effects of mishandling food.'			
risk expression	qualitative		'..the risk of food borne disease …have not been shown to be any greater than..'	
	quantitative			
recommended value (unit)	no	X		
	yes			
request for further information/data	no	X		
	yes			
refusal / impossibility to answer	no	X		
	yes			

Committee: SCF op 4
Opinion: on Bisphenol A diglycidyl ether (BADGE)

<table>
<tr><td colspan="6">Terms of reference of the opionion. To re-evaluate Bisphenol A diglycidylether (BADGE) in the light of new toxicological and analytical information and of previous opinions.</td></tr>
<tr><td rowspan="3">requested by EC</td><td rowspan="3">X</td><td>specific</td><td></td><td>adressing specific agents</td><td>X</td></tr>
<tr><td>detailed</td><td>X</td><td>- complex media</td><td></td></tr>
<tr><td>generic</td><td></td><td>- commercial, industrial process, procedures or sites</td><td></td></tr>
<tr><td colspan="2"></td><td colspan="2"></td><td>- guidelines for assessment or regulation</td><td></td></tr>
<tr><td rowspan="4">spontaneously by SC</td><td rowspan="4"></td><td colspan="2" rowspan="4"></td><td>adressing specific agents</td><td></td></tr>
<tr><td>- complex media</td><td></td></tr>
<tr><td>- commercial, industrial process, procedures or sites</td><td></td></tr>
<tr><td>- guidelines for assessment or regulation</td><td></td></tr>
<tr><td colspan="6">Source of information used</td></tr>
<tr><td>not specified</td><td></td><td colspan="4"></td></tr>
<tr><td rowspan="4">specified</td><td rowspan="4">X</td><td>public</td><td colspan="3"></td></tr>
<tr><td>grey or proprietary</td><td colspan="3"></td></tr>
<tr><td>both</td><td colspan="3">X</td></tr>
<tr><td>others</td><td colspan="3"></td></tr>
<tr><td colspan="6">Existing guidelines or regulations used as reference for the opinion</td></tr>
<tr><td>not specified</td><td>X</td><td colspan="3"></td></tr>
<tr><td>specified</td><td></td><td>European</td><td colspan="3"></td></tr>
<tr><td colspan="2"></td><td>International</td><td colspan="3"></td></tr>
<tr><td colspan="6">Transparency of numerical calculations presented</td></tr>
<tr><td>Not applicable</td><td>X</td><td colspan="4"></td></tr>
<tr><td>no</td><td></td><td colspan="4"></td></tr>
<tr><td>yes</td><td></td><td colspan="4"></td></tr>
<tr><td colspan="6">Uncertainty in the assessment or risk evaluation specifically mentioned or discussed</td></tr>
<tr><td>no</td><td></td><td colspan="4"></td></tr>
<tr><td>yes</td><td>X</td><td>form of expression</td><td colspan="3">Pending clarification of any potential…Committee is still unable to set and ADI..'</td></tr>
<tr><td colspan="6">Editorial format of the opinion</td></tr>
<tr><td>title of main chapters</td><td colspan="2">Terms of reference</td><td>Background</td><td colspan="2">Discussion</td></tr>
<tr><td colspan="2"></td><td>Conclusion</td><td>References</td><td colspan="2">Annex</td></tr>
</table>

paragraph conclusion(s)	no		
	yes X		
Wording used for expression of risk			
key wording or expressions			
risk expression	qualitative		'..the Committee reiterates its concern over their presence in canned food.?
	quantitative		
recommended value (unit)	no		
	yes	X	
request for further information/data	no		
	yes	X	
refusal / impossibility to answer	no	X	
	yes	(X)	

Committee: SCF op 5
Opinion: on coumarin

Terms of reference of the opionion. To re-evaluate Bisphenol A diglycidylether (BADGE) in the light of new toxicological and analytical information and of previous opinions.					
requested by EC		specific		adressing specific agents	
		detailed		- complex media	
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC	X	not spontaneously		adressing specific agents	X
				- complex media	
				- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
Source of information used					
not specified					
specified	X	public			
		grey or proprietary			
		both		X	
		others			
Existing guidelines or regulations used as reference for the opinion					
not specified	X				
specified		European			
		International			
Transparency of numerical calculations presented					
Not applicable	X				
no					
yes					
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed					
no					
yes	X	form of expression		lack of information	
Editorial format of the opinion					
title of main chapters		Terms of reference		Background	Evaluation of additional…
		Conclusions		References	

paragraph conclusion(s)	no		
	yes X		
Wording used for expression of risk			
key wording or expressions			
risk expression	qualitative		'..did not ensure the Committee that..is so minor that no further concern..' '..suggest that hepatotoxicity may occur in humans..' '..reaffirm concerns that a toxic epoxide may be produced..'
	quantitative		
recommended value (unit)	no	X	
	yes		
request for further information/data	no		
	yes	X	
refusal / impossibility to answer	no		
	yes	X not all aspects could be answered	

Committee: SCF op 6
Opinion: on Zinc Acetate as a flavour enhancer in chewing gum

Terms of reference of the opionion. To advise the Commission on the safety in use of zinc acetate as a food additive (flavour enhancer) in chewing gum.					
requested by EC	X	specific	X	adressing specific agents	X
		detailed		- complex media	
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	
				- complex media	
				- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
Source of information used					
not specified					
specified	X	public			
		grey or proprietary			
		both		X	
		others			
Existing guidelines or regulations used as reference for the opinion					
not specified	X				
specified		European			
		International			
Transparency of numerical calculations presented					
Not applicable					
no					
yes	X				
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed					
no	X				
yes		form of expression			
Editorial format of the opinion					
title of main chapters		Terms of reference		Background	Evaluation
		Conclusion		References	

paragraph conclusion(s)	no	
	yes X	
Wording used for expression of risk		
key wording or expressions	'.. is acceptable because of the non-toxicity…'	
risk expression	qualitative	
	quantitative	
recommended value (unit)	no	
	yes	X
request for further information/data	no	X
	yes	
refusal / impossibility to answer	no	X
	yes	

Committee: SCMPMD 1

Opinion: on the Effects of Xylitol and Other Polyols on Caries Development adopted by the Scientific Committee on Medicinal Products and Medical Devices on 2 June 1999

<table>
<tr><td colspan="6">Terms of reference of the opionion. DG XXI requested from SCMPMD an opinion on xylitol and polyols with respect to the possibility of beneficial effects on the development of dental caries. In particular the Committee was asked if it agrees with the conclusions of the report "Assessment of the beneficial effects of xylitol and other polyols on caries development" as prepared by a group of independent scientists on behalf of the Commissions Services, and specifically with the opinion that, as today, no clear data exists to support the concept that xylitol possesses specific effects in vivo which validate a superiority claim over other polyols.</td></tr>
<tr><td rowspan="3">requested by EC</td><td rowspan="3">X</td><td>specific</td><td>X</td><td>adressing specific agents</td><td>X</td></tr>
<tr><td>detailed</td><td></td><td>- complex media</td><td></td></tr>
<tr><td>generic</td><td></td><td>- commercial, industrial process, procedures or sites</td><td></td></tr>
<tr><td colspan="2"></td><td colspan="2"></td><td>- guidelines for assessment or regulation</td><td></td></tr>
<tr><td rowspan="4">spontaneously by SC</td><td rowspan="4"></td><td colspan="2" rowspan="4"></td><td>adressing specific agents</td><td></td></tr>
<tr><td>- complex media</td><td></td></tr>
<tr><td>- commercial, industrial process, procedures or sites</td><td></td></tr>
<tr><td>- guidelines for assessment or regulation</td><td></td></tr>
<tr><td colspan="6">Source of information used</td></tr>
<tr><td>not specified</td><td></td><td colspan="4"></td></tr>
<tr><td rowspan="4">specified</td><td rowspan="4">X</td><td colspan="2">public</td><td colspan="2"></td></tr>
<tr><td colspan="2">grey or proprietary</td><td colspan="2"></td></tr>
<tr><td colspan="2">both</td><td colspan="2">X (reference list)</td></tr>
<tr><td colspan="2">others</td><td colspan="2"></td></tr>
<tr><td colspan="6">Existing guidelines or regulations used as reference for the opinion</td></tr>
<tr><td>not specified</td><td></td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td>specified</td><td></td><td colspan="2">European</td><td colspan="2"></td></tr>
<tr><td colspan="2"></td><td colspan="2">International</td><td colspan="2"></td></tr>
<tr><td colspan="6">Transparency of numerical calculations presented</td></tr>
<tr><td>Not applicable</td><td>X</td><td colspan="4"></td></tr>
<tr><td>no</td><td></td><td colspan="4"></td></tr>
<tr><td>yes</td><td></td><td colspan="4"></td></tr>
<tr><td colspan="6">Uncertainty in the assessment or risk evaluation specifically mentioned or discussed</td></tr>
<tr><td>no</td><td>X</td><td colspan="4"></td></tr>
</table>

yes		form of expression		
Editorial format of the opinion				
title of main chapters		Question	Terms of Reference	Answer
paragraph conclusion(s)		no X	in Answer	
		yes		
Wording used for expression of risk				
key wording or expressions		none		
risk expression		qualitative		
		quantitative		
recommended value (unit)		no	X	
		yes		
request for further information/data		no	X	
		yes		
refusal / impossibility to answer		no	X	
		yes		

