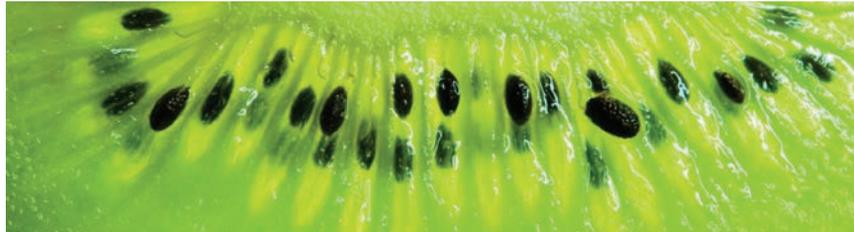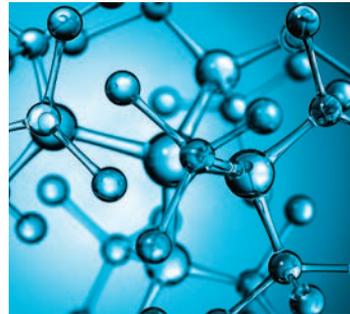# 5

Assessing food-related
health risks

5   Assessing food-related health risks

5.1   Risk assessment in a food context – overview and general principles

Risk assessment involves a process of identifying, analysing and characterising food-related health risks. Each risk assessment is done on a case-by-case basis, using the best available scientific evidence to decide whether an identified food-related hazard might pose any public health and safety issues. Risk managers use the outcomes of risk assessments to formulate responses to food health and safety concerns.

Risk assessments aim to estimate the likelihood and severity of an adverse health effect occurring from exposure to a hazard. They can examine substances deliberately added to food (e.g. food additives, processing aids, agricultural or veterinary chemicals), substances that occur inadvertently in food (e.g. environmental contaminants, naturally-occurring toxins or pathogenic microorganisms), novel foods, nutritive substances and the impact of new technologies. In this context, risk is a function of both the hazard and the level of exposure to that hazard. A food risk assessment therefore consists of an assessment of the hazard and an assessment of exposure which together enable characterisation of the risk.

The above model can be applied to assessing potential risks resulting from exposure to chemicals, microbiological agents and nutrients. However, there are some specific features of microorganisms and nutrients that make risk assessment of these substances different from that of the general class of chemicals. For example, microbiological risk assessments identify the likelihood of the microbe's association with food and the severity of the consequences of its presence, such as gastroenteritis, long-term illness or death. Identifying and describing microbiological hazards is complicated by the broad range of factors that may influence the associated risk of an adverse effect, including the intrinsic variability of the pathogen and host related factors that influence pathogenicity.

The model can also be applied to assessing whole foods. The first step in assessing potential risks from whole foods that are complex mixtures of constituents [e.g. foods derived from genetically modified (GM) crops, foods that have undergone irradiation or whole novel foods] is to compare the food to the conventional counterpart food with a history of safe use as the benchmark—a process termed a safety assessment. Any identified hazards are further characterised to determine their effect on the safety of the food[8].

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8   FSANZ (2007) *Safety Assessment of Genetically Modified Foods – Guidance Document.*
    http://www.foodstandards.gov.au/consumer/gmfood/safety/documents/GM%20FINAL%20Sept%2007L%20_2_.pdf

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The risk assessment should address the food health and safety issue and questions developed by the risk managers in consultation with the risk assessors (see Section 6.2.1). The scope of the assessment will be defined by these parameters.

The risk assessment process is often iterative. Risk assessment outputs are communicated to risk managers to inform the development and selection of appropriate risk management options. The risk characterisation step may need to be repeated numerous times for each proposed risk management scenario. This may apply particularly when there is the potential for the proposed risk management strategies to precipitate changes in consumer behaviour.

Scientific evidence used in a risk assessment may include unpublished reports in addition to publicly available studies such as scientific journal articles. Irrespective of the source, in all cases, FSANZ uses the best available scientific evidence and exercises professional judgement about the quality and relevance of the data and information, including that obtained from peer reviewed literature.
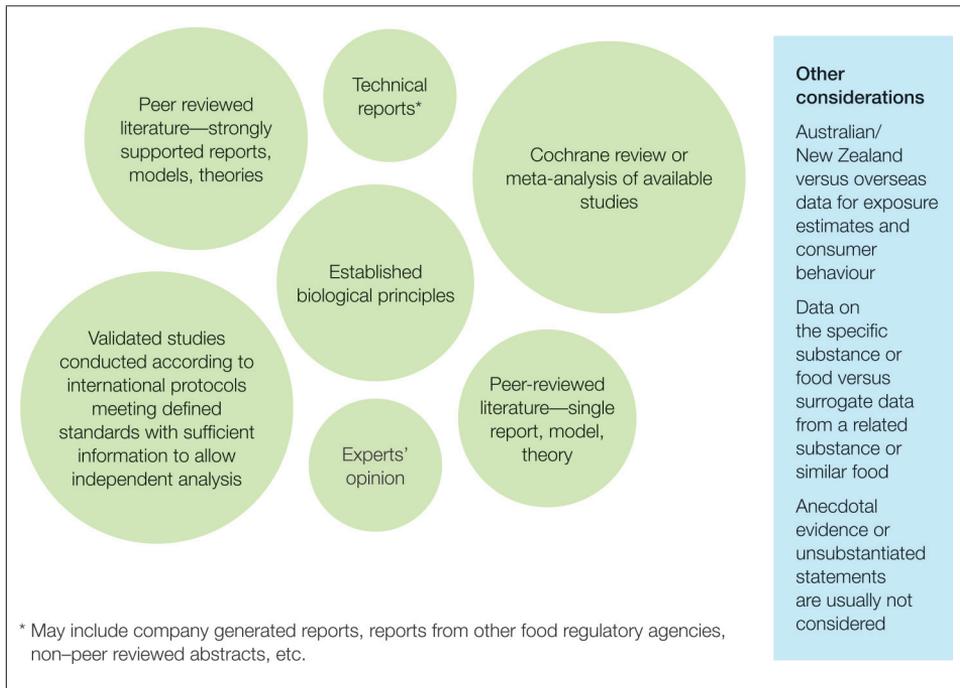
In assessing the quality of individual studies, including epidemiological studies, FSANZ will typically assess various elements of the study design and method. These might include: the purpose of the study; appropriateness of the study design for the purpose; appropriateness of the instruments used to measure the outcome variables of interest; the duration of the study; and the appropriateness of the statistical analyses undertaken. This is not an exhaustive list but is indicative of study parameters that must be considered.

While grading of the evidence is more traditionally applied when evaluating evidence from epidemiological studies, there are increasing efforts to adapt this approach for other types of studies e.g. toxicological studies. In general, studies designed and conducted in accordance with the principles and intent of good laboratory practice (GLP) are accorded a higher weighting as there is the expectation that these studies have been conducted with good quality control.

An indication of the relative weighting that FSANZ may give to different sources of evidence is illustrated in Figure 2, using circles of differing size.

Figure 2. Different sources of evidence used by FSANZ and relative weighting given

Peer reviewed literature—strongly supported reports, models, theories

Technical reports*

Cochrane review or meta-analysis of available studies

Established biological principles

Validated studies conducted according to international protocols meeting defined standards with sufficient information to allow independent analysis

Experts' opinion

Peer-reviewed literature—single report, model, theory

Other considerations

Australian/ New Zealand versus overseas data for exposure estimates and consumer behaviour

Data on the specific substance or food versus surrogate data from a related substance or similar food

Anecdotal evidence or unsubstantiated statements are usually not considered

* May include company generated reports, reports from other food regulatory agencies, non–peer reviewed abstracts, etc.

Drawing a conclusion about the level of risk using the available scientific evidence requires both scientific judgement and reference to any agreed practices on addressing uncertainty imposed by limited or incomplete information. Examples include practices such as (i) the use of safety (or uncertainty) factors to account for species differences and human variability; and (ii) the use of 90th or 95th percentile dietary exposure levels to represent high level consumers.

Peer review is an important quality control mechanism used by FSANZ to maintain the scientific integrity of its regulatory decisions (see the *FSANZ Science Strategy 2010–2015*[9]). Each risk assessment prepared by FSANZ is internally peer reviewed to ensure conclusions are scientifically robust. In addition, stakeholders have the opportunity to comment on risk assessments via a public consultation process. For more scientifically complex or contentious risk assessments, advice may be sought from experts in the preparation of the assessment and/or an external peer review may also be sought from national or international experts.

9   The intention of the *FSANZ Science Strategy 2010–2015* is to facilitate the identification of strategies that lead to continuous improvement in FSANZ's food regulatory science.
FSANZ (2010) *FSANZ Science Strategy 2010–2015*.
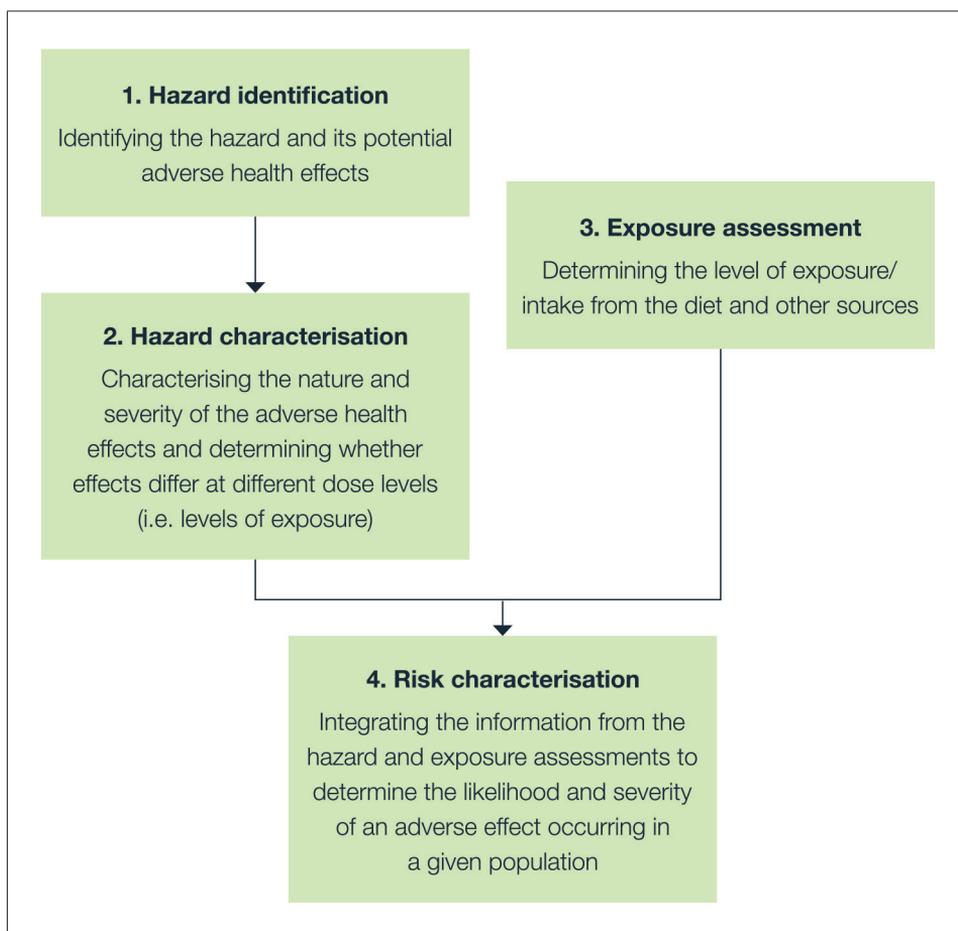http://www.foodstandards.gov.au/science/strategy/Pages/default.aspx

Collectively, this peer review process ensures that the scientific basis of a risk assessment is transparent, robust and benchmarked against international best practice risk assessment methodologies.

5.2   Steps in risk assessment

The risk assessment process used by FSANZ follows the Codex framework (see Section 4.2) and involves four key steps: hazard identification and hazard characterisation (together called hazard assessment, when considering chemical entities), exposure assessment and risk characterisation.

The four key steps of risk assessment are shown in Figure 3 and described in more detail below.

Figure 3. The four key steps in risk assessment

1. Hazard identification

Identifying the hazard and its potential adverse health effects

3. Exposure assessment

Determining the level of exposure/ intake from the diet and other sources

2. Hazard characterisation

Characterising the nature and severity of the adverse health effects and determining whether effects differ at different dose levels (i.e. levels of exposure)

4. Risk characterisation

Integrating the information from the hazard and exposure assessments to determine the likelihood and severity of an adverse effect occurring in a given population

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5.2.1   Hazard identification

Hazard identification seeks to clearly describe the hazard being assessed and to identify potential adverse health effects that could occur as a result of exposure to the chemical (food additive, contaminant etc.), nutrient, other food component or microorganism in food.

Inadequate intake of essential nutrients, by definition, leads to adverse effects whereas intake in the range that covers human requirements provides a health benefit. Some, but not all, essential nutrients also have adverse effects when intake is excessive. The hazard identification process for nutrients therefore requires consideration of the health effects at low, moderate and high intakes. Other nutritive substances that are not essential nutrients may also be assessed using this approach. These are discussed separately (see Section 5.3.4).

Hazard identification involves examining the available scientific data on the health effects of the chemical, nutrient, other food component or microorganism, specifically, relevant toxicological, microbiological, physiological, epidemiological or other technical information. If possible, the biological mechanism by which the adverse health effect occurs is also described.

Chemicals

For non-nutrient chemicals (food additives, processing aids, contaminants, agricultural and veterinary chemicals and active novel constituents), hazard identification involves examining their characteristics (including physical and chemical properties and method of manufacture and composition). Toxicity studies (in laboratory animals, for example) and relevant human studies, if available, are also considered to determine adverse health effects.

Laboratory animal studies provide information on the absorption, distribution, metabolism and excretion pathway of the chemical, possible adverse effects following a single exposure (acute toxicity) and adverse effects (e.g. cancer) following long-term exposure (chronic toxicity). In assessing any adverse effects observed in laboratory animals, consideration is always given to their relevance for humans. Relevant human studies may include volunteer studies, occupational or accidental exposure studies and epidemiology studies. Adverse effects or poisoning case reports for humans may also be available.

In the case of whole novel foods, if an initial comparative safety assessment identifies a potential hazard, then the potential toxicity of the hazard will be investigated. In addition to traditional toxicity studies or