Probabilistic approaches to food risk assessment

Report of a workshop held on 8–9 June 1998

MRC Institute for Environment and Health

FORA 1

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Edited by GM Price and LK Shuker

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MRC Institute for Environment and Health
University of Leicester
94 Regent Road
Leicester LE1 7DD
UK

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Preface

This report is based on a workshop which was convened as part of the MAFF-sponsored Food Risk Assessment (FORA) project — a collaborative research programme between the MRC Toxicology Unit and the MRC Institute for Environment and Health in Leicester and the MRC Dunn Clinical Nutrition Unit in Cambridge. The programme aims to consider and conduct research into fundamental and applied approaches to risk assessment, most specifically in the context of diet and cancer.

Workshop participants are listed at the end of the report. Their affiliations are given as well as an indication of any special role: speaker, rapporteur or chairman. Many thanks are due to all the workshop participants and especially to the chairman and speakers for their contributions.

Dr David Shuker
Co-ordinator, MAFF Food Risk Assessment Collaborative Research Project

Executive summary

Background

The international regulatory and risk management community needs consistent and transparent approaches for risk assessment of internationally traded food. The UK government has acknowledged similar national needs among a list of guiding principles laid down in the White Paper (UK Government, 1998) preparing for the establishment of the Food Standards Agency*. There is a universal need, which applies generally and not just to food, for a way to express uncertainty and variability in risk assessments, to be able to justify and test assumptions, and to be able to reproduce assessments and update them when new information becomes available. Among the main problems for regulatory safety assessors are the inadequacy of scientific data available to support the decision-making process, and the diverse nature of the information that may be available. There is, therefore, an urgent need to be able to combine different types of often imperfect and incomplete information, and to use the opinions of experts in a consistent and accountable manner. The use of probabilistic methods in risk assessment may help to resolve some of the difficulties.

The Food Risk Assessment (FORA) project is a collaborative research programme between the MRC Toxicology Unit and the MRC Institute for Environment and Health (IEH) in Leicester and the MRC Dunn Clinical Nutrition Unit in Cambridge, and is sponsored by the Ministry of Agriculture, Fisheries and Food (MAFF). As part of the project IEH hosted an expert workshop, held in Leicester in June 1998, to discuss whether a probabilistic approach might benefit risk assessments of both chemicals and microbiological contaminants in food. Participants in the workshop included scientists from the fields of food microbial and food chemical safety, and from the statistical area of probabilistic modelling.

This report is based on presentations made at the workshop and ensuing discussions. It outlines existing methods for addressing the safety of chemicals and microbes, respectively, in food, and discusses some of the strengths and limitations of the current approaches, focusing particularly on food chemicals. Recommendations for, and advances in, classical probabilistic modelling of risks from microbial contamination of food are followed by an introduction to Bayesian probability concepts and modelling. An example of the use of Bayesian belief networks in a microbial risk assessment and a case study of a recent food chemical issue are presented, with a recommendation to attempt a Bayesian modelling exercise to inform and assist such problems in future. This report concludes with some general comments and conclusions about the use of probabilistic methods in food risk assessment, based on the workshop general discussion.

Probabilistic risk assessment

Probabilistic methods for risk assessment express the variability and uncertainty in an input factor as a probability distribution, which can be thought of as a frequency diagram of all the possible values of a variable in relation to the probability of each value occurring. The different components and stages of the risk assessment are linked together by mathematical relationships and the variabilities in the inputs at each stage are propagated throughout to the final output variable, which is also expressed in the form of a probability distribution. This may give a better and more realistic representation of the risk being assessed than the current tendency to use

* The Food Standards Agency Bill was published 11 June 1999 and received Royal Assent on 11 November 1999: The Food Standards Act 1999

a single value. In addition, probabilistic methods allow sensitivity analysis of inputs, which indicates which factors are the most important to the result. This approach assists in prioritising the allocation of resources to further research on the factors that most significantly influence the overall outcome.

Probabilistic methods may be used under a classical or a Bayesian statistical paradigm. The differences between these are not only in the underlying philosophy, but also in the manner with which new evidence may be incorporated into an analysis.

In the classical view, probability is regarded as a frequency with which an event will occur in a series of repeated observations, and probability distributions specified for the inputs to an analysis or on future events will be estimated from available data. Monte Carlo simulation may then be used to simulate from these distributions and hence form a predictive distribution over the outputs of the analysis, for example the risks of specific events occurring.

According to the Bayesian view, probability is regarded as a 'degree of belief', or how likely it is thought to be, based on judgement as well as such data as are available, that an event will occur. One of the major technical advantages of Bayesian over classical methods is their ability to propagate variability backwards as well as forwards through a risk assessment model, so that accumulating evidence can be incorporated into the analysis. Bayesian methods use Bayes' theorem to propagate the effects of evidence through a model, which combines background information expressed as a 'prior' distribution and a likelihood function (analogous to a probability distribution) of the new data. The resulting joint 'posterior' distribution is normalised to a total probability of 1. The link between prior, new data and posterior distributions is the basic building block in a Bayesian 'belief network', which links many pieces of information, including data quality; the 'posterior' from one link forms the 'prior' for the next. Modern advances in mathematics and computer technology allow the construction and operation of increasingly complex Bayesian belief networks. Graphical representation, another relatively recent development, assists and enhances the process and provides an attractive aid for the definition and communication of risk assessment issues.

Conclusions

Despite the potential advantages, the mathematical and statistical complexity of probabilistic methods (including Bayesian approaches) for risk assessment could be a barrier to acceptance; this is one of the main reservations of both lay people and scientific experts about the introduction of such an approach. However, the graphical representation of Bayesian approaches using facilities of modern software can assist greatly and, after the initial highly skilled work of setting it up has been completed, a model could be adapted to a generic format, usable by anyone with a little training. Actual or simulated data inputs could be changed easily using the computerised model to assess the impact on the results. Full documentation of all inputs is an essential part of the process and of increasing transparency.

A probabilistic risk assessment model could be used by scientists, experts on Government committees, risk managers and communicators, as a tool to aid decision-making in risk assessment. The additional potential benefits of Bayesian methods over classical probabilistic methods such as Monte Carlo simulation are the ability of Bayesian models to deal with interdependency of co-factors and with incomplete data, subjective opinion and bi-directional updating of information.

The Bayesian modelling approach should be tested on a number of risk assessment issues in parallel with current methods so that a full evaluation of their relative usefulness and efficiency can be made.

Reference

UK Government (1998) *The Food Standards Agency: A Force for Change* (Cm 3830), London, UK, The Stationery Office

1 General introduction

1.1 Background

There is a recognised need, at both the national and international level, for consistent and transparent approaches to food risk assessment.

Uncertainties and variabilities in risk assessment need to be clearly identifiable, as do the justifications for any assumptions made in such assessments. In particular, uncertainty may arise because of limitations in available data, and expert judgement is often needed both to evaluate the relevance of incomplete data sets and to weigh evidence of a diverse nature. Probabilistic approaches may help to define more clearly some of these and other areas of uncertainty and judgement in the risk assessment process and to set risk estimates in context.

To investigate the possibility of improving current risk assessment methods by the use of probabilistic (also sometimes termed 'quantitative') approaches, and in particular Bayesian approaches, the Institute for Environment and Health (IEH) hosted a workshop, held in Leicester in June 1998. This workshop was part of the Ministry of Agriculture Fisheries and Food (MAFF)-sponsored Food Risk Assessment (FORA) project, which is a collaborative research programme between the MRC Toxicology Unit and the MRC IEH in Leicester and the MRC Dunn Clinical Nutrition Unit in Cambridge. The ideas behind the workshop have several sources, including previous workshops held at IEH (notably a workshop on 'The Relative Ranking of Carcinogenic Risk' held in 1995), developments in risk assessment methods in North America (Olin *et al.*, 1997), UK national preparations for the establishment of the Food Standards Agency and international developments driven by the World Trade Organisation (FAO/WHO, 1995).

The aim of the workshop was to bring together leading scientists in the fields of food chemical and food microbiological safety in order to foster cross-fertilisation and cooperation among them, and to discuss whether a probabilistic approach to risk assessment might benefit both fields. Workshop participants (listed at the end of the report) were identified and invited following recommendations from MAFF and other invitees, with the aim of including representatives from each of the different areas of work. It is hoped that the initiative provided by the workshop will be continued and will promote opportunities for collaboration on a much wider scale.

Topics for discussion were identified by the FORA team at IEH and the MRC Toxicology Unit, in consultation with MAFF. They were selected to provide some background to the need for new approaches to food risk assessment, to introduce Bayesian techniques as they might be used in this context and to describe some experiences with probabilistic methods in food risk assessment. Selected invitees were asked to make presentations at the workshop and summaries of these presentations are given herein.

The interest in new methods for food risk assessment is outlined in the introductory presentation by MN Meah of MAFF. In Section 2 on food chemical risk assessment, S Barlow sets out the successes and limitations of the current method of regulatory assessment of chemicals in food, an approach which is not probabilistic, and D Lovell discusses some quantitative approaches to risk assessment used in the USA. These methods could be described as a deterministic form of quantitative assessment; they use mathematical equations to estimate biological quantities that are difficult or impossible to measure. As Lovell explains, probability modelling can be added to such deterministic models in order to express the

variability and uncertainty in the estimates used and produced.

The first of two types of truly probabilistic approach discussed in this report is the so-called 'classical' probability model, which is based on premises of classical, also called 'frequentist', statistics, and uses Monte Carlo simulation as its main tool. In Section 3 on food microbial risk assessment, J Back discusses how this could be useful, from a risk manager's viewpoint, in microbial risk assessment, and A Lammerding gives an example of how this approach has been used to estimate the variability and uncertainty in risk of *Esherichia coli* O157:H7 infection from eating a single hamburger meal. In Section 4 on Bayesian methods and their application, D Spiegelhalter introduces the principles of Bayesian probabilistic modelling, which adds to the features and overcomes some of the limitations of the classical probabilistic approach. Bayesian methods use a different philosophy and different mathematical mechanics from classical probabilistic methods. These differences are described in Section 1.2 and in Spiegelhalter's presentation. An example of the use of a Bayesian approach for risk assessment of *Clostridium botulinum* in food is given by G Barker. This section concludes with a presentation on the risk assessment of vitamin B_6, which was considered in 1997 by the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), and the possibilities for modelling the problem using Bayesian methods are explored.

The general discussion (based on precirculated questions), which followed the individual presentations at the workshop, is summarised in Section 5. The main issues addressed were:

- whether probabilistic methods, and specifically Bayesian methods, would be useful in food chemical and food microbial risk assessment and the reasons for this opinion;
- the use and validation of models;
- expert resources; and
- future research.

The conclusions of the workshop are presented in Section 6.