Committee: SCMPMD 2
Opinion: on Toxicological Data on Colouring Agents for Medicinal Products: Amaranth.

<table>
<tr><td colspan="6">Terms of reference of the opionion. The Committee has been asked to respond to the following question:Would use of the colourants listed in Annex IV ("colours permitted for certain uses only") of Directive 94/36 (in particular: E123 Amaranth, E127 Erythrosin, E161 Canthaxanthine, E173 Aluminium, E174 Silver and E175 (Gold) in medicinal products represent a consumer health/safety concern?</td></tr>
<tr><td rowspan="3">requested by EC</td><td rowspan="3">X</td><td>specific</td><td>X</td><td>adressing specific agents</td><td>X</td></tr>
<tr><td>detailed</td><td></td><td>- complex media</td><td></td></tr>
<tr><td>generic</td><td></td><td>- commercial, industrial process, procedures or sites</td><td></td></tr>
<tr><td colspan="3"></td><td>- guidelines for assessment or regulation</td><td></td></tr>
<tr><td rowspan="4">spontaneously by SC</td><td rowspan="4"></td><td colspan="2" rowspan="4"></td><td>adressing specific agents</td><td></td></tr>
<tr><td>- complex media</td><td></td></tr>
<tr><td>- commercial, industrial process, procedures or sites</td><td></td></tr>
<tr><td>- guidelines for assessment or regulation</td><td></td></tr>
<tr><td colspan="6">Source of information used</td></tr>
<tr><td>not specified</td><td></td><td colspan="3"></td></tr>
<tr><td rowspan="4">specified</td><td rowspan="4">X</td><td>public</td><td colspan="2">X (reference list)</td></tr>
<tr><td>grey or proprietary</td><td colspan="2"></td></tr>
<tr><td>both</td><td colspan="2"></td></tr>
<tr><td>others</td><td colspan="2"></td></tr>
<tr><td colspan="6">Existing guidelines or regulations used as reference for the opinion</td></tr>
<tr><td>not specified</td><td></td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td>specified</td><td>X</td><td>European</td><td colspan="2">X</td></tr>
<tr><td colspan="2"></td><td>International</td><td colspan="2"></td></tr>
<tr><td colspan="6">Transparency of numerical calculations presented</td></tr>
<tr><td>Not applicable</td><td></td><td colspan="4"></td></tr>
<tr><td>no</td><td></td><td colspan="4"></td></tr>
<tr><td>yes</td><td>X</td><td colspan="4"></td></tr>
<tr><td colspan="6">Uncertainty in the assessment or risk evaluation specifically mentioned or discussed</td></tr>
<tr><td>no</td><td>X</td><td colspan="4"></td></tr>
<tr><td>yes</td><td></td><td colspan="2">form of expression</td><td colspan="2"></td></tr>
<tr><td colspan="6">Editorial format of the opinion</td></tr>
</table>

title of main chapters	summary - not titled		Full opinion (with sub-chapters: terms of reference, context of question, assessment,….)	Opinion
	References			
paragraph conclusion(s)	no X		in Opinion	
	yes			
Wording used for expression of risk				
key wording or expressions				
risk expression	qualitative		'..the actual margin remains elevated..'	
	quantitative			
recommended value (unit)	no	X		
	yes			
request for further information/data	no	X		
	yes			
refusal / impossibility to answer	no	X		
	yes			

Committee: SCMPMD 3
Opinion: on guidelines on the concept of "similarity" regarding legislation on Orphan medicinal products

Terms of reference of the opionion. The Scientific Committee on Medicinal Products and Medical Devices has been asked to provide guidance on the "similarity" test for use in establishing marketing rights of producers of orphan medicinal products.					
requested by EC	X	specific		adressing specific agents	
		detailed	X	- complex media	
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	X
spontaneously by SC				adressing specific agents	
				- complex media	
				- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
Source of information used					
not specified					
specified	X	public		X (reference list)	
		grey or proprietary			
		both			
		others			
Existing guidelines or regulations used as reference for the opinion					
not specified					
specified	X	European		X (proposed legislation)	
		International			
Transparency of numerical calculations presented					
Not applicable	X				
no					
yes					
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed					
no	X				
yes		form of expression			
Editorial format of the opinion					
title of main chapters		Executive Summary		Full opinion	Assessment
		Opinion		References	

paragraph conclusion(s)	no X	in Opinion	
	yes		
Wording used for expression of risk			
key wording or expressions	none		
risk expression	qualitative		
	quantitative		
recommended value (unit)	no	X	
	yes		
request for further information/data	no	X	
	yes		
refusal / impossibility to answer	no	X	
	yes		

Committee: SCP 1

Opinion: Submission for placing on the market of glufosinate tolerant corns (*Zea mays*) transformation event T25 by the AgrEvo Company (Notification C/F/95/12/07)

Terms of reference of the opionion The Scientific Committee on Plants was asked to consider whether there is any reason to believe that the placing on the market of the T25 genetically modified maize with the purpose to be used as any other maize, is likely to cause any adverse effects on human health and the environment.					
requested by EC	X	specific	X	adressing specific agents	X
		detailed		- complex media	
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	
				- complex media	
				- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
Source of information used					
not specified	X	'existing information'			
specified	X	public			
		grey or proprietary	X		
		both			
		others			
Existing guidelines or regulations used as reference for the opinion					
not specified					
specified	X	European	X		
		International	X		
Transparency of numerical calculations presented					
Not applicable					
no	X				
yes					
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed					
no					
yes	X	form of expression	question about used methodology		
Editorial format of the opinion					
title of main chapters		1. Title		2. Terms of reference	3. Background
		4. Proposed uses		5. Description of project	6. Opinion of the committee

	7. Overall assessment		
paragraph conclusion(s)	no X	overall assessment	
	yes		
Wording used for expression of risk			
key wording or expressions			
risk expression	qualitative	no significant risk risk is considered to be remote, low, extremely low transfer of…is not considered to be a problem no evidence…is likely to cause adverse effects	
	quantitative		
recommended value (unit)	no X		
	yes		
request for further information/data	no X		
	yes		
refusal / impossibility to answer	no X		
	yes		

Committee: SCP 2

Opinion: inclusion of Spiroxamine in annex 1 to Directive 91/414/EEC concerning the placing of plant protection products on the market (SCP/SPIROX/004-Final)

Terms of reference of the opionion. The draft Commission Directive proposing the inclusion of spiroxamine in Annex 1 to Directive 91/414/EEC had been referred to the Scientific Committee on Plants for consultation with the following questions: 1. Does the data submitted allow an appropriate risk assessment for operators? 2. Having regard to the intrinsic aquatic ecotoxicological effects of spiroxamine and the proposed uses, the Committee is requested to evaluate the risk to the environment which could occur from its uses.					
requested by EC	X	specific	X	adressing specific agents	X
		detailed		- complex media	
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	
				- complex media	
				- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
Source of information used					
not specified					
specified		public			
		grey or proprietary		X	
		both			
		others		X: confidential from the Commission	
Existing guidelines or regulations used as reference for the opinion					
not specified					
specified	X	European		X	
		International			
Transparency of numerical calculations presented					
Not applicable					
no					
yes	X				
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed					
no					

yes	X	form of expression		the use of a non-specific value due to lack of specific one	
Editorial format of the opinion					
title of main chapters		Terms of reference		Background	Opinion of the committee
		Conclusion		Acknowledgements	
paragraph conclusion(s)		no			
		yes X			
Wording used for expression of risk					
key wording or expressions		may result in unacceptable risk to algae, sediment-dwelling organism, and possibly plants			
risk expression		qualitative		is highly toxic to algae potential risk may result in unacceptable risk	
		quantitative		'Toxicity-exposure ratio would be below 10'	
recommended value (unit)		no	X		
		yes			
request for further information/data		no	X		
		yes			
refusal / impossibility to answer		no	X		
		yes			

Committee: SCP 3
Opinion: the genetically modified cotton, tolerant to glyphosate herbicide notified by the Monsanto Company (notification C/ES/97/01)

Terms of reference of the opionion. The Scientific Committee on Plants (SCP The Working Group Plant GMOs comprises members from the following Scientific Committees: Plants, Animal Nutrition, Food, and Toxicity, Ecotoxicity and the Environment) is asked to consider whether there is any reason to believe that production and marketing of varieties of Roundup Ready® Cotton line RRC 1445 and any progeny derived from crosses between Cotton line RRC 1445 and other cotton varieties and import of commodity cotton grain that contains Roundup Ready Cotton® grain mixed with other genetically modified and non-modified cotton grain, is likely to cause any adverse effects on human health and on the environment.

requested by EC	X	specific	X	adressing specific agents	X
		detailed		- complex media	
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	

			- complex media	
			- commercial, industrial process, procedures or sites	
			- guidelines for assessment or regulation	
Source of information used				
not specified	X			
specified	X	public		
		grey or proprietary	X	
		both		
		others		
Existing guidelines or regulations used as reference for the opinion				
not specified				
specified	X	European	X	
		International		
Transparency of numerical calculations presented				
Not applicable				
no				
yes				
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed				
no	X			
yes		form of expression		
Editorial format of the opinion				
title of main chapters		1. Title	2. Terms of reference	3. Background
		4. Proposed use	5. Description of the product	6. Opinion of the committee
		7. Overall assessment and conclusion		
paragraph conclusion(s)		no		
		yes X		
Wording used for expression of risk				
key wording or expressions				
risk expression		qualitative	no evidence to indicate…is likely to cause adverse effects..	
		quantitative		
recommended value (unit)		no	X	
		yes		
request for further information/data		no	X	
		yes		
refusal / impossibility to answer		no	X	
		yes		

Committee: SCP op 4
Opinion: regarding the inclusion of Azimsulfuron in annex 1 to Directive 91/414/EEC concerning the placing of plant protection products on the market (SCP/AZIM/002-Final)

<table>
<tr><td colspan="6">Terms of reference of the opionion. 1. Are the male reproductive effects seen in the 2-generation rat study of relevance for health and the environment? 2. Having regard to the intrinsic aquatic ecotoxicological properties of azimsulfuron, the Committee is requested to evaluate the risk to the environment which could occur from its uses.</td></tr>
<tr><td rowspan="3">requested by EC</td><td rowspan="3">X</td><td>specific</td><td></td><td>adressing specific agents</td><td>X</td></tr>
<tr><td>detailed</td><td>X</td><td>- complex media</td><td></td></tr>
<tr><td>generic</td><td></td><td>- commercial, industrial process, procedures or sites</td><td></td></tr>
<tr><td colspan="2"></td><td colspan="2"></td><td>- guidelines for assessment or regulation</td><td></td></tr>
<tr><td rowspan="4">spontaneously by SC</td><td rowspan="4"></td><td colspan="2" rowspan="4"></td><td>adressing specific agents</td><td></td></tr>
<tr><td>- complex media</td><td></td></tr>
<tr><td>- commercial, industrial process, procedures or sites</td><td></td></tr>
<tr><td>- guidelines for assessment or regulation</td><td></td></tr>
<tr><td colspan="6">Source of information used</td></tr>
<tr><td>not specified</td><td></td><td colspan="4"></td></tr>
<tr><td rowspan="4">specified</td><td rowspan="4">X</td><td colspan="2">public</td><td colspan="2"></td></tr>
<tr><td colspan="2">grey or proprietary</td><td colspan="2"></td></tr>
<tr><td colspan="2">both</td><td colspan="2">X</td></tr>
<tr><td colspan="2">others</td><td colspan="2"></td></tr>
<tr><td colspan="6">Existing guidelines or regulations used as reference for the opinion</td></tr>
<tr><td>not specified</td><td>X</td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td>specified</td><td></td><td colspan="2">European</td><td colspan="2"></td></tr>
<tr><td colspan="2"></td><td colspan="2">International</td><td colspan="2"></td></tr>
<tr><td colspan="6">Transparency of numerical calculations presented</td></tr>
<tr><td>Not applicable</td><td>X</td><td colspan="4"></td></tr>
<tr><td>no</td><td></td><td colspan="4"></td></tr>
<tr><td>yes</td><td></td><td colspan="4"></td></tr>
<tr><td colspan="6">Uncertainty in the assessment or risk evaluation specifically mentioned or discussed</td></tr>
<tr><td>no</td><td></td><td colspan="4"></td></tr>
<tr><td>yes</td><td>X</td><td colspan="2">form of expression</td><td colspan="2">general discussion</td></tr>
<tr><td colspan="6">Editorial format of the opinion</td></tr>
</table>

title of main chapters	Terms of reference		Background	Opinion of the committee
	References			
paragraph conclusion(s)	no			
	yes X		In Opinion of the committee	
Wording used for expression of risk				
key wording or expressions	'..that there is a risk of phytotoxic effects..'			
risk expression	qualitative		'..that endocrine modulation is very unlikely to occur with azimsulfuron in the environment…'	
	quantitative			
recommended value (unit)	no	X		
	yes			
request for further information/data	no	X		
	yes			
refusal / impossibility to answer	no	X (but attention to the quality of information supplied to the committee was made)		
	yes			

Committee: SCP op 5
Opinion: on Plants on the Draft Guidance Document on Persistence in Soil (DG VI - 9188/VI/97-Rev.5 of 20.12.1998)

Terms of reference of the opionion. 1. Do the criteria for conducting field dissipation studies adequately reflect a 'realistic worst case' (chapter 3)? 2. What is the opinion of the SCP with regard to the use of the Arrhenius equation to extrapolate degradation over different temperatures (c.f. Special Aspects of Laboratory Studies)? 3. What is the opinion of the SCP with regard to the relevance of non-extractable residues (chapter 6)?					
requested by EC	X	specific		adressing specific agents	
		detailed	X	- complex media	X
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	
				- complex media	
				- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
Source of information used					
not specified					
specified	X	public			
		grey or proprietary			
		both		X	
		others			
Existing guidelines or regulations used as reference for the opinion					
not specified					
specified	X	European X			
		International			
Transparency of numerical calculations presented					
Not applicable					
no					
yes					
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed					
no					
yes		form of expression			
Editorial format of the opinion					

title of main chapters	1. Terms of reference	2. Background	3. General observations
	4. Determination of the soil accumulation potential	5. Plateau concentration versus..	6. Non-extractable residues
	Executive summar	1. Answers of the SCP to the specific questions	2. Observations and recommendations of the SCP to other issues
	6. Acknowledgements	7. References	
paragraph conclusion(s)	no		
	yes X	In Answers of the SCP..	
Wording used for expression of risk			
key wording or expressions	Not applicable		
risk expression	qualitative		
	quantitative		
recommended value (unit)	no	X	
	yes		
request for further information/data	no	X	
	yes		
refusal / impossibility to answer	no	X	
	yes		

Committee: SCP op 6

Opinion: on the Invocation by Austria of Article 16 ('safeguard' clause) of Council Directive 90/220/EEC with respect to the placing on the market of the Monsanto genetically modified maize (MON810) expressing the Bt cryia(b) gene, notification C/F/95/12-02

Terms of reference of the opionion. In background.

(a) Whether the information submitted by Austria constitutes relevant scientific information that was not taken into account by the SCP at the time its opinion was delivered? (b) Whether the information constitutes relevant scientific information that invalidates the original risk assessment for this product? (c) Whether this information constitutes relevant scientific information that invalidates the original risk assessments for the other Bt-products that have been approved or are pending approval following the SCP's appraisal? (d) Would this information cause the Committee to consider that these Bt-products constitute a risk to human health and the environment, including non-target organisms such as butterflies?

requested by EC	X	specific		adressing specific agents	X
		detailed	X	- complex media	X
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	
				- complex media	
				- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	

Source of information used			
not specified			
specified	X	public	
		grey or proprietary	
		both	X
		others	

Existing guidelines or regulations used as reference for the opinion			
not specified			
specified		European	
		International	

Transparency of numerical calculations presented		
Not applicable	X	
no		

yes					
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed					
no					
yes		form of expression			
Editorial format of the opinion					
title of main chapters		Background		Comment	Summary
paragraph conclusion(s)		no X		under Comments	
		yes			
Wording used for expression of risk					
key wording or expressions		Not applicable			
risk expression		qualitative			
		quantitative			
recommended value (unit)		no	X		
		yes			
request for further information/data		no	X		
		yes			
refusal / impossibility to answer		no	X		
		yes			

Committee: SCVPH 1

Opinion: The evaluation of microbiological criteria for food products of animal origin for human consumption

Terms of reference of the opionion. To provide a scientific opinion from the Scientific Committee on Veterinary Measures relating to Public Health on the evaluation of microbiological criteria for food products of animal origin for human consumption					
requested by EC	X	specific		adressing specific agents	
		detailed	X	- complex media	X
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	X
spontaneously by SC				adressing specific agents	
				- complex media	
				- commercial, industrial process, procedures or sites	

			- guidelines for assessment or regulation	
Source of information used				
not specified				
specified	X	public		
		grey or proprietary		
		both	X (reference list)	
		others		
Existing guidelines or regulations used as reference for the opinion				
not specified				
specified	X	European	X	
		International		
Transparency of numerical calculations presented				
Not applicable	X			
no				
yes				
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed				
no				
yes	X	form of expression		
Editorial format of the opinion				
title of main chapters		1. Terms of reference	2. Mandate	3. Definitions
		4. Introduction	5. Risk assessment, risk management and microbiological criteria	6. Components of microbiological criteria for foodstuffs
		7. Microorganisms to be considered	8. Sampling plans for microorganisms in foods	9. Laboratory methods
		10. Purpose of microbiological criteria	11. Limitations of using microbiological testing	12. The haccp approach
		13. European union legislation	14. Problems with the current eu microbiological criteria	15. Setting microbiological criteria based on decision trees and icmsf sampling plans
		16. Proposed revisions to the current eu microbiological criteria	17. Conclusions	18. Recommendations
		19. References		
paragraph conclusion(s)		no		
		yes X		

Wording used for expression of risk		
key wording or expressions	not applicable	
risk expression	qualitative	
	quantitative	
recommended value (unit)	no	X
	yes	
request for further information/data	no	X
	yes	
refusal / impossibility to answer	no	X
	yes	

Committee: SCVPH 2

Opinion: assessment of potential risks to human health from hormone residues in bovine meat and meat products

Terms of reference of the opionion. TITLED 'MANDATE' In the context of the WTO case on Hormones, the European Commission intends to evaluate the potential for adverse effects to human health from residues in bovine meat and meat products resulting from the use of the six hormones for growth promotion purposes in cattle and whether the currently available scientific information necessitates the revision of previous risk assessments. The Commission consequently requests the SCVPH to deliver an opinion on the potential for adverse effects to human health arising from the administration of the six hormones oestradiol-17b, progesterone, testosterone, zeranol, trenbolone acetate and melengestrol acetate used individually or in combinations for animal growth promotion.					
requested by EC	X	specific		adressing specific agents	X
		detailed		- complex media	
		generic	X	- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	
				- complex media	
				- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
Source of information used					
not specified					
specified	X	public		X (reference list)	
		grey or proprietary			
		both			
		others			
Existing guidelines or regulations used as reference for the opinion					
not specified					
specified	X	European		X	
		International		X	
Transparency of numerical calculations presented					
Not applicable	X				
no					
yes					
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed					
no					

yes	X	form of expression	'..has been considered inadequate to complete an assessment..'	
Editorial format of the opinion				
title of main chapters		1. Introduction	2. Emerging concerns related to hormonally active substances	3. General considerations relating to exposure assessment
		4. Characteristics of the individual compounds under consideration	5. Executive summary	6. Answers to the questions in the mandate
		7. Annex	8. References	9.
paragraph conclusion(s)		no X	in: Answers to the questions in the mandate	
		yes		
Wording used for expression of risk				
key wording or expressions				
risk expression		qualitative	'..a risk to the consumer has been identified..' '..products presents a potential risk to public health..'	
		quantitative		
recommended value (unit)		no	X	
		yes		
request for further information/data		no	X	
		yes		
refusal / impossibility to answer		no	X	
		yes		

Committee: SCVPH 3
Opinion: on cooling of carcasses during transport

Terms of reference of the opionion. Council Directive 64/433/EEC as amended by Directive 91/497/EC Chapter XV, Transport: Para 69. 3rd Indent (a) states - " by way of derogation from the 1st paragraph, carcasses, half carcasses, half carcasses cut into no more than three wholesale cuts, and quarters may be transported at temperatures higher than those laid down in Chapter XIV under conditions to be set after consultation of the Scientific Committee in accordance with the procedures laid down in Article 16 of this Directive".

The Committee was asked to evaluate whether, from a consumer health point of view, [hygienic equivalence] it is possible with the current available transport cooling equipment to cool during transport, carcasses, half carcasses, cuts into no more than three wholesale cuts, and quarters, as referred to in Directive 64/433/EEC, and if so under which conditions. The Committee is asked to assess the additional risk for consumer health introduced by cooling of carcasses during transport instead of the usual practiced stationary cooling.

requested by EC	X	specific		adressing specific agents	
		detailed	X	- complex media	
		generic		- commercial, industrial process, procedures or sites	X
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	
				- complex media	
				- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	

Source of information used			
not specified			
specified	X	public	X (reference list)
		grey or proprietary	
		both	
		others	

Existing guidelines or regulations used as reference for the opinion			
not specified			
specified	X	European	X
		International	

Transparency of numerical calculations presented		
Not applicable		
no	X	not all formula given

yes				
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed				
no				
yes	X	form of expression	lack of information	
Editorial format of the opinion				
title of main chapters		1. Terms of reference	2. Background	3. Introduction
		4. Refrigeration effects	5. Bacteriological parameters to take into account	6. Refrigeration in practice
		7. Bacteriological changes on carcasses during cooling	8. Calculation of bacterial mulitiplication rates	9. Conclusions
		10. Summary and recommendations	11. References	
paragraph conclusion(s)		no		
		yes X		
Wording used for expression of risk				
key wording or expressions		'..will introduce an additional risk..'		
risk expression		qualitative	'.. an additional risk..'	
		quantitative		
recommended value (unit)		no	X	
		yes		
request for further information/data		no	X	
		yes		
refusal / impossibility to answer		no	X	
		yes		

Committee: SSC op 1
Opinion: Scientific Opinion on the conditions related to "BSE Negligible risk (closed) bovine herds"

Terms of reference of the opionion. Under what conditions could it be considered that the concept of 'Closed herds' (where there are controlled and documented conditions of breeding and slaughter), offers the same guarantees as the so called 'BSE-free regions'? It is understood that these 'Closed herds' may not necessarily be themselves situated in 'BSE free regions'.					
requested by EC	X	specific	X	adressing specific agents	
		detailed		- complex media	
		generic		- commercial, industrial process, procedures or sites	X
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	
				- complex media	
				- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
Source of information used					
not specified					
specified	X	public		X	
		grey or proprietary			
		both			
		others			
Existing guidelines or regulations used as reference for the opinion					
not specified					
specified	X	European			
		International X		OIE	
Transparency of numerical calculations presented					
Not applicable	X				
no					
yes					
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed					
no					
yes	X	form of expression		Detalied discussion	
Editorial format of the opinion					
title of main chapters		1. Term of reference		2. Scope of question	3. Definitions

	4. Critical factor in …		5. Information neede for establishment…	6. Further conlusions
	7. Acknowledgements			
paragraph conclusion(s)	no			
	yes X			
Wording used for expression of risk				
key wording or expressions	'it may be classified as a negligible BSE-risk herd..' Detailed discussion of risk aspects			
risk expression	qualitative		'the risk of transmission of BSE via embryo transfer is low to negligible' '..constitute a risk..' '..are regarded to be safe .'	
	quantitative			
recommended value (unit)	no	X		
	yes			
request for further information/data	no	X		
	yes			
refusal / impossibility to answer	no	X		
	yes			

Committee: SSC op2
Opinion: Opinion on Monitoring Some Important aspects of the evolution of the Epidemic of BSE in Great-Britain

Terms of reference of the opionion. Named The questions:
1. How does the SSC assess the current and expected (1999-2004) evolution of the number of BSE cases-in the UK?
2. Is the current number of cases in line with the scientific expectations?
3. If not, what are the most probable explanations for the difference between the observed and the predicted values (e.g. routes of transmission, problems in the statistical models on which the predictions are based)?
4. What is the significance of the observed development of the epidemic in terms of consumer health protection?
5. In the light of the above, would an extension of the Selective Cull Scheme to currently not covered birth cohorts reduce the risk, and if yes to what extent, that BSE-infected animals enter the food chain?
6. In the light of the above, would the continuation of the OTM Scheme for animals falling under the Date-based Export Scheme reduce the risk, and if yes to which extent, that BSE-infected animals enter the food chain?

requested by EC	X	specific		adressing specific agents	
		detailed	X	- complex media	X (trend in BSE cases)
		generic		- commercial, industrial process, procedures or sites	

			- guidelines for assessment or regulation	
spontaneously by SC			adressing specific agents	
			- complex media	
			- commercial, industrial process, procedures or sites	
			- guidelines for assessment or regulation	
Source of information used				
not specified		A non-exhaustive list of consulted literature		
specified	X	public	X	
		grey or proprietary		
		both		
		others		
Existing guidelines or regulations used as reference for the opinion				
not specified	X			
specified		European		
		International		
Transparency of numerical calculations presented				
Not applicable				
no	X	advanced model calculations		
yes				
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed				
no				
yes	X	form of expression	uncertainties in ther models used	
Editorial format of the opinion				
title of main chapters		1. The questions	2. Evaluation	3. Opinion
		4. Acknowledgements	5. Non-exhaustive list of the consulted leterature and documents	Annex 1
paragraph conclusion(s)		no		
		yes X	Under Opinion	
Wording used for expression of risk				
key wording or expressions		NB		
risk expression		qualitative		
		quantitative		
recommended value (unit)		no		
		yes		

request for further information/data	no	X
	yes	
refusal / impossibility to answer	no	X (one point needed more reflection and was postponed to the next meeting)
	yes	X (one final conclusion could not be given because toxicological data required would not be available before August 2001)

Committee: SSC op3
Opinion: Opinion on the safety of organic fertilisers derived from mammalian animals

Terms of reference of the opionion. Named the question. "Can organic fertilisers derived from materials from mammalian animals, naturally or experimentally susceptible to Transmissible Spongiform Encephalopathies, be safely used? If so, under what conditions?"					
requested by EC	X	specific	X	adressing specific agents	X
		detailed		- complex media	
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	
				- complex media	
				- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
Source of information used					
not specified	X	Not exhaustive list of scientific and technical documents			
specified	X	public		X	
		grey or proprietary			
		both			
		others			
Existing guidelines or regulations used as reference for the opinion					
not specified					
specified	X	European X			
		International			
Transparency of numerical calculations presented					
Not applicable	X				
no					
yes					
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed					
no					
yes	X	form of expression		general discussion	
Editorial format of the opinion					
title of main chapters		1. The question		2. Definitions	3. Background

	4. Identification of possible hazards and elements of risk assessment	5. Not exhaustive list of scientific and technical documents used by the working group	6. Acknowledgements
paragraph conclusion(s)	no X		
	yes		
Wording used for expression of risk			
key wording or expressions	'not possible to assess the potential risk…'		
risk expression	qualitative	' as carrying a negligible BSE-risk'	
	quantitative		
recommended value (unit)	no	X	
	yes		
request for further information/data	no	X	
	yes		
refusal / impossibility to answer	no	X	
	yes		

Committee: SSC op4
Opinion: on the possible vertical transmission of Bovine spongiform encephalopathy (BSE)

Terms of reference of the opionion. Named the question.

"What is the nature and extent of the risks of vertical transmission (to include via semen, embryos or other ways of maternal transmission) of the BSE agent between cattle or between small ruminants of the same species, based on current data?"

requested by EC		specific		adressing specific agents	
		detailed		- complex media	
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC	X			adressing specific agents	
				- complex media	X
				- commercial, industrial process, procedures or sites	

			- guidelines for assessment or regulation	
Source of information used				
not specified	X	Opinion based on an existing report		
specified		public		
		grey or proprietary		
		both		
		others		
Existing guidelines or regulations used as reference for the opinion				
not specified	X			
specified		European		
		International		
Transparency of numerical calculations presented				
Not applicable	X			
no				
yes				
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed				
no				
yes	X	form of expression	i) lack of knowledge ii) inadequate data	
Editorial format of the opinion				
title of main chapters		The question	Definitions used in this opinion	Answer
		ANNEX		
paragraph conclusion(s)		no		
		yes		
Wording used for expression of risk				
key wording or expressions				
risk expression		qualitative	'..suggest an extremely low risk of transmission..' '..no enhanced risk of the development…' '..unlikely that semen constitutes a risk-factor for ..'	
		quantitative		
recommended value (unit)		no	X	
		yes		
request for further information/data		no	X	
		yes		
refusal / impossibility to answer		no	X	
		yes	X (some details could not be judged because of inadequate and conflicting data)	

Committee: SSC op 5
Opinion: on possible links between BSE and Organophosphates used as pesticides against ecto- and endoparasites in cattle

Terms of reference of the opionion. Named the question. The hypothesis that there is a link between the use of some organopohosphates, especially Phosmet, and the initiation of BSE by the formation of delayed neuro-excitatoric proteins as a consequence of the phosphorylation of the PrP in the foetuses of the treated cows to the toxic PrP^{Sc} protein					
requested by EC	X	specific		adressing specific agents	X
		detailed	X	- complex media	
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	
				- complex media	
				- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
Source of information used					
not specified					
specified	X	public		X	
		grey or proprietary			
		both			
		others			
Existing guidelines or regulations used as reference for the opinion					
not specified					
specified		European			
		International			
Transparency of numerical calculations presented					
Not applicable	X				
no					
yes					
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed					
no					
yes		form of expression			
Editorial format of the opinion					

title of main chapters	I. Framework and mandate		II. Scientific bacgground information…	III. Comments on the papers of Purdey
	IV. Opinion		V. Acknowledgements	VI. Literature
paragraph conclusion(s)	no			
	yes X		in opinion	
Wording used for expression of risk				
key wording or expressions	'..there is at present no scientific evidence of possible links between BSE...'			
risk expression	qualitative			
	quantitative			
recommended value (unit)	no	X		
	yes			
request for further information/data	no	X		
	yes			
refusal / impossibility to answer	no	X		
	yes			

Committee: SSC op6
Opinion: on possible health effects from exposure to electromagnetic fields (0 Hz- 300 GHz)

Terms of reference of the opionion. Named request. An opinion on non-thermal, long-term health effects of exposure to EMFs, in particular addressing epidemiological evidence and also biophysical and biological evidence on genetic and cancer-related effects, effects on the immune system and effects on the nervous system. The opinion should indicate whether any recommendations for exposure limits can be made, and B. an opinion on whether for thermal effects, the scientific advice of the International Commission on Non-Ionising Radiation Protection (ICNIRP) is the appropriate basis for a system of health protection against risks from non-ionising radiation.					
requested by EC	X	specific		adressing specific agents	X (e.mag. fields)
		detailed	X	- complex media	
		generic		- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
spontaneously by SC				adressing specific agents	
				- complex media	
				- commercial, industrial process, procedures or sites	
				- guidelines for assessment or regulation	
Source of information used					
not specified					
specified	X	public			
		grey or proprietary			
		both		X	
		others			
Existing guidelines or regulations used as reference for the opinion					
not specified	X				
specified		European			
		International			
Transparency of numerical calculations presented					
Not applicable	X				
no					
yes					
Uncertainty in the assessment or risk evaluation specifically mentioned or discussed					
no					

yes	X	form of expression	detailed discussion	
Editorial format of the opinion				
title of main chapters		Request	Definition, Sources of Exposure	Background
		Health effects	Ongoing studies	Proposed opinion
		List of abbreviations	Acknowledgements	List of relevant, recent scientific and technical material
paragraph conclusion(s)		no X	Specific conclusion given in sub-chapters	
		yes X	Main conclusion given in Proposed Opinion	
Wording used for expression of risk				
key wording or expressions		'..literature does not provide sufficient evidence to conclude that longterm effects occur..'		
risk expression		qualitative	'..insufficient evidence to suggest that …'	
		quantitative		
recommended value (unit)		no	X	
		yes		
request for further information/data		no	X	
		yes		
refusal / impossibility to answer		no	X	
		yes	X (some definite conclusion not done due to insufficient information).	

APPENDIX 7

LEGAL FRAMEWORKS FOR RISK ASSESSMENT ACTIVITIES RELATED TO NEW AND EXISTING CHEMICALS

Risk Assessment of new industrial chemicals.

Community legislation on new industrial chemicals grew out of discussions at the OECD in the 1970's. The result of these discussions was agreement that for new chemicals entering the market for the first time, a certain level of data should be required. This "minimum" level of data is often referred to as the "base-set". Provisions to require producers and importers of new chemicals were introduced in the 6th. Amendment[2] of Council Directive 67/548/EEC[3].

This introduced a number of new concepts.
Firstly, "new" chemicals were defined by exclusion: "new" chemicals are chemicals that were not already on the Community market. In order to make this definition operational, an inventory of substances on the European market in the period from 1. January 1971 to 18. September, 1981 was compiled[4]. This inventory consists of 100.106 entries. Roughly 80 additional entries, omitted in error from the original compilation, have later been added[5].
Secondly, the Directive introduced testing requirements for new chemicals, which are related to the tonnage of the substance placed on the European market. These are shown in Annexes VII and VIII of the Directive[6].
Thirdly, the Directive included detailed test methods to acquire the relevant data[7]. These test methods are based almost entirely on methods agreed as part of the OECD Test method programme. The use of test methods agreed by the OECD is part of an international agreement on the Mutual Acceptance of Data (MAD), intended to ensure widespread acceptance of test methods carried out world wide, in order to prevent unnecessary duplicate testing.

The additional tests required at higher production volumes reflects a form of testing strategy. In practice, there can be a need to modify both the choicer of tests and the timing of certain studies. In order to formalise these needs and to ensure a systematic evaluation of the risks associated with these substances, a formal requirement for risk assessment was introduced in the 7th. Amendment

[2] Council Directive 79/831/EEC. OJ L259 of 15. October, 1979, p.1.
[3] Council Directive 67/548/EEC. OJ 196 of 16. September 1967, p.1.
[4] Einecs: European Inventory of existing commercial chemical substances. OJ C146A, of 15. June, 1990. p.1.
[5] Notification of New Chemical Substances in accordance with Directive 67/548/EEC on the Classification, Packaging and Labelling of Dangerous Substances. March, 1997. EINECS Corrections (English). Luxembourg: Office for Official Publications of the European Communities. CR-04-97-985-EN-C.
[6] The tests required at different production volumes are shown in Annex VII and Annex VIII of Directive 67/548/EEC. Annex VII A-C is shown in the 7th Amendment of the Directive, Council Directive 92/32/EEC: OJ L154, 5. June 1992 and Annex VIID in Commission Directive 93/105/EEC; OJ L294, 30. November 1993. Annex VIII is shown in the 7th Amendment, Council Directive 92/32/EEC : OJ L154, 5. June 1992.
[7] Test methods are given in Annex V to Directive 67/548/EEC. These can be found in the following Adaptations to Technical Progress: 9th Adaptation, Commission Directive 88/302/EEC: OJ L133 of 30. May 1988, 17th Adaptation, Commission Directive 92/69/EEC: OJ L383A of 29. December 1992; 18th Adaptation, Commission Directive 93/21/EEC: OJ L110 of 4. May 1993; 22nd Adaptation, Commission Directive 96/54/EC: L248 of 30. September 1996; 24th Adaptation, Commission Directive 98/73/EC: OJ L305 of 16. November 1998; 26th Adaptation, Commission Directive 2000/32/EC: OJ L136 of 8. June 2000; 27th Adaptation, Commission Directive 2000/32/EC: OJ L136 of 8. June, 2000.

of the Directive[8]. This was followed by a Commission Directive "laying down the principles for assessment of risks to man and to the environment of substances notified in accordance with Council Directive 767/548/EEC"[9]. These principles include the recognition that among a number of possible conclusions, a risk assessment can lead to the conclusion that additional data is needed, either immediately or at the next tonnage level. The risk assessment can also recommend a number of measures for risk reduction. These include changes to the classification, labelling, the information given in the safety data sheet or indeed, formal restrictions on the marketing and use of the substance. Three new substances, Ugilec 141, Ugilec 121 (also known as Ugilec 21) and DBBT have been banned under Council Directive 76/769/EEC[10] in the 11th Adaptation of this Directive[11].

The practical aspects of carrying out a Risk Assessment are complicated, and are not suited to formal legislation. The Commission has therefore prepared a "Technical Guidance Document" which describes in detail the elements of the risk assessment process. Originally developed for new chemicals it is now extended to include guidance for the risk assessment of existing chemicals[12]. Work is going on to extend the scope of this Technical Guidance Document to include biocides. The Commission has sought the advice of the Scientific Committee on Toxicology, Ecotoxicology and the Environment on these developments.

New chemical substances are in many cases speciality chemicals with a fairly limited production volume and well defined use pattern. In order to limit the need for unnecessary risk assessment, this is required only in cases where the substance fulfils the criteria in Annex VI to Directive 67/548/EEC for classification as "dangerous". The Competent Authorities in the Member States carry out risk assessments of these new chemicals, which can be done on the basis of a first risk assessment prepared by the producer or importer.

The Commission has not yet asked a Scientific Committee to evaluate these risk assessments.

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[8] Council Directive 92/32/EEC, OJ L84 of 5. June, 1992. p.1.
[9] Commission Directive 93/67/EEC; OJ L227 of 8. September, 1993.
[10] Council Directive 76/769/EEC; OJ L262 of 27. September 1976, p. 201.
[11] Council Directive 91/339/EEC, OJ L186 of 12. July, 1991, p. 64.
[12] Technical Guidance Document in support of Commission Directive 93/67/EEC on Risk Assessment for New Notified Substances and Commission Regulation (EC) No. 1488/94 on Risk Assessment for Existing Substances. 1996. Luxembourg: Office for Official Publications of the European Communities. Part I: General Introduction and Risk Assessment for Human Health, CR-48-96-001-EN-C, ISBN 92-827-8011-2. Part II: Environmental Risk Assessment, CR-48-96-002-EN-C, ISBN 92-827-8012-0. Part III: Use of QSAR, Use Categories, Risk Assessment Format, CR-48-96-003-EN-C, ISBN 92-827-8013-9. Part IV: Emission Scenario Documents. CR-48-96-004-EN-C, ISBN 92-827-8014-7.
Corrigendum: Technical Guidance Document in support of Commission Directive 93/67/EEC on risk assessment for new notified substances and Commission Regulation (EC) 1488/94 on risk assessment for existing substances. 1997. Luxembourg, Office for Official Publications of the European Communities. Part II. EC Catalogue No. CR-48-96-002-EN-C.

Risk Assessment of existing industrial chemicals.

The agreement at the end of the 1970's to require at least base-set testing of chemicals put on the market for the first time led to renewed discussions on how to establish an adequate data base for the much larger number of "existing" chemicals. It was recognised that a number of measures were required in order to address this issue. Firstly, the data on the hazardous properties of existing substances already available should be systematically compiled. Secondly, this data should be used to develop a system to set priorities for substances where additional data is needed. Finally, risk assessments of these existing substances should be carried out with a view to drawing the same type of conclusions given above for new substances.

The discussions on a legal instrument to provide the necessary legislation were long drawn out, and reflected the complexity of the issues involved, and not least, the economic consequences of these requirements. After a period of consultation with Member State experts, the Commission put forward a proposal to the Council
in 1990[13], the Council Regulation (EEC) No. 793/93[14] on the evaluation and control of risks of existing substances was adopted nearly three years later. As for new substances, legal requirements for carrying out a risk assessment were adopted[15]

The Existing Substances Regulation included a requirement on Industry to submit data on all high volume chemicals in two phases. This data was sent to the Commission and included in the "IUCLID" database[16]. The availability of data in this database has recently been reviewed[17]. Much of the data is publicly available[18].

110 chemicals have been included in formal priority lists[19]. These lists have been based mainly on lists of substances prepared by the Member States of chemicals known as candidates for risk assessment. Whilst systematic priority setting tools have been developed[20] these have not yet been used as the basis of a priority list.

[13] OJ C276, of 5. November, 1990, p.1.
[14] Council Regulation (EEC) no. 793/93; OJ L84 of 5. April 1993.
[15] Commission Regulation (EC) No. 1488/94, OJ L 161 of 29. June, 1994
[16] Heidorn CJA, Hansen BG & Nørager O (1996). IUCLID: A databse on Chemical Substances Information as a tool for the EU Risk Assessment programme. J. Chem. Inf. Comput. Sci. 6, 949-954.
[17] Allanou et al., EUR 18996 EN. It can be found on the ECB website: http://ecb.ei.jrc.it/
[18] IUCLID CD-ROM. Year 2000 Edition. Public data on high volume chemicals. European Commission. Joint Research Center. IHCP, European Chemicals Bureau. EUR 19559 EN.
[19] The first priority list is published in Commission Regulation (EC) No. 1179/94, OJ L131 of 26. May, 1994, p. 3; the 2nd. list in Commission Regulation (EC) 2268/95, OJ L231 of 28. September, 1995, p. 18 and the third list in Commission Regulation (EC) 143/97, OJ L25 of 28 January, 1997, p.13. A fourth list has been adopted, but not yet published in the OJ (12.10.2000).
[20] van der Zandt P & van Leeuwen CJ (1992). A proposal for priority setting of Existing Chem,ical substances-. "EPS" report commissioned by EU/DG XI.

The preparation of the formal risk assessments of these 100 chemicals has taken considerable time. The need to develop techniques for the evaluation that are acceptable to all stakeholders is a lengthy process. This discussion has also included the Scientific Committee on Toxicology, Ecotoxicology and the Environment, and this Committee has commented on a number of the risk assessments. More recently, the Committtee has been invited to comment on drafts of the risk assessment reports. As a result, the Member State acting as Rapporteur for the substance can include the comments of the Committee together with comments from other Member States and other stakeholders.

At the present time, four risk assessments have been formally concluded, and a Commission Recommendation published[21]. The risk assessment reports for three of these substances have also been published[22]

The Technical Guidance document[11] gives advice on a wide variety of issues. Included in the guidance is a calculation program to evaluate the environmental distribution following emission of a chemical from a variety of processes (EUSES)[23]. This system is designed to estimate concentrations in relevant environmental compartments, as well as exposure routes that can lead to indirect exposure of man. The model is intended to provide an estimate of the concentrations. Should however this estimate prove unreliable, the Rapporteur can in cases of doubt require more measured data on which to base a more refined risk assesssment. The use of these techniques has been the subject of discussion in the Scientific Committee for Toxicology, Ecotoxicology and the Environment.

In additon, the Technical Guidance document provides recopmmendations for the risk characterisation of effects. For effects on humans, the approach evaluates the margin of safety, ("MOS") between normally the relevant No-adverse-effect-level and the exposure. The latter can be measured or predicted from an appropriate model such as EASE, contained in the EUSES program. In some cases, fixed minimal values for the MOS have been recommended, depending on the forms and type of erxtrapolations used. These include the inter- and intra-species differences discussed in Annex ???. The Scientific Committee has also expressed its opinions on this approach, and was represented at a workshop organised in the Netherlands to discuss interpretations of MOS values[24]. This discussion is still continuing in the Scientific Committee.

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[21] Commission Recommendation on the results of the risk evaluatiuon and on the risk reduction strategies for the substances 2-(2-butoxyethoxy)ethanol, 2-(2-methoxyethoxy)ethanol, Alkanes, C_{10-13}, chloro, Benzene, C_{10-13}-alkyl derivs. OJ L 292 of 13 November 1999, p. 42.

[22] European Union Risk Assessment report Volume 1. 2-(2-methoxyethoxy)ethanol, EUR 18998 EN. European Union Risk Assessment report Volume 2. 2-(2-butoxyethoxy)ethanol, EUR 18998 EN. European Union Risk Assessment report Volume 3. Benzene, C_{10-13}-alkyl derivs. EUR 19011 EN.

[23] EUSES: European Union System for the Evaluation of Substances. Joint Reseach Center, European Chemicals Bureau. EUR 17308 EN.

[24] Report of the Joint EU/RIVM/TNO Workshop on Interpreations of margins of Safety in Human Health Risk Assessment. 21 – 22 April 1999. RIVM, Bilthoven. The Netherlands.

The Hazard and risk assessment of chemicals in the EU has been reviewed at greater length by van Leeuwen & Hermans (1995)[25] and Hart et. al. in 1998[26].

[25] CJ van Leeuwen and JLM Hermens, Risk Assessment of Chemicals, An Introduction. Kluwer Academic Publishers Dordrecht, Boston, London. 1995.
[26] J.W.Hart, B.G.Hansen and W.Karcher. Hazard Assessment and Risk Assessment of Chemical Substances in the EU. In: Regulation for Chemical Safety in Europe: Analysis, Comment and Criticism. Eds: D. Michael Pugh, José V. Tarazona. Kluwer Academic Publishers. Dordrecht, Boston, London. 1998. p. 113-124.

APPENDIX 8

MANDATES OF THE SCIENTIFIC ADVISORY COMMITTEES

High quality scientific advice for the drafting and amendment of Community rules regarding Consumer protection in general and Consumer Health in particular is of utmost importance. This is also underlined in the recent April 1997 Commission Communication on Consumer health and food safety. CONSUMER HEALTH is here defined as including matters on consumer health in its strictest sense, animal health and welfare, plant health and environmental health.

Many issues relating to consumer health are of a multidisciplinary nature and require input from various scientific disciplines. Presently, the advice is provided by 6 different Scientific Committees: Food, Veterinary, Animal Nutrition, Cosmetology, Pesticides and Toxicity and Ecotoxicology. In addition, and in accordance with the above Communication, the European Commission decided on 10 June 1997, to create a Scientific Steering Committee (SSC) in the field of consumer health and food safety. The detailed mandate of this Committee is available on this site.

The scientific advice by these 7 Committees is made available without undue delay following a request by the Commission for a scientific advice or opinion on a new development that may cause concern for consumer health. The advice and opinions, in the interest of consumers and industry, are based on the principles of excellence, independence and transparency.

So far, the multi-disciplinary aspects of the recent Bovine Spongiform Encephalopathy (BSE) epidemic were addressed by a Multidisciplinary Scientific Committee (MDSC), established in 1996. The decision of 10 June 1997, end the existence of the MDSC and foresees that the scientific advice on multidisciplinary aspects of transmissible spongiform encephalopathies (including bovine spongiform encephalopathy) is from now onwards delivered by the SSC, with the support of a specific ad-hoc group.

Scientific Steering Committee

Commission Decision of 10 June 1997 setting up a Scientific Steering Committee (Commission Decision N° 97/404/EC of 10 June 1997; Official Journal L169 of 27.06.97)

The Commission of the European Communities,
Having regard to the Treaty establishing the European Community;
Whereas sound scientific advice is an essential basis for Community rules concerning consumer health, including matters onconsumer health in its strictest sense, but also on animal health and welfare, plant health and environmental health;
Whereas scientific advice on consumer health matters is currently provided by six scientific committees, set up by theCommission and addressing the topics of food, animal nutrition, cosmetology, pesticides, toxicity and ecotoxicity, and veterinary matters;
Whereas several issues relating to consumer health are of a multidisciplinary nature and require input from various scientific committees which would benefit from an effective co-ordination;
Whereas the Commission must be able to obtain sound and timely scientific advice;

Whereas scientific advice on matters relating to consumer health must, in the interest of consumers and industry, be based on the principles of excellence, independence and transparency,
Has adopted this decision:

Article 1.
A Scientific Steering Committee (hereinafter called "SSC") in the field of consumer health and food safety is hereby established.

Article 2
1. The SSC shall assist the Commission to obtain the best scientific advice available on matters related to consumer health.

2. The SSC shall co-ordinate the work of the scientific committees set up by the Commission to address matters of consumer health, in particular:

a. The SSC shall evaluate and monitor the working procedures used by the scientific committees and will harmonise them when necessary.

b. For matters which require consultation of two or more scientific committees, the SSC shall identify those scientific committees which should be involved, taking account of compulsory consultation requirements, shall consider opinions issued by the different committees and may, in case of substantial differences of opinions, provide an overall view.

c. When Community measures are based on the evaluation carried out by scientists from organisations in the Member States, the SSC shall assist the Commission, on its request, in assessing if scientific advice at Community level is needed, and if so, in determining which scientific committee is to provide it.

3.The SSC shall, in the area of consumer health,:

a. deliver scientific advice only on matters which are not covered by the mandates of the other scientific committees. It shall prepare this advice following a request of the Commission and relying on the most appropriate scientific expertise;

b. specifically deliver scientific advice on multidisciplinary aspects of transmissible spongiform encephalopathies, including bovine spongiform encephalopathy). To this end it shall create an ad-hoc group which shall be chaired by a member of the SSC and may include external experts;

c. assist the Commission with the identification of those areas where compulsory consultation of the scientific committees could be appropriate.

d. arrange for the review of existing and newly developed risk assessment procedures and, where appropriate, propose the development of new risk assessment procedures relating to areas such as, for example, food-borne diseases and the transmissibility of animal diseases to man.

e. draw the attention of the Commission to any specific or emerging consumer health problem.

4. Those members of the SSC, who are not chairpersons of scientific committees, shall contribute to the selection of the members of the scientific committees by advising the Commission with regard to the excellence and independence of the candidates.
5. The Commission may, when requesting an output from the SSC, ask for a deadline for its delivery to be adhered to.

Article 3
1. The SSC shall be composed of eight scientific experts not being a member of any other scientific committee, and the chairpersons of the scientific committees. The latter may, should they not be able to participate in a meeting of the SSC, be replaced by one of the vice chairpersons of their scientific committee.
2. The full SSC will elect by simple majority one chairperson and two vice-chairpersons from amongst its members who are not chairpersons of scientific committees.
3. The members of the SSC shall be scientific experts in one or more fields of consumer health, collectively covering the widest possible range of scientific disciplines related to this subject..
4. The members of the SSC, who are not chairpersons of scientific committees, will be nominated by the Commission following publication in the *Official Journal of the European Communities* of a call for expressions of interest, together with the selection criteria and a description of the selection procedure. The selection procedure shall identify in a transparent manner the most suitable candidates for working in the SSC.
From these the Commission will nominate the members of the SSC not being chairpersons of scientific committees. The names of the members of the SSC will be published in the OJ.
5. The term of office of members of the SSC not being chairpersons of scientific committees will be three years. Those members of the SSC may not serve more than two consecutive terms of office. After the period of three years they remain in office until their replacement or renewal of their mandate.
6. In the event that a Member of the SSC not being a chairperson of a scientific committee is not longer able to contribute effectively to the work of the SSC, or in the case of his/her voluntary resignation, the Commission will nominate an appropriate replacement for the remaining term of office, drawn from the most suitable candidates identified in accordance with Article 3(4).
7. Members of the SSC, and external experts invited to contribute to its work, will receive an indemnity for the service they provide to the Commission in addition to the reimbursement of travel and subsistence expenses in accordance with the rules laid down by the Commission.

Article 4
1. Members of the SSC have to act independently of external influences in their capacity as members of the SSC
2. Members of the SSC shall inform the Commission annually of any interests which might be perceived as prejudicial to their independence.
3. Members of the SSC and external experts shall declare specific interests which might be perceived as prejudicial to their independence with regard to the work of the SSC, its working groups or its *ad hoc* group.

Article 5
The SSC may create specific working groups with clearly defined mandates. Each working group shall be chaired by a member of the committee and may include external experts. The working groups shall report to the SSC.

Article 6
1. The SSC will adopt its rules of procedure which will be made publicly available.
2. These rules shall ensure that:
    a. the tasks outlined above are completed in a manner which satisfies the principles of excellence, independence and transparency, while respecting legitimate requests for commercial confidentiality;

    b. the co-ordination of the work of the scientific committees is carried out in an efficient and flexible manner, in particular by a timely reporting of the chairpersons on the workplans of the Scientific Committees;

    c. the SSC provides opinions and other scientific advice in good time;

    d. the SSC may appoint rapporteurs for the preparation of background information and documentation and the drafting of its opinions;

    e. the SSC verifies that appointed rapporteurs can carry out their specific tasks as independently as possible from all external influences.

Article 7
The agenda, minutes and opinions of the SSC will be made publicly available without undue delay and with regard being had to the need to respect commercial confidentiality. Minority views shall always be included and shall be attributed to Members only at their request.

Article 8
Without prejudice to Article 214 of the Treaty, members shall be obliged not to divulge information which they acquire as a result of the work of the committee or one of its working groups when they are informed that this information is subject to a request for confidentiality.

Article 9
The Commission will provide the secretariat for the SSC, its working groups and its *ad hoc* group.

Done in Brussels, 10 June 1997
For the Commission
Emma Bonino
Member of the Commission

Scientific Committee for Foods

Scientific and technical questions concerning consumer health and food safety associated with the consumption of food products and in particular questions relating to toxicology and hygiene in the entire food production chain, nutrition, and applications of agrifood technologies, as well as those relating to materials coming into contact with foodstuffs, such as packaging.

Scientific Committee on Animal Nutrition

Scientific and technical questions concerning animal nutrition, its effect on animal health, on the quality and health of products of animal origin, and concerning the technologies applied to animal nutrition.

Scientific Committee on Animal Health and Animal Welfare

Sub-committee Animal Health:
Scientific and technical questions concerning all aspects of animal health, hygiene, animal diseases and therapies, including zoonoses of non-food origin and zootechnics.
Sub-committee Animal Welfare:
Scientific and technical questions concerning the protection of animals, notably in regard to animal husbandry, herd management, transport, slaughter and experimentation.

Scientific Committee on Veterinary Measures relating to Public Health

Scientific and technical questions concerning consumer health and food safety, and relating to zoonotic, toxicological, veterinary and notably hygiene measures applicable to the production, processing, and supply of food of animal origin.

Scientific Committee on Plants

Scientific and technical questions relating to plants intended for human or animal consumption, production or processing of non-food products as regards characteristics liable to affect human or animal health or the environment, including the use of pesticides.

Scientific Committee for Cosmetic Products, and Non-food Products intended for Consumers

Scientific and technical questions concerning consumer health relating to cosmetic products and non-food products intended for the consumer especially substances used in the preparation of these products, their composition, use as well as their types of packaging.

Scientific Committee on Medicinal Products and Medical Devices

Scientific and technical questions relating to Community legislation concerning medicaments for human and veterinary use, without prejudice to the specific competences given to the Committee for Proprietary Medicinal Products and the Committee on Veterinary Medicinal Products (1) in the context of the evaluation of medicaments. Scientific and technical questions relating to Community legislation concerning medical materials and equipment.
(1) Committees established in the European Agency for the Evaluation of Medicinal Products

Scientific Committee for Toxicity, Ecotoxicity and the Environment

Scientific and technical questions relating to examination of the toxicity and ecotoxicity of chemical, biochemical and biological compounds whose use may have harmful consequences for human health and the environment.