References

FAO/WHO (1995) *Application of Risk Analysis to Food Standards Issues* (Report of the Joint FAO/WHO Expert Consultation, Geneva, Switzerland, 13–17 March, 1995), Geneva, Switzerland, World Health Organization

Olin SS, Neumann DA, Foran JA & Scarano GJ (1997) Topics in cancer risk assessment. *Environ Health Perspect, 105 (suppl 1)*, 117–126

1.2 Probabilistic risk assessment

Many types of quantitative approach to chemical and microbial risk assessment are being explored, most notably in the USA and Canada. Quantitative methods commonly use probabilities to describe risks in the context of the variability and uncertainty associated with any of the information used in the assessment. The term 'quantitative risk assessment (QRA)' is taken, for the purposes of this report, to be synonymous with 'probabilistic risk assessment'. The most important features of the probabilistic approach are that quantitative estimates of risk are obtained, and that the variability of the risk and uncertainty associated with its determination are evident, quantifiable and expressed in terms of probabilities.

Probabilistic risk assessment uses mathematical or statistical models to relate elements of the assessment to each other. Repeated samples are taken by a computer program from distributions of input variables, as distinct from taking a single (e.g. 'worst case') value from each; this is the aspect involving probability. The whole process results in a distribution of the probability of the output variable (such as risk), called a 'probability density function', which reflects the combined probability of the input data given their quantified inter-relationships. From this output distribution the median and any percentile results can be found — for example, the median probability for exposure to a carcinogenic pesticide, or the upper 95th percentile for risk of *Salmonella enteritidis* infection from eating a single egg.

Sensitivity analysis is then performed to determine which variables in the model have the most influence on the results. This is achieved by changing the value for each input variable in turn by a fixed amount (e.g. ten percent) while keeping the others constant. Sensitivity analysis enables identification of significant requirements for further or better data and highlights the relative importance to the results of all aspects of the model.

In 'classical' (also called 'frequentist') probabilistic risk assessment, probability is regarded as a frequency, that is how likely it is, based on repeated sampling, that an event will occur. Monte Carlo simulation is the method most commonly used for classical probabilistic risk assessment. This is a computational method developed over 50 years ago for gambling predictions, and which is used to achieve multiple samples of the input distributions, analogous to doing repeated experiments.

Attention in the risk assessment field has recently been turning to a Bayesian probabilistic approach. Bayesian statistical methods are based on Bayes' theorem which was originally stated in 1763 by the Revd Thomas Bayes and was one of the first expressions, in a precise and quantitative form, of one of the modes of inductive inference (Barnard, 1958). According to the Bayesian view, probability is regarded as a 'degree of belief', or how likely it is thought to be, based on judgement as well as such observational data as are available, that an event will occur. Bayesian theory requires a 'prior distribution' which is a probability density function relating to prior knowledge about the event at issue. This is combined with the distribution of a new set of experimental data in a likelihood framework (analogous to a probability distribution) to obtain the so-called 'posterior distribution' of probability, the updated knowledge (see Figure 1.1). Obtaining this posterior distribution can involve solving a complex integral, which is increasingly dealt with by means of Markov Chain Monte Carlo methods. Thus Monte Carlo methods are used both in Bayesian and classical probabilistic methods, although Bayesian analysis extends the use beyond simply simulating predictive distributions.

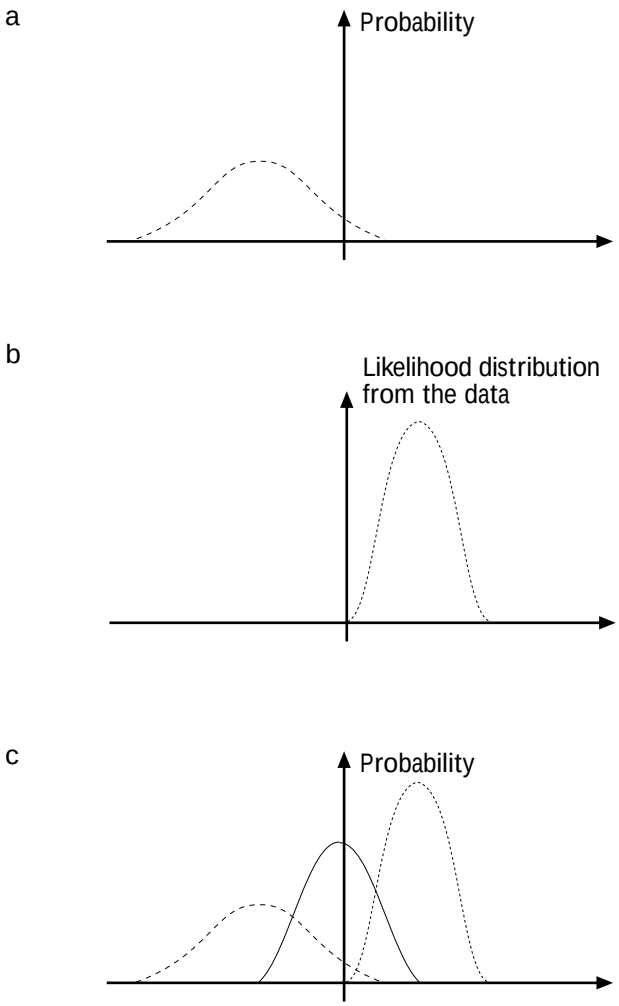
The Bayesian link between 'prior' and new data is the basic building block in a Bayesian 'belief network', which links many pieces of information, including data quality; the 'posterior' from one link forms the 'prior' for the next. Modern advances in mathematics and computer technology allow the construction and operation of increasingly complex Bayesian belief networks. Graphical representation, another relatively recent development, assists and enhances the process and provides an attractive aid for the definition and communication of risk assessment processes.

A Bayesian approach to risk assessment can be used to integrate probabilities for any type of observational data and expert judgement together with ongoing developments, in order to produce a revised probability of an event occurring or of an hypothesis being true.

Reference

Barnard GA (1958) Studies on the history of probability and statistics IX. Thomas Bayes's essay towards solving a problem in the doctrine of chance. *Biometrika, 45*, 293–315

Figure 1.1 Graphical representation of Bayes' theorem



Bayes' theorem is used to multiply a prior distribution (a) by a likelihood distribution derived from the data (b), resulting in the joint 'posterior' distribution (solid line in diagram (c)) which is normalised to a total probability of one.

1.3 Why MAFF needs a new approach to food risk assessment

MN Meah, Ministry of Agriculture, Fisheries and Food, London, UK

It is the Government's policy to protect the public from harm arising from hazardous substances in food. Much of the research on food safety and on food quality and applied nutrition, currently conducted by MAFF, is expected to be transferred to the Food Standards Agency (FSA) which will be established in the near future. Some of the 'guiding principles' of the FSA, outlined in a recent White Paper (UK Government, 1998) and summarised below, will have an impact on the way food risk assessment is carried out in the UK.

- The protection of public health in relation to food is an essential aim of the FSA.
- The Agency's assessments of food standards and safety will be based on the best available scientific evidence.
- Decisions and actions taken should be proportionate to the risk, and should take account of costs as well as benefits.
- The public are to have access to adequate, clearly presented information to enable them to make informed choices.
- Decision-making should be open, transparent and consultative.

At the international level, the World Trade Organisation Sanitary and Phytosanitary Agreement (SPS) has stated a requirement for

> Members to ensure that their SPS measures are based on an assessment, as appropriate to the circumstances, of risks to humans, animals or plant life or health, taking into account risk assessment techniques developed by the relevant international organisations (FAO/WHO, 1995).

The Codex Alimentarius Commission (CAC) of the Food and Agricultural Organisation (FAO) and World Health Organization (WHO) is the international body entrusted with setting the standards for methods used to support regulation of international trade in food. Member countries will be expected to justify levels of protection higher than those in Codex standards by using risk assessment techniques. The CAC has issued some guidance documents to this end, while standards for some risk assessment procedures are still under discussion. Therefore, it will be important for the UK to have an input into determining the standards set by Codex committees and to ensure that these are based on the best available science.

The current paradigm for the assessment of risks from chemicals in food envisages a sequence of events whereby a hazard characterisation is carried out on the chemical of interest followed by an assessment of human exposure after which a risk characterisation is arrived at. At this point the information is handed over to a risk manager to carry out a risk analysis and, taking account of societal factors, develop a risk management strategy.

Such an approach was initially developed to set Acceptable Daily Intakes (ADIs) for food additives. In this approach, *in vivo* toxicological testing in animals is used in the hazard characterisation to establish a No-Observed-Adverse-Effect Level (NOAEL) for single chemicals. This almost invariably requires the use of high doses. The experimental result is then extrapolated to possible effects in humans (who are usually exposed at much lower doses) with the application of uncertainty (or safety) factors to take account of inter-species differences and intra-species variability. An analogous approach has been developed for chemical contaminants in food which results in the estimation of a Provisional Tolerable Weekly Intake (PTWI). This approach to toxicological testing takes no account of the metabolic fate of the chemical in question and, indeed, assumes that the metabolism is the same in humans as in the test animal. In addition, the approach tends towards over-conservatism, taking no account of the protective or antagonistic effects of other dietary components. Thus there are a number of sources of uncertainty and variability in the hazard characterisation process. Furthermore, it is very difficult to integrate newly-acquired information into existing ADI and PTWI values.

When considering potential carcinogenic chemicals in the diet, it is assumed that a NOAEL cannot be established, and extrapolation from high dose to low dose is assumed to be linear with no threshold effect. In the USA, QRA models have been developed which can be used to extrapolate from dose–response curves obtained in *in vivo* animal studies to derive, for a given chemical, a maximum intake which will give rise to no more than one excess cancer in 10^6 people with lifetime exposure. However, recent advances in the understanding of the cancer process have shown that detoxification mechanisms and DNA repair play an important

part in the development of cancer and the 'no threshold' assumption is now open to question.

Currently, issues such as variation in human susceptibility to toxic chemicals in food, genetic predisposition to particular diseases, age-related and gender-related susceptibility factors, nutritional status and variation in population exposure are being seen as increasingly important to the overall risk assessment. This is in part because the current approaches to food chemical risk assessment, which yield discrete numbers, give little or no indication of the variability or uncertainty in either the underlying data or the likely impact on public health. Better characterisation of uncertainty and variability will provide a clearer idea of what further information is needed to reduce them both and, just as importantly, will enable regulators to make the value judgement as to whether it is worth the additional resource to do so. Furthermore, improved characterisation of uncertainty and variability should facilitate greater transparency and increased involvement of stakeholders in risk assessment decision-making (Stern & Fineberg, 1996).

Whereas considerable effort has gone, with varying degrees of success, into developing quantitative approaches to chemical risk assessment, quantitative risk assessment for microbiological hazards is still in its infancy (Lammerding, 1997). The contrasts between chemical and microbiological hazards are illuminating. For most chemical hazards, the concentrations in foodstuffs can now be determined with a high degree of accuracy and precision using modern analytical techniques. Pathogens, in contrast, are difficult to detect in foodstuffs and a great deal of effort has gone into developing methods sensitive enough to detect low numbers. Pathogens, unlike chemicals in food, can multiply in the right environments so, given the optimum temperature, water activity and pH conditions, the level of contamination of a foodstuff might increase considerably in a matter of hours. It is thus very difficult to estimate exposure. The infective dose of most common pathogens required to produce an adverse response in humans is another area of uncertainty. This can vary considerably, depending on factors such as age, gender, health status and previous exposure in humans, and also differs across host species, thus rendering animal models of limited use to researchers. In addition, mutation may cause the virulence of a pathogen to change, giving rise to new hazards. However, in spite of the difficulties in formally assessing the risk from foodborne pathogens, in most cases the adverse response in humans is manifested by acute illness of varying degrees of severity and is, therefore, relatively easily recognised.

Control of microbiological foodborne hazards in the UK and elsewhere, relies on the Hazard Analysis Critical Control Point (HACCP) system. This system seeks to identify specific hazards that might arise in a food production process and develop preventative measures for their control, with criteria for evaluation set for the critical control points. Thus the emphasis is on prevention of contamination or reduction of contamination to acceptable levels.

One avenue of research being followed in the MAFF programme on microbiological safety of food uses the Bayesian belief network method to evaluate risk arising from *Clostridium botulinum* growth and toxin production. This approach to risk analysis is probabilistic and seeks to map the causal connections and interdependencies relevant to the assessment of hazard from botulism, such that all the probabilities can be combined to give an overall joint probability of a hazard occurring. Importantly, the approach allows estimates of uncertainty to be made for the various factors that influence the risk assessment; once the areas of greatest uncertainty have been identified, further data collection can be directed towards them.

Although different processes have been developed for assessing and controlling risks from chemicals and pathogens, respectively, in foods, both processes have to deal with uncertainty and variability in the underlying data and in the output of the process. It is, perhaps, in dealing with such uncertainty and variability that probabilistic approaches will prove useful, as they may facilitate the development of procedures that will enable the scientific evidence to be used in a more rational and transparent way in the formulation of food safety policy (Kaplan, 1997).

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2 Food chemical risk assessment

2.1 Current practices in food chemical risk assessment: Successes and limitations

SM Barlow, Brighton, East Sussex, UK

Practices in risk assessment of food chemicals have changed little over the past 40 years (WHO, 1987; Hathaway, 1993). Are the old methods still reliable and robust? Has there been a lack of intellectual effort to improve the science of toxicology and risk assessment? Classical methods seem to have served well in protecting human health, but has this been because they are over-conservative?

For the majority of food additives and contaminants, risk assessment is carried out by extrapolation from the results of tests in laboratory animals. Occasionally, human data are also available. As outlined in the previous section, for non-genotoxic food chemicals, critical toxicological effects and doses without effects are identified and these are used to estimate an Acceptable Daily Intake (ADI). The concept of the ADI was introduced by Truhaut and others in early meetings of the Joint WHO/FAO Expert Committee on Food Additives (JECFA) in 1956–1961. The Committee used the proposal, from the early 1950s, of Lehman and Fitzhugh of the US Food and Drugs Administration (FDA) to apply a 100-fold uncertainty (safety) factor to the maximum no-effect dose determined in long-term animal studies in order to derive an acceptable intake for humans.

This procedure is based on a number of assumptions which contribute to uncertainty. These include, for example, the assumptions that animals are good models for humans, that relatively small numbers can predict the diversity of responses in large populations, that the currently used range of tests and the clinical and pathological indices they include are adequate predictors of chemical-induced illness and disease, and that chemicals in isolation behave the same as in a food matrix. Once acceptable intakes are established there are few opportunities to verify from human experience whether the assumptions on which the assessments were based are correct.

Since the ADI concept was devised it has been questioned, evaluated and refined but not essentially altered. One of the significant areas of research has been the investigation of interspecies and intraspecies differences in toxicokinetics and toxicodynamics, which has, in fact, tended to justify the numerical size of the original 100-fold uncertainty factor, and its subdivision into 10-fold for interspecies differences and 10-fold for intra-human differences (WHO, 1994). Such conclusions are not widely appreciated, and these uncertainty factors still have the unfortunate image of being considered non-scientific ('fudge factors'), even within the scientific community.

Minor refinements to the classical ADI model, such as the use of a benchmark dose rather than a No-Observed-Adverse-Effect Level (NOAEL), of more doses or more animals per dose in dose–response studies, and of allometric scaling of dose to account for metabolic differences between humans and animals, and the division of interspecies and intraspecies uncertainty factors into toxicokinetic and toxicodynamic components, have been proposed and used but, in practice, they make little difference to the outcomes.

While state-of-the-art toxicological research is striving to address the issues of uncertainty and refine risk assessment methods, it is important to note that present methods, while erring on the side of safety rather than precision, do give added reassurance for consumer safety. However, there is currently little effort devoted to predicting the

likelihood of an adverse effect occurring in an individual or population exposed to levels above the estimated ADI. It is in the latter area, particularly, that probabilistic methods are seen to offer a major potential benefit. The current method for assessing such risks does not depend on statistical techniques, but consists of investigating, on a case by case basis, the severity and reversibility of the possible toxicological outcomes, the duration and extent of exceedance, the physiological characteristics of the subpopulation groups in which exceedance occurs and the toxicokinetics of the chemical in the body (Renwick & Walker, 1993; Renwick & Lazarus, 1998). Better use should be made of toxicokinetic, toxicodynamic and other data currently available to make such predictions, but new approaches are also needed to take this aspect of the science forward.

For risk assessment of ingredients, novel foods, micronutrients, vitamins and minerals, it is still difficult to find appropriate models, either human or animal, for prediction of toxic effects or development of chronic disease. Here benefits as well as risks have to be assessed. At present the skills required to weigh up benefits in one area against risks in another are poorly developed, and intake margins between benefit and risk may be very small.

Possible further refinements to strengthen the ADI model might include: the extension of toxicity endpoints to cover, for example, better examination of endocrine effects, developmental neurotoxicity and immunotoxicity; the use of animal models of known common human diseases (such as diabetes or diseases of the liver or kidney), to test the effects of food chemicals in animals with wider metabolic deviations; and the modelling of genetic polymorphisms affecting metabolism of xenobiotics. It is conceivable that taking account of such factors might indicate that there is greater variability in the human population than previously thought, thus rendering the classical uncertainty factor of 10, to account for such variation, insufficient to assure protection from the adverse effects of chemicals for the majority of the human population. Thus although classical methods are criticised for their conservatism it is possible that they may not be conservative enough to encompass the total range of variability among humans.

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2.2 Application of quantitative methods to carcinogenic risk assessment: Some practical examples

DP Lovell, BIBRA International, Carshalton, Surrey, UK

Estimates of the risks posed to the human population from food additives, pesticides, veterinary residues and contaminants have traditionally been assessed by different approaches depending on whether or not the chemical is considered to be a carcinogen. Approaches to carcinogen risk assessment have differed between countries. Quantitative risk assessment (QRA) methods using mathematical modelling and extrapolation from high dose animal data to low dose human exposures have been widely used in the USA. However, this approach has been avoided by many European countries, particularly the UK.

Probabilistic approaches include the use of the linearized multistage (LMS) model and the development of a threshold of regulatory concern to assess the risks of exposure from chemicals. The LMS model has been used to extrapolate from the dose–response data obtained in animal experiments to the 'virtually safe' dose (VSD) expected to be associated with a 'tolerated' risk of one excess cancer in 10^6 people with lifetime exposure. In 1986, Environmental Protection Agency (EPA) guidelines suggested that the 95% upper confidence limit of the risk/dose slope estimate (commonly called q_1*) predicted by the LMS model would be the parameter of choice to estimate the VSD in regulatory decisions, 'in the absence of adequate information to the contrary'.

However, there are many questions about the assessment of risk from carcinogens which are unanswered by the LMS model. For example, the q_1* slope is potentially insensitive to variations in the tumour data upon which it is based. It appears to be closely related to the maximum tolerated dose and, counter-intuitively, decreases in value if the top experimental dose is excluded from the model, while the data from low doses appear, paradoxically, to carry little weight in the estimate. The general uncertainty regarding the way to approach assessment of the risks of environmental chemicals is illustrated by the range of values for the Tolerable Daily Intake (TDI) for tetrachlorodibenzo-*p*-dioxin (TCDD) that have been set by different agencies and countries over the past three decades. A lowest VSD for TCDD of less than 0.01 pg/kg/d that has been derived using the LMS method is at least two orders of magnitude lower than the highest regulatory levels of 10 pg/mg/d, set in the UK and Canada using the traditional NOAEL technique with uncertainty factors.

Alternative approaches are being developed, most notably by US regulatory authorities such as the EPA, to take more account of the within- and between-species differences in transport and metabolism of carcinogens within the body. The new EPA guidelines accordingly emphasise mode of action and toxicokinetic information, and propose methods such as the benchmark dose and categorical regression, thus breaking down the dichotomy between the approaches for cancer risks and non-cancer risks, although they still retain a default 'linear at low dose' assumption. One of the newer methods is physiologically-based pharmacokinetic (PBPK) modelling, which divides into compartments the body with its circulation and organs, and attempts to estimate mathematically the likely dose arriving at a target organ of concern. Biologically-based dose–response (BBDR) modelling similarly attempts to use experimental data to predict the metabolism and excretion rates of the chemical in the experimental animal or in man. The ideal would be to use PBPK and BBDR modelling to predict human metabolism, from experimentally observed metabolism in an animal, by comparing doses and measurable excreted compounds in both species. However, much of this highly sophisticated mechanistic and deterministic modelling is still at the experimental stages and requires medium- to long-term development, as do other approaches, such as the use of biomarkers of DNA damage to provide mechanistic information.

Monte Carlo methods can be used in addition to any of the above to model variability in the concentrations and consumption of food chemicals in the intake or exposure assessment. They can also be used to model variability in sophisticated biologically-based models of the toxicokinetics and toxicodynamics of chemicals by simulating vulnerable or susceptible individuals.

The various probabilistic methods for carcinogenic risk assessment have advantages and disadvantages in terms of both their potential to improve on the current methodologies and the potential costs they may introduce. QRA should take advantage of improved understanding of mechanisms and can take into account advances in molecular biology as well as in measures of exposure. Risk–benefit

analysis may provide additional improvements on the current custom of restricting outcomes to health indices.

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3 Food microbial risk assessment

3.1 Recommendations for microbial risk assessment

J Back, Ministry of Agriculture, Fisheries and Food, London, UK

At present food microbiological safety relies on the practice of Hazard Analysis and Critical Control Points (HACCP), as described in Section 1.3; there is no risk assessment as such currently used for regulatory purposes. However, from the point of view of a risk manager the introduction of quantitative microbial risk assessment (MRA) holds several potential benefits.

The Codex Alimentarius Commission (CAC) Draft Principles and Guidelines for the 'Conduct of Microbiological Risk Assessment' suggest that MRA should be soundly based on science and that the assessment of risk should be kept separate from issues concerning its management. In contrast, developments in the USA indicate a recognition that some integration of these functions is necessary.

The draft guidelines potentially provide a structure for MRA based on the four-step procedure of chemical risk assessment, namely hazard identification, hazard characterisation, exposure assessment and risk characterisation. Hazard identification in MRA entails the identification of microorganisms with known or potential health effects. Hazard characterisation includes an estimation of the severity of adverse effects, consideration of factors in the food and in the host which influence the outcome, and determination of a dose–response. The last of these is one of the main areas in which development of knowledge is needed. Exposure assessment includes quantitative estimation of intake of microorganisms, consideration of how they get into the food from the source, and estimation of how their numbers vary, through growth and death, throughout the 'life' of the food. Predictive modelling of the dynamics of microorganisms is usually used as a tool in exposure assessment. Risk characterisation, which is the integration of the first three steps, can include qualitative as well as quantitative elements and must take into account areas of uncertainty in the risk assessment.

For MRA to be useful to risk managers, it is important to agree at the outset the questions to be asked and the format in which they should be presented. The phrasing and definition of questions to be addressed in a risk assessment exercise are recognised as being particularly important issues, not only for MRA but for risk assessment in general.

As in all risk assessment, MRA should take account of all relevant information, be transparent, identify clearly any constraints on the use of the data and describe and minimise uncertainty. No relevant data, including historical or qualitative data, or even data which at first sight do not appear credible, should be ignored. Ideally re-evaluation of risks should be carried out whenever relevant new data become available.

In addition to acute illnesses, the chronic sequelae of long-term exposures to food pathogens and associated secondary infections should be addressed. The dynamics of hazard–host interactions and of bacterial growth represent substantial differences from the circumstances surrounding food chemical risks and their assessment. However, there are issues of scientific judgement common to both chemical and microbial risk assessment; these include the choice of any animal model to be used, the choice of endpoint, whether to consider a threshold effect and what relative weights to assign to data derived from animals and humans.

In conclusion, the development of useful MRA is likely to be a lengthy but ultimately essential process.

3.2 A classical probabilistic approach to risk assessment in microbial food safety

AM Lammerding, Health Canada, Ontario, Canada

In the field of microbial food and water safety quantitative risk assessment (QRA) is an emerging tool. Risk assessment practices are not new; however, the application of this approach to evaluation of the microbial safety of foods is a recent development driven by public health concerns, the implementation of HACCP systems and international trade agreements.

The essence of QRA is in the description of a system in which a hazard reaches and causes harm to its host. The process is generally considered to consist of four steps, namely hazard identification, hazard characterisation or dose–response assessment, exposure assessment and risk characterisation. The knowledge in each step is combined to link prevalence and concentration of the hazard to the probability and magnitude of human health impacts.

Assessing the risks associated with the presence of a microbial pathogen in food poses unique challenges. Microbial risks are primarily the result of single exposures, unlike the cumulative effects of carcinogens and other toxicants causing chronic effects. Each exposure to a pathogen or its toxin represents an independent, non-cumulative event, resulting in outcomes ranging from asymptomatic infection to acute illness, chronic syndromes, or mortality. Multiple exposures over time may lead to the development of immunity and actually lessen risk.

Microorganisms can multiply in foods, and their survival, growth or inactivation is influenced by many intrinsic and extrinsic factors. It is often necessary to rely on data related to the raw ingredients of a food product because the levels of the pathogen in the finished product are too low to make enumeration practical. Yet the finished product may represent a significant risk if it is subsequently subjected to temperature abuse, allowing growth of a pathogenic population. In such cases, the effects of processing and post-process handling of the food on the microbial population must be taken into consideration.

For dose–response assessments, estimating the numbers of pathogens required to cause infection has traditionally been an extremely difficult area in which to acquire good data. Human populations are not homogeneous with respect to the immune response to microbes, nor are all microorganisms, even those that are closely related, equally capable of causing an adverse outcome. However, even limited knowledge of the dose–response function can be informative in comparing the magnitudes of human health impacts. The use of conservative dose–response values based on available epidemiological and food survey data has been proposed as an alternative to human volunteer feeding trials.

Nevertheless, several examples have recently been published that demonstrate that, by combining risk assessment and predictive microbiology, it is possible to generate risk assessment models that can adequately address the complexity associated with the production, processing, distribution and consumption of foods.

A Process Risk Model (PRM) has been developed at Health Canada for *Escherichia coli* O157:H7 in ground beef, to support comparative assessment of control strategies (Cassin *et al*., 1998). The model describes the fate of the pathogen population during the production of ground beef, from carcass processing to consumer cooking and consumption. Predictive microbiological models, estimating likely growth or inactivation during the stages of processing, distribution and preparation, have been incorporated into the model. A dose–response sub-model estimates the probability of illness and mortality, based on data from human feeding studies with *Shigella dysenteriae* which is genetically similar to *E. coli* O157:H7 and also produces verotoxins. Variability and uncertainty in the model have been accommodated through the use of probabilistic representations of many of the parameters. To generate a representative distribution of risk the model can be simulated many times, with different values selected from the probability distributions of input parameters, using Monte Carlo techniques.

The final output of the model is the distribution for the probability of illness from a single ground beef hamburger meal; the probability has been estimated to range from 10^{-22} to 10^{-2}, with a central tendency of probability of risk at 10^{-12}. The distribution includes both variability between meals and the combined sources of uncertainty about the estimate.

More important, however, than the final estimate of risk produced by this model, is its ability to describe the change in health risk associated with changes in various model parameters: importance analysis can be performed to identify the input factors most highly correlated with the predicted probability of illness. By changing parameters describing, for example, pathogen prevalence or concentration in raw material, parameters of temperature abuse in transportation and retail, consumer cooking preference, or infectious dose, the impact of trends in disease risk factors can be studied.

Because the model encompasses the 'farm-to-fork' continuum, it is possible to assess the relative efficacy of interventions, such as specifying on-farm controls or HACCP criteria, that would otherwise never be compared in the same analysis. In addition, the relative importance of better data at different points in the process can be estimated. Probabilistic models such as this one provide a framework to organise and evaluate all available information and knowledge pertaining to the risk at issue in a highly systematic way, while also providing the tool needed to understand the process and identify gaps in knowledge.

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4 Bayesian methods and their application

4.1 How Bayesian models work: A brief introductory guide

DJ Spiegelhalter, MRC Biostatistics Unit, Cambridge, UK

Important issues in quantitative food risk assessment include:

- the complexity of the problem;
- the need to combine data and judgement;
- endemic uncertainty and variability;
- a requirement for transparency and accountability; and
- a need for sensitivity analysis to test assumptions that may not be rigorously justifiable.

It is worth considering whether formal probabilistic reasoning may be of benefit in handling these difficult challenges.

Bayesian reasoning is a quantitative means of assessing uncertainty in the light of incomplete evidence. A basic premise is that probability is not only an appropriate tool for handling *variability* in potentially observable events but also for handling *uncertainty* concerning unobservable but meaningful quantities. A more controversial use of probability is in handling lack of knowledge ('ignorance'), in the sense of a lack of understanding of the fundamental underlying mechanisms.

Bayesian reasoning is based on the philosophy of quantifying uncertainty as new evidence accumulates, so that beliefs in hypotheses are revised as new knowledge is acquired, and the importance of all new data is assessed in the light of what is currently known. This view would seem to be consistent with the problems of scientific judgement for food risk assessment.

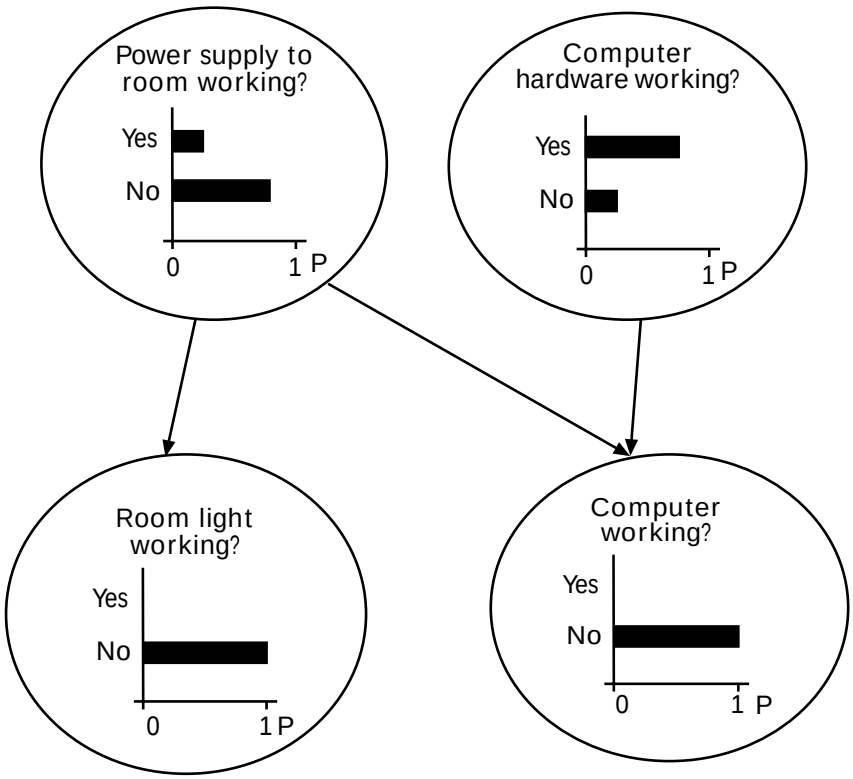
Bayesian methods are increasingly used in expert systems and artificial intelligence and are widely used for technical diagnostic systems. Recent theoretical and computational developments in artificial intelligence and statistics have extended Bayesian reasoning into highly complex problems, in which fragmentary and multiple items of information need to be combined with informed expert judgements and background knowledge. The stages in this process can be defined as described below.

Qualitative structuring

An initial qualitative structural model is created, in which domain (or subject) knowledge is used to identify the 'pathways' by which precipitating events influence empirical observations. This may take the form of a graph or network.

A simple example can be used to illustrate the Bayesian network concept (see Figure 4.1). The observed event is that the computer has stopped working. This event may have been due to one or both of two possible causes: either the computer itself might have suffered a fault or the power supply to the room might have failed. The power supply is also linked downwards in the causal pathway to an observation as to whether or not the switched-on light in the room is lit. An additional observation that the light is not lit can be propagated through this simple network and will increase the probabilities that the computer's stoppage is due to a general power failure rather than to an inherent computer fault. This model of simple logical reasoning demonstrates the working

Figure 4.1 Graphical model of a simple Bayesian belief network



Nodes are shown as areas within ellipses and links are shown as arrows between nodes. The nodes represent unknown quantities, some of whose values may be provided as evidence. The links represent dependence, modelled as far as possible in a causal direction. Since we generally cannot assume logical dependence the links have to be accompanied by a probability distribution. The influence of any observed items of evidence can be propagated throughout the whole network by using Bayes' theorem. In this example, the observation that the light does not work strongly suggests that the power supply is not working, which in turn would explain the computer not working and hence reduce the chance that the computer has a hardware fault.

of the Bayesian link, allowing the updating with new observations of conclusions about causes and effects and, in particular, showing the capacity of such networks to deal with additional knowledge that 'explains away' anomalous findings. The efficacy of such a network is obviously dependent on how the pathways of dependency are set up in the model in the first place.

An example of a graphical model of cause-and-effect pathways in the food safety literature is the analysis of Whiting and Buchanan (1997) who developed a risk assessment model for *Salmonella enteridis* in pasteurised liquid eggs. Stages in this (non-Bayesian) model included the incidence and prevalence of pathogens in raw ingredients, changes in pathogen population during processing and home storage, and serving size. Another application of such a structured risk assessment, also using classical probabilistic methods, is that of Cassin *et al*. (1998) on *Escherichia coli* in ground beef hamburgers (see Section 3.2).

One possible part of such a network would be an explicit model for between- and within- species variation, which could take account of information from a variety of relevant sources. This could potentially provide explicit guidance as to doses that would satisfy certain safety requirements (such as a 99% chance that fewer than 1 in 10^4 consumers will suffer a particular occurrence over a specified time period).

Quantitative modelling

Probability distributions are placed on the links of the network, expressing the extent to which 'causes' influence 'effects'. These distributions may often follow particular functional forms (such as dose–response models) but have unknown parameters. These parameters then become part of the network; they are given prior distributions based on whatever background knowledge or experiments are available.

Propagating the effects of evidence

Observational data are then taken into account, and their effect propagated through the network by systematic use of Bayes' theorem in order to arrive at probability distributions for whatever quantities are of particular interest. Special computational techniques are required; in some circumstances the propagation may be done exactly, but in many cases simulation methods are necessary. Developments in Markov Chain Monte Carlo methods have greatly extended earlier use of basic Monte Carlo techniques, and now problems of essentially arbitrary complexity can be handled. Special software with graphical user interfaces is becoming available.

Sensitivity analysis

Finally, it is essential to carry out a thorough sensitivity analysis of both quantitative and structural inputs (i.e. data and models). The US Environment Protection Agency (EPA) has already set standards for probabilistic analysis in risk assessment, including the need for sensitivity analysis.

Discussion

An example of non-Bayesian probabilistic modelling is the 'farm-to-fork' assessment of risk from infection with *S. enteritidis* from eating pasteurised liquid eggs in the form of a portion of mayonnaise, referred to above (Whiting & Buchanan, 1997). The model requires data input about factors such as the prevalence of contaminated flocks and times and temperatures of storage of eggs during transit and at home. Mathematical sub-models predict the probability of quantities such as survival of *S. enteritidis* during storage, and classical Monte Carlo simulation techniques propagate variability and uncertainty forwards throughout the model to the final risk estimate.

Use of Bayesian structures (or 'full probability modelling') and of recently developed Markov Chain Monte Carlo methods would enhance the model of Whiting and Buchanan by enabling its use in 'backwards', that is 'fork-to farm', mode. This would allow information such as the prevalence of pathogen in eggs to be entered into the network in order to estimate the rate of occurrence of pathogen in flocks. Markov Chain Monte Carlo methods would also allow the updating of earlier inputs into the model; for example, the results of a new survey of the proportion of flocks which are contaminated with *S. enteritidis* could be included and propagated through the network, to assess their effect on the final estimation of risk of infection.

An important advantage of the Bayesian paradigm is that there is no need to choose between judgements based on data, deterministic biological models and judgements based on expert opinion. They can all be incorporated in the same structure, but their justification must be recorded.

Utility, which is an index of value used for decision analysis, can also be incorporated as an outcome of these models to aid decisions in risk management. The distribution of values (e.g. Bayesian posterior distributions) for some quantity (e.g. population risk of illness, economic gain or social benefit from consumption of stated quantities of a food item) would be linked to the utility for the different values of the quantity, defined outside the usual boundaries of scientific risk assessment. The expected utility would be obtained by integration of the utility function by the original quantity.

Conclusions

A primary aim in quantitative risk assessment is the explicit and accountable fusion of multiple sources of knowledge and evidence. Bayesian reasoning appears to provide a possible structure for handling many of the issues that arise, although the difficulties of obtaining an acceptable model, which balances the wish for a holistic, simple judgement, against the reductionist desire to represent the detailed underlying processes explicitly, should not be underestimated.

An initial aim should be to produce case-studies that use attractive software, are explicit and accountable in their assumptions, and allow sensitivity analyses to be carried out by experts in the relevant fields. Such case-studies should ideally develop concepts and methods that can be used in a wider range of applications.

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Software for manipulating Belief Networks,
http://www.stat.washington.edu/almond/belief.html — Details of all free and commercial software, plus reference list

When Decisions Count - Count on Hugin,
http://www.hugin.dk/ — Good page for background and good product

The Bugs Project,
http://www.mrc-bsu.cam.ac.uk/bugs — Software for Gibbs sampling in complex models. Freely available with manual and examples

First Bayes,
http://www.shef.ac.uk/~st1ao/1b.html — Free software for teaching Bayesian analysis, runs under Windows

Welcome to Palisade.com,
http://www.palisade.com/ — An add-on to spread sheet packages, allowing probability distributions to be placed over inputs to spreadsheets

A brief introduction to Graphical Models and Bayesian Networks,
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Probabilistic Analysis in Risk Assessment,
http://www.epa.gov/ORD/spc/2probana.htm

*As at December 1999

4.2 Risk assessment for *Clostridium botulinum* in food: Bayesian belief networks in microbial risk assessment

GC Barker, Institute of Food Research, Norwich Research Park, Norwich, UK

Probabilistic methods for food risk assessment enable a more efficient use of the available data, and offer a way to keep up with rapid changes in food products and associated problems for food safety. Bayesian methods are able to incorporate the complexity, uncertainty and interdependency of causal factors that characterise these problems.

With recent advances in mathematics, software and computer technology, Bayesian belief networks have become realistic tools for the evaluation of increasingly complex problems. Using probability as their currency, they are able to calculate and, with software such as Hugin*, portray graphically the joint distributions of many inter-related factors. An example of such a joint distribution is the concept of 'risk' which is a combination of a detriment (hazard) and a frequency, each of these being complex functions of many other interdependent factors.

A mathematical framework has been constructed for the representation of hazards and risks posed by microbial contamination of food, specifically those hazards that arise from *Clostridium botulinum* growth and toxin production. Botulism has been recognised as a serious foodborne illness for over a century and, more recently, has become the subject of increased concern due to changing processing and consumption patterns associated with novel foods. In this respect quantitative risk assessment (QRA) has an increasingly important role to play in ensuring the acceptability and reliability of the food chain.

The mathematical framework employs Bayesian belief networks. These networks combine a graphical representation (like a flow diagram) of the model domain (or subject) knowledge with a powerful rule, based on Bayes' theorem, for combining probabilities. Accumulated understanding and experience of a particular hazard domain are incorporated into the structure of the network, through the choice of numerical values for uncertain quantities and their dependencies. Modern algorithmic advances ensure that the probability rule (Bayes' theorem) can be applied very efficiently, so that extremely large domains that include many uncertain quantities can be updated with new information very rapidly. This scheme provides an interactive picture of a complex system of uncertain quantities in which each variable is represented by a probability distribution.

The operation of the belief network ensures that connected or 'dependent' distributions are consistently updated by information that relates to either or both variables. The consistent set of probability distributions contained within the whole network forms the basis for expressing pertinent quantities such as value, sensitivity and risk. The precise calculation of these quantities may depend on particular circumstances but, within the Bayesian belief network formalism, all calculations can be based on the consistent use of the same information set. In this respect it is clear that 'risk' is a compound quantity; it does not have a unique representation as a simple number and is not separable from other quantities such as costs and benefits.

Analysis of the hazards associated with foodborne botulism involves a belief network that includes components to represent contamination processes, thermal death kinetics for spores, germination and growth of cells, toxin production, operational control actions, and patterns of consumer behaviour. One of the most difficult tasks is estimating the number of spores of *C. botulinum* in food, since they often occur at concentrations too small to detect. Under favourable conditions spores germinate to cells which produce the potentially fatal botulinum toxin.

Mathematical functions to predict lagged exponential microbial growth can be incorporated in the Bayesian network. Thus the prior distribution of unknown values, such as spore concentration, are linked to and combined with experimental data, resulting in a posterior distribution of concentration, which can then form the prior distribution for the next part of the model. It is even possible to combine, without bias, the results from two different mathematical models predicting the same variable, for example distinct microbial growth kinetics.

* The Hugin software package (Hugin A/S Aalborg, Denmark) used for this modelling runs under Microsoft Windows and allows the user to set up a flow diagram like representation of all the factors relevant to a hazard domain with arrows indicating the direction of influence (as in Figure 4.1). Data are incorporated and each variable is represented by a probability distribution whose shape and spread change when inputs are varied in other factors.

Information inputs include laboratory microbiological data, predictive microbiological models, quality control criteria, health records, retail statistics and expert opinion. The Bayesian formalism handles this information diversity consistently and with minimal bias.

Quality control or value-of-information data play an important role in the Bayesian network. Such data are entered, for example in the form of a standard deviation for a distribution function, as an expression of variability or uncertainty. Higher variability (greater standard deviation) produces a wider, flatter probability distribution in the outcome variable, indicating the wider range of possible values. Information about the quality of the input data can determine whether an initial prediction or a new experimental result is dominant in the model output.

There is a need for greater transparency in the risk assessment process concerning ways in which input variables are weighted for their relative values, for example using a weight-of-evidence approach. It is possible, even with structured approaches, that these quality assessment factors become buried in the models. Even with a model-based approach it can be very difficult to explain quality-weighting, and this remains a challenge for improvements in transparency.

The botulism network indicates that large uncertainties in the analysis are associated with unknown levels of contamination and that the analysis is strongly sensitive to the decoupling of germination and growth responses. The underlying probabilistic framework supports and prioritises decisions and actions that minimise the chances and extent of detrimental events and maximise opportunities for awareness and control.

4.3 Risk assessment for vitamin B_6: A case study

Based on discussions by the workshop participants

The toxicity of vitamin B_6 was discussed in 1997 by the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT). An extract from a public statement issued by the COT, via the Department of Health, describing the background to the problem and the basis for the Committee's decisions is reproduced in Annex 1.

As described in the COT's statement, a Lowest-Observed-Adverse-Effect Level (LOAEL) of 50 mg/day was used to arrive at the maximum food supplement intake of 10 mg/day. This LOAEL was based on Dalton and Dalton's (1987) clinical observations of neurological symptoms in women receiving high doses of vitamin B_6 as a treatment for pre-menstrual syndrome. It was supported by the results of the Phillips *et al.*, 1978 study in dogs. The COT's decision was criticised because of (a) the questionable quality of the paper used to reach its decision, and (b) the uncertainty factors used to derive the maximum daily safe dose for humans from the animal data.

Criticism of the COT's maximum recommended daily level of vitamin B_6 intake as a food supplement of 10 mg/day came from various quarters and was linked, in part, to the current availability of food supplements containing more than this recommended level of vitamin B_6. Also, the Institute of Medicine of the US National Academy of Sciences had provided a pre-publication copy of a report recommending an estimate of 100 mg/day for the 'tolerable upper intake level', based on a No-Observed-Adverse-Effect Level (NOAEL) of 200 mg/day and an uncertainty factor of two. The data contained in the Dalton and Dalton paper had not been used for the US estimate nor had the time of exposure to the dose been taken into account.

There have, therefore, been substantial differences in scientific judgements associated with the setting of an acceptable level for vitamin B_6; the issue is thus a valuable example of the difficulties faced by those with the responsibility for making recommendations and decisions when the available database is limited.

As an exercise in identifying the factors pertinent to the risk assessment and how to deal with them, a Bayesian approach could be adopted. The initial objective of such an exercise would be to reproduce the reasoning used by the COT, by modelling the use of LOAELs and uncertainty factors. This would translate the uncertainty factors into variability factors at the different stages of the model, giving a better idea about the relationship between the uncertainty factors and the standard deviations in the data. Once the variability factors had been set in this way, they could be adjusted in 'what-if' analyses, and the sensitivity of the model to the various factors could be evaluated.

Figure 4.2 shows a very preliminary graphical representation of this issue as a Bayesian belief network, resulting in a distribution of probabilities, presented here on a $\log_{10}$ scale, for a NOAEL in humans. From this distribution the lower 95% confidence interval might be taken as the acceptable intake; on a $\log_{10}$ scale this would be equivalent to division of the derived NOAEL with mean probability by a safety factor of 100. An exercise of this nature is potentially very enlightening, in terms of both the process of constructing a Bayesian network and the process of arriving at a proposal for an acceptable level of intake of a food constituent. It is hoped that such approaches will be pursued.

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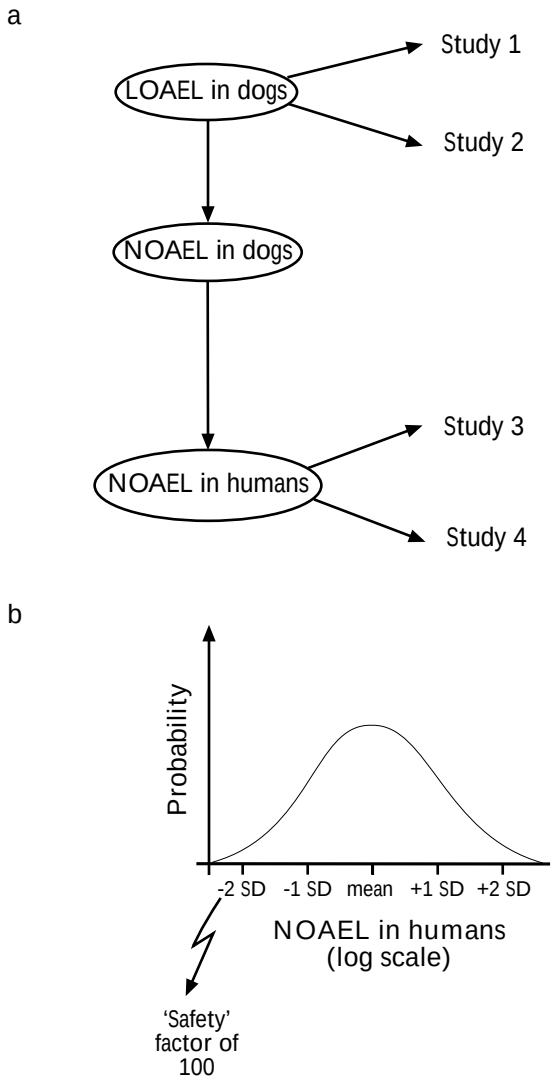
Figure 4.2 Modelling an assessment of vitamin B_6 safety in humans



Preliminary graphical representation of a Bayesian belief network proposed to model the data available and their use in estimating a maximum safe level of vitamin B_6 in humans by the NOAEL/safety factor approach. Arrows in (a) indicate the direction of probabilistic dependence and follow the way in which the network is naturally constructed; for example, the likely results observed in studies are influenced by the true values of LOAEL and NOAEL, while judgements about plausible values of NOAEL in humans would be influenced by knowledge of NOAEL in dogs. Existing estimates of between-dog and between-human variability, for example, may be used in quantifying the strengths of the links. The direction of 'learning' may be, by Bayes theorem, against the arrows; for example, evidence from studies propagates back to provide plausible values of LOAEL and NOAEL in dogs, which in turn add to other evidence to provide a final distribution over plausible values of NOAEL in humans. The distribution in (b) is a hypothetical output for NOAEL in humans.

5 General discussion

This section highlights some of the many factors that will influence the desirability and practicability of developing and introducing probabilistic approaches, and in particular Bayesian approaches, to food risk assessment. The discussion is structured around some specific questions as outlined below.

Approaches to food risk assessment

- Should a probabilistic approach to food risk assessment be adopted?
- How comparable are current risk assessment practices for chemicals and microbes in food?

Models

- What models are suitable for decision analysis?
- Can models be evaluated and validated?
- What data are required for probabilistic models?

Expert resources

- What skills are needed?
- Can expert opinion be better used?

5.1 Approaches to food risk assessment

5.1.1 A probabilistic approach

The introduction of any new approach to food risk assessment would not be expected to replace current methods, but to improve them by providing a useful, additional tool for decision-making. The debate is not so much about whether the approach used should be quantitative or not, since all methods used are quantitative, but whether a model-based approach should be used. Undertaking some worked examples of a probabilistic approach, preferably in parallel with current methods (including the contribution of expert committees, such as the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment; COT), would improve understanding of the workings and outcomes of the proposed new methods and help determine whether they would, in fact, confer any overall advantage (considering both cost and benefit) over current practice.

An example of such an approach is a three-year European Union (EU) collaboration to evaluate Bayesian belief networks in parallel with traditional methods in the assessment of hazards posed by spore-forming bacteria in vegetables. Both groups in the collaboration will have access to exactly the same data, so that the conclusions reached by each method can be compared. The complementarity of the two approaches is also being investigated.

Some of the perceived advantages of a probabilistic and specifically a Bayesian probabilistic approach to risk assessment can be summarised as follows.

- Variability and uncertainty in risk assessments can be expressed in a numerical form.
- Lack of knowledge as well as knowledge about aspects of a subject can be expressed.
- There is potential for enhanced transparency of decision-making.
- Conclusions can be updated easily when new data become available.

- A structure is provided for information (whether currently available or not) relating to the problem.
- With appropriate cautionary measures, available data, even if only indirectly relevant to the problem and of limited quality, can be used.
- Sensitivity analyses can be used to assess the relative importance of any aspect of the model for more effective resource allocation.
- Multiple dependent relationships can be processed.
- Safety analysis can be extended by evaluation of the risks involved in exceeding set safety levels — a potential asset to risk managers.
- Expert opinion can be incorporated in a structured and scientific way, especially where directly relevant data are lacking or unobtainable.
- Graphical representation can be used to communicate both the issue at hand and the outcome.

However, concerns have been expressed about the adoption of probabilistic approaches to risk assessment, some of which are listed below.

- As existing methods may be thought to work sufficiently well, they should not be changed.
- Both the general public and the food industry are perceived by some to be comfortable with current methods of decision-making and would not like to see changes.
- Non-mathematicians, whether members of expert committees or the general public, might not be able to understand or trust the statistical modelling methods.
- There are fears that expert opinion might be replaced by statistical models.
- Risk managers might not find a numerical range useful, as in practical terms it is sometimes thought to be simpler to work with a single number.
- Modelling methods might not be able to accommodate relationships, for example between exposures to a chemical and health effects, that are either not very well defined or are very complex.

In addition to the above, the main objection to the Bayesian paradigm as a specific type of probabilistic approach is its subjectivity. However, such subjectivity may reflect quite accurately the way in which scientific data are gathered and used. The statistical concepts could be considered more rational than more classical approaches, in that they do not depend on an assumption of infinite unbiased sampling, and are not restricted to comparison with a single null hypothesis. In addition, a Bayesian prior distribution can be chosen in an objective way and the effect it has on the result can be tested by repeating the analysis with a different prior distribution.

Whether or not a Bayesian or any other probabilistic approach should be used would depend on its acceptability and transparency to all users and this should be tested.

5.1.2 Risk assessment practices for chemicals and microbes in food

Although it is held that risk assessment methods for food chemicals are currently much more advanced than for food microbial safety, it is notable that two examples are presented in this report (Sections 3.2 and 4.2) of probabilistic models that address microbial food safety in an integrated manner not often seen in chemical risk assessment.

In both chemical and microbial fields it is a chemical (in the case of food microbes, the chemical toxin released by the pathogenic organisms) that is usually the immediate cause of illness. It could be argued that the only difference in possible impact between ingestion of a pathogen and a chemical is infection, in which there is competition for survival among different microorganisms. Some similarities and differences in factors influencing chemical and microbial food risk assessment are summarised in Annex 2.

Some of the issues encountered in the two fields are, however, different in nature. In food microbiology there is virtually no ‘zero risk’ option, as is assumed in food chemical risk assessment. Microbial risk assessments are often carried out to estimate the costs of reducing risks to health, using an estimation of a range of probabilities of illness of varying severity. This aspect is lacking in chemical risk assessment, which uses a combination of No-Observed-Adverse-Effect Level (NOAEL) in animals and uncertainty factors to determine an acceptable level, and does not include any estimation of the costs of exceeding that level.

Another major difference is the extent to which health effects can be traced back to a specific cause. It is relatively easy to achieve this for overt morbidity that has microbial pathogenic causes, but in many cases it is nearly impossible to link effects with exposures to food chemicals. This is mainly due to the multitude of interactions possible, to the lack of a serotyping equivalent and to a lag time between exposure and health effects, which is typical of chemical exposures. Countering this distinction, there is a growing recognition that many of the possible health effects of microbial ingestion are not investigated because they may be subclinical or chronic in nature, or both, and may not be immediately distinguishable from illness due to other causes.

Quantitative approaches to food chemical risk assessment such as the linearized multistage model, or physiologically-based pharmacokinetic or biologically-based dose–response techniques could be seen to be analogous to the microbial growth models used in food microbial risk assessments. Both approaches attempt to simulate biological processes that are difficult to measure, and both could be used within a probabilistic framework, such as classical Monte Carlo simulation or Bayesian networks. The statistical framework would be able to add estimates of variability and uncertainty to the deterministic estimates of dose and risk, whether from microbes or chemicals. Furthermore, such a framework could link information from mathematical biological models with, for example, exposure data, as well as with encoded expert opinion; probability distributions would be attached to each of these.

5.2 Models

5.2.1 Models for decision analysis

Various models are available to provide a statistical means of handling the different types of data available for risk assessment purposes. These could also be viewed as inference systems to assist decision-making.

Within the category of so-called 'expert systems' there are two main subcategories of models. The first, based on event trees (including fault trees) is rule-based, with mutually exclusive alternatives at the decision nodes. Expert systems commonly used for supporting decisions in technology have often been based on the event-tree model, but they are susceptible to changes in the rules, and can fail if a situation does not fit into the categories offered. The other main subcategory can be described as 'domain models' ('domain' referring to the scope of subject-information being addressed by the model), or 'normative expert systems'. These include the probabilistic models discussed in this report, and are more robust than the former category because they can accommodate a continuum of degrees of certainty about any option within the structure of the model. Furthermore, it is possible to update retrospectively decisions made earlier on in a normative expert system, and to propagate the effects throughout the system. This is not possible with fault-tree or event-tree models.

The more robust models, of which the Bayesian belief network is a prime example, are better suited to problems as complex and uncertain as food risk assessment.

5.2.2 Evaluation and validation of models

Evaluation and validation of models is, in theory, possible by experimentally measuring intermediate stages of the process being modelled and, ideally, also by comparing actual final outcomes with the model prediction. Although for some issues epidemiological evaluation of time trends of morbidity and mortality can be used to evaluate predictions of effects and acceptability of standards, validation is in general easier for microbial than chemical risk assessment. This is because in the latter case the outcome of concern is often cancer, for which the mechanism is not fully elucidated but is suspected to be multifactorial. Also, interactions among contributing factors are likely, and there is also usually a lag period between exposure and the development of health effects.

Although it is claimed that the current model for food chemical risk assessment is sufficient to protect against cancer-causing agents in food, this is very difficult to assess scientifically because of the difficulties in establishing causality.

Testing models for over-conservatism is one of the most difficult and limiting factors in current methods for setting ADIs for food chemicals.

Evaluation of the transparency, credibility and ease of use of the models is important and should be part of an overall assessment of efficacy. There are currently concerns about these aspects of food risk assessment.

New approaches to food risk assessment should be evaluated not only for their ability to determine risk accurately but also for their usefulness to those responsible for making decisions and to the public.

5.2.3 Data for models

Probabilistic models require extensive datasets. Therefore one strength of Bayesian belief networks is that they can make use of information that might not pertain exactly to the issue at hand; the information can be weighted according to relevance or quality, and sensitivity analysis can be used to assess the priority to be given to collecting more directly relevant data. Thus it may be possible to use existing data, even if not directly or immediately relevant to the problem in hand, rather than having to generate new data.

One of the types of information likely to be found lacking, even when using a Bayesian belief network, is the nature of causal relationships, dependencies and interactions among factors thought to contribute to cancer incidence. A Bayesian link simply describes a dependency of one probability on another (or a set of others); indeed one of the significant advantages of Bayesian networks is their ability to take account of information dependencies. However, to achieve a useful outcome to the assessment it is still necessary to increase knowledge about causation.

In setting up a domain model a graphical model (like a flow-diagram) is drawn up to represent the problem, the various intermediate stages and the likely influencing factors. This mapping-out of the skeleton of the problem includes opportunities to express lack of knowledge as well as knowledge about aspects of the issue, although the former remains more difficult to model than the latter. The process of making a graphical representation of the problem is extremely useful and enlightening, and requires close collaboration between the modelling and domain (or subject) experts.

The graphical representation of questions and arguments also facilitates communication. The construction of graphical representations when forming a model helps to define and refine questions, and graphical representation, as probability distributions, can facilitate the communication and understanding of issues such as variability and uncertainty.

The next step is to examine all available data and literature pertaining, even if only indirectly, to the question. This step would commonly include some transformations of data or statistical processing, as well as weighting for quality or uncertainty. For the gaps that remain, a structured interview system may be used to elicit expert opinion on the most likely range of values, thus providing an accountable and formal way of using expert opinion where data are lacking.

Thus the process of assembling information into a Bayesian model is a multi-stage one, using data and information of many types. It is important to note that, even though these models provide a structure into which the available data can be incorporated and also use expert opinion where there are no data, this does not mean that the models are a substitute for experimental data. Scientific experimentation and analysis should continue simultaneously, and appropriate additional studies can be identified by the sensitivity analyses that are part of probabilistic risk assessment.

Nonetheless, one of the greatest advantages of Bayesian models is that they can be used to facilitate decision analysis despite inadequate data; this is especially important as some types of data are not likely to be readily collected at all.

Bayesian models have been used extensively to analyse risks when the available data have been totally inadequate for use in the usual classical or frequentist statistical approaches to risk assessment. Probabilities of nuclear accidents or of earthquakes cannot be assessed using classical approaches because such incidents do not occur often enough to sample and draw global conclusions. In these situations, in the absence of objective data, the subjectivity for which Bayesian methods are criticised becomes an important asset.

5.3 Expert resources

5.3.1 Major skills requirements

The initial setting up of suitable probabilistic models to be used in risk assessment, either in the chemical or in the microbiological field, requires a sophisticated level of skill and expertise, presently scarce commodities, on the part of the modeller. However, once models have been created, piloted and adjusted, it should be possible to fashion both the models and the software used into a generic format, which would be usable by anyone with some training.

A very valuable feature of such software would be a hypertext function, which would accommodate the textual justification of the scientific basis for each part of the model and would therefore greatly foster transparency to anyone using it. Thus toxicological or microbial experts, members of expert committees and risk managers should be able to run the software and use the models to test

scenarios with varying inputs, while also having access to the reasoning behind the data used.

5.3.2 Use of expert opinion

The communication of decisions taken by expert committees and the transparency of the processes used by such committees need to be improved. A structured model of the path taken in making decisions with regulatory implications would not only foster transparency but also might allow a more efficient use of expert opinion. Agreed rules should be established to guide decisions about the relative or absolute quality of different sets of data available to expert committees.

There are several methods for eliciting expert opinion; these can be divided roughly into two classes — informal and formal. Expert opinion is often sought by individual personal interviews and various methods exist for the numerical interpretation of opinions, which can be expressed as a single number or as a probability distribution. Variations in the methods include whether or not the experts are allowed to revise their opinions after those of the rest of the group are revealed, and how to use the results. The methods used for a specific issue depend on the purpose for which they are required, for example whether a consensus view or a range of individual opinions with an expression of their individual variability is sought.

One advantage of structured modelling of expert opinion is that less vocal experts could be given a more egalitarian voice. In contrast, a disadvantage might be that individual experts on committees would not welcome the possibility of a range of opinions being attributed to them. One of the undisputed benefits would be the potential for the modelling of lack of knowledge (individual or collective) on any parts of the problem; this is arguably as important a part of the process as the modelling of knowledge.

5.4 Research recommendations

A probabilistic approach to some food risk assessments should be undertaken in parallel with more conventional methods (including the use of expert committees) to determine whether such new approaches confer any advantage over current practice.

Basic research on causal mechanisms of food-related health problems should continue, since more knowledge about causal links will be useful to the construction of probabilistic models.

6 Conclusions

There are many similarities between the issues to be addressed in the risk assessment of chemicals and microbes in food and, although the technical details differ in some respects between the two types of problem, much could be gained by experts in each field working together.

While a probabilistic approach to risk assessment for microbes in food seems likely to be beneficial, there are concerns that such new approaches might not add anything except unwanted complexity to current methods for food chemical risk assessment. Nonetheless a probabilistic modelling approach has the potential to help in some key areas.

Potential benefits include the ability to:

- combine evidence from many different types of source;
- improve transparency and reproducibility;
- update decisions when new data became available and perform 'what-if' analyses; and
- express uncertainty and variability in risk assessments.

Most of these potential benefits of a probabilistic modelling approach are strongly related to, if not explicitly stated in, the 'guiding principles' for the operation of the Food Standards Agency.

Despite the potential advantages, the mathematical and statistical complexity of probabilistic methods (including Bayesian approaches) for risk assessment could be a barrier to acceptance; this is one of the main reservations of both lay people and scientific experts about the introduction of such an approach. However, the graphical representation of Bayesian approaches using facilities of modern software can assist greatly and, after the initial highly skilled work of setting it up has been completed, a model could be adapted to a generic format, usable by anyone with a little training. Actual or simulated data inputs could be changed easily using the computerised model to assess the impact on the results. Full documentation of all inputs is an essential part of the process and of increasing transparency.

Thus, in principle, a probabilistic risk assessment model could be used by scientists, experts on Government committees, risk managers and communicators, as a tool to aid decision-making in risk assessment. The additional potential benefits of Bayesian methods over classical probabilistic methods such as Monte Carlo simulation are the ability of Bayesian models to deal with interdependency of co-factors and with incomplete data, subjective opinion and bi-directional updating of information.

The practicalities and the potential for a Bayesian probabilistic approach to assist in food risk assessment should, however, be properly assessed, as this is still a developing field. The Bayesian modelling approach should be tested on a number of risk assessment issues in parallel with current methods so that a full evaluation of their relative usefulness and efficiency can be made. This would be a collaborative task for those with specialised skills in the required statistical modelling techniques in the first instance, together with experts in the subject at issue.

Annexes

Annex I: Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment: Statement on vitamin B_6 (pyridoxine) toxicity*

Introduction

1. We were asked to review the safety of vitamin B_6, following concerns expressed about the potential toxicity of high dose dietary supplements. One vitamin B_6 supplement was highlighted since a single dose contained 100 mg - more than 50 times the amount required to maintain normal bodily function. Dietary supplements, classified as foods, are freely available to the general public and are consumed by individuals who wish to supplement their diet. We note that vitamin B_6 products with Marketing Authorizations (i.e. licensed as medicines) are also freely available under the General Sales List Order to individuals for the self-treatment of specific medical conditions. Other licensed vitamin B_6 products, which contain higher doses, are available from pharmacies or on prescription from General Practitioners.

2. The generic term vitamin B_6 includes six vitamers: the alcohol pyridoxine, the aldehyde pyridoxal, the amine pyridoxamine and their 5'-phosphates. At one time pyridoxine was used as a generic descriptor but since 1973, IUPAC-IUB and IUNS nomenclature has been used. This nomenclature is shown below. As can been seen, the vitamers are interconvertible.

Pyridoxine	↔	Pyridoxine phosphate
		↓
Pyridoxal	↔	Pyridoxal phosphate
		↑↓
Pyridoxamine	↔	Pyridoxamine phosphate

3. Vitamin B_6 is essential for good health and plays a major role in amino acid metabolism. Protein intake affects vitamin B_6 requirements. For example, adults maintained on vitamin B_6-deficient diets develop abnormalities in tryptophan and methionine metabolism faster and their blood vitamin B_6 levels fall faster when they have a diet high in protein (approximately 80–160 g/day) in comparison with low protein intakes (30–50 g/day). During repletion of vitamin B_6-deficient subjects, tryptophan and methionine metabolism and blood vitamin B_6 levels are returned to normal faster at low levels of protein intake. The EC's Scientific Committee for Food and the UK Government's Committee on Medical Aspects of Food Policy have both reported that 15 µg vitamin B_6 per gram protein per day is sufficient for the needs of healthy people. This approximates to a daily amount of between 1.1 mg and 1.5 mg for those with an average protein intake. Results of the National Food Survey (Ministry of Agriculture, Fisheries and Food, 1995) show that the average amount of vitamin B_6 in the diet of the population is sufficient to meet the estimated requirements.

4. Pyridoxal phosphate, one of the vitamers, is a coenzyme in transamination, deamination, decarboxylation and trans-sulphuration reactions within the body. Individuals with deficiencies in some enzymes such as cystathionine synthetase, cystathionase, peroxisomal glyoxylate amino transferase and glutamine decarboxylase, may show improvement following vitamin B_6 administration. For example, homocystinuria, an autosomal recessive aminoacidopathy resulting from a defect in cystathionine β-synthase, is characterised by excessive homocysteine in plasma and urine.

* From http://www.doh.gov.uk/cot/b6.htm, as of December 1999

Plasma methionine levels are elevated and patients develop ectopia lentis, mental retardation, and hepatomegaly as well as deformities in the cardiovascular system and skeleton. Because of the many metabolic differences in individuals with this and other similar hereditary diseases, it is not appropriate to use the data from case studies of such patients receiving vitamin B_6 medication when assessing the safety of vitamin B_6 supplements sold as foods.

Human toxicity data

5. Severe sensory peripheral neuropathy in individuals following ingestion of large doses of vitamin B_6 was first described in the early 1980s. Symptoms of toxicity include hyperaesthesia, paraesthesia, muscle weakness, numbness and loss of proprioception and vibration sense. Electrophysiological measurements and examination of nervous tissue by biopsy in some individuals have demonstrated nerve damage. The lowest dose reported to have been followed by symptoms consistent with sensory nerve damage is 50 mg per day (Dalton K, Dalton MJT, Acta Neurol Scand 1987; 76: 8–11). Signs of toxicity were observed after an average of 35 months. We are aware that the study by Dalton and Dalton has some methodological deficiencies but, nevertheless, the symptoms reported by the patients are consistent with the well described clinical syndrome of peripheral sensory neuropathy. The observations of Dalton and Dalton are also consistent with the reported symptoms of patients in other studies undertaken at higher doses which contained objective measures as well as subjective observations (e.g. Berger AR, Schaumberg HH, Schroder C *et al.*, Neurology 1992; 42: 1367–1370, Albin RL, Albers JW, Greenberg HS *et al.*, Neurology 1987; 37: 1729–1732, Albin RL, Albers JW, Neurology 1990; 40: 1319, Waterston JA, Gilligan BS, 1987; 146: 640–642). In most instances, the clinical signs of toxicity were reversible once ingestion of high doses of vitamin B_6 had ceased. However, in some instances where the dose of this vitamin was especially high, signs of damage remained. The clinical studies suggested an inverse relationship between the daily dosage and the time required before symptoms were detected. We consider that the small number of individuals involved and/or the short duration of administration may explain the absence of signs of sensory peripheral neuropathy in some studies. As stated above in paragraph 4, we consider that studies of individuals with hereditary diseases such as homocystinuria, are inappropriate in the assessment of vitamin B_6 toxicity from dietary supplements.

Animal toxicity data

6. Several studies have shown that administration of high doses of vitamin B_6 to different animal species, including the rat and dog, resulted in ataxia and muscle weakness. Neuropathological damage, including degeneration of the dorsal root ganglia, axonopathy and demyelination have been observed. The lowest reported adverse effect level in animals is 50 mg/kg bodyweight/day in the dog after approximately 16 weeks administration (Phillips *et al.*, Toxicol Appl Pharmacol 1978; 44: 323). We are aware of a report of a no observed adverse effect level in the dog of 20 mg/kg bodyweight/day for 80 days (Unna. J. Exp Ther 1940; 70: 400), but, bearing in mind the age of the study and without further experimental detail, we have not used this figure in our consideration. With a safety factor of 300 (10 for the use of animal data, 10 for inter-individual human variation, 3 for the use of a lowest observed adverse effect level) and assuming that an individual weighs 60 kg, extrapolation from the lowest observed adverse effect level in dogs (50 mg/kg bw/day) would give a maximum daily safe dose for humans of 10 mg.

Conclusions

7. There is no doubt that consumption of vitamin B_6 by humans in excess of the amount required to maintain bodily function can result in symptoms which are consistent with sensory peripheral neuropathy. Furthermore, the animal toxicity data are consistent with the study of Dalton and Dalton (1987) which reported adverse effects at daily intakes of 50 mg in humans. Electrophysiological measurement and examination of nerve tissue confirm neuropathological changes. With the exception of the instances where especially high doses (in the order of grams) of this vitamin were ingested by some individuals, the signs of toxicity are reversible after cessation of ingestion. The lowest dose reported to have adverse effects in humans is 50 mg per day; although there are methodological deficiencies in the study showing effects at this level of intake, we consider it would be unwise to ignore this evidence in the light of other supporting human and animal data.

Recommendation

8. Allowing for a margin of safety between the lowest observed adverse effect level in humans and bearing in mind the supporting animal toxicity data, we *recommend* that the maximum daily intake of vitamin B_6 from dietary supplements should be 10 mg per day. *June 1997*

Annex II: Factors influencing chemical and microbial risk assessment in food: Similarities and differences*

Features of:	Chemical risk	Microbial risk
Agent (organism/molecule)		
Latency of illness	✔	✔
Low dose can cause a severe effect	✔	✔
Possibility of accumulation in host	✔	
Persistence in an individual & continued excretion leads to continued risk of spread		✔
Organism self-replicating		✔
DNA transfer between organisms		✔
Transmissibility — allows secondary and tertiary spread		✔
Food		
Fat content, metal content, acidity, background flora, preservatives, temperature, irradiation, physical state, buffering, storage history can each influence infectivity/effect	(✔)	✔
Host		
Asymptomatic 'carriers'		✔
Genetic factors influence susceptibility	✔	✔
Physiological status of host/sub-population susceptibility	✔	✔
Immunological/ detoxification/ anti-oxidant status	✔	✔
Population characteristics - immunity, social behaviour		✔
Variety of exposure routes; route can influence effect	✔	✔
Biological barriers - may be broken	✔	✔
Previous exposure may influence current response	✔	✔
Possibility of measuring infected status of host		✔
Environment		
Persistence of agent in environment	✔	✔
Breakdown in public health systems due to natural/man-made disasters (e.g. flooding)	✔	✔
Intervention strategies, e.g. vaccination, pasteurisation		✔
Conditions allowing survival		✔
Alternative host species may be available		✔
Interactions and risk assessment		
Interaction of organism with host and environment with dynamic evolution of virulence		✔
Experimental exposure (for dose–response data) in humans problematic	✔	✔
Animal-to-human model equivalences to be made with caution	✔	✔
Need to combine data of different types	✔	✔
Extrapolation problems from high to low doses	✔	✔
Question whether a single organism / molecule can have an effect ('critical dose')	✔	✔
Dose–response: single-hit model possible	✔	✔
Dose–response: threshold model possible	✔	✔

* Sources: (Hathaway, 1993; Notermans, 1995; Advisory Committee on Dangerous Pathogens, 1996)

List of workshop participants

Dr Jonathan Back
Ministry of Agriculture, Fisheries and Food, Ergon House,
c/o Nobel House, 17 Smith Square, London SW1P 3JR
(Speaker)

Dr Gary Barker
Institute of Food Research, Norwich Research Park, Colney,
Norwich NR4 7UA *(Speaker)*

Dr Sue Barlow
8 Harrington Road, Brighton, East Sussex BN1 6RE *(Speaker)*

Dr Diane Benford
School of Biological Sciences, University of Surrey, Guildford,
Surrey GU2 5XH

Dr Martyn Brown
Microbiology Department, Unilever Research, Colworth House,
Sharnbrook, Bedford MK44 1LQ

Mr Michael Cassin
81 Devonshire Mews, Cambridge CB1 2BB *(Rapporteur)*

Dr Paul Cook
Department of Health, Skipton House, Elephant and Castle,
London SE1 6LW

Dr Raquel Duarte-Davidson[a]
MRC Institute for Environment and Health, 94 Regent Road,
Leicester LE1 7DD *(Rapporteur)*

Dr David Gompertz
17 Oakmere Lane, Potters Bar, Herts EN6 5LS

Dr Paul Illing[b]
MRC Institute for Environment and Health, 94 Regent Road,
Leicester LE1 7DD *(Rapporteur)*

Dr Louise Kelly
Risk Research Department, Veterinary Laboratories Agency,
New Haw, Addlestone, Surrey KT15 3NB *(Rapporteur)*

Dr Anna Lammerding
Food Safety Risk Assessment Unit, Health Protection Branch,
110 Stone Road West, Guelph, Ontario Canada N1G 3W4
(Speaker)

Dr Len Levy
MRC Institute for Environment and Health, 94 Regent Road,
Leicester LE1 7DD *(Co-Chairman)*

Dr David Lovell
BIBRA International, Woodmansterne Road, Carshalton,
Surrey SM5 4DS *(Speaker)*

Dr Nafees Meah
Ministry of Agriculture, Fisheries and Food, Ergon House
c/o Nobel House, 17 Smith Square, London SW1P 3JR
(Speaker)

Dr Gill Price[c]
MRC Institute for Environment and Health, 94 Regent Road,
Leicester LE1 7DD *(Rapporteur)*

Mr Steve Pugh[d]
Ministry of Agriculture, Fisheries and Food,
St. Christopher House, Southwark Street, London SE1 0UD

Dr Lesley Rushton
MRC Institute for Environment and Health, 94 Regent Road,
Leicester LE1 7DD *(Rapporteur)*

Dr David Shuker
MRC Toxicology Unit, Hodgkin Building,
University of Leicester, Lancaster Road, Leicester LE1 9HN
(Co-Chairman)

Dr Andy Smith
MRC Toxicology Unit, Hodgkin Building,
University of Leicester, Lancaster Road, Leicester LE1 9HN
(Speaker)

Dr David Spiegelhalter
MRC Biostatistics Unit, Institute of Public Health,
University Forvie Site, Robinson Way, Cambridge CB2 2SR
(Speaker)

Dr Andrew Wadge
Department of Health, Skipton House, Elephant and Castle,
London SE1 6LW

Dr Jan Whitby[e]
Ministry of Agriculture, Fisheries and Food,
St. Christopher House, Southwark Street, London SE1 0UD

[a] Now at Environment Agency, Steel House, 11 Tothill Street, London SW1H 9NF

[b] Now at Centre for Occupational Health, Medical School, University of Manchester, Stopford Building, Manchester M13 9PT

[c] Now at 76 Histon Road, Cottenham, Cambridge CB4 8UD

[d] Now at Joint Food Safety and Standards Group, Skipton House, Elephant and Castle, London SE1 6LW

[e] Now at Wellcome Trust, The Wellcome Building, 183 Euston Road, London NW1 2BE

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Air Pollution and Respiratory Disease: UK Research Priorities	Report R2 (1994)
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Special reports

Understanding Asthma (1995)

Health Effects of Ozone and Nitrogen Dioxide in an Integrated Assessment of Air Pollution (1997)

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Risk Assessment and Toxicology Steering Committee reports

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For further details please contact:
MRC Institute for Environment and Health, University of Leicester, 94 Regent Road, Leicester LE1 7DD, UK
Phone +44 (0)116 223 1600; Fax +44 (0)116 223 1601; E-mail ieh@le.ac.uk; Web site http://www.le.ac.uk/ieh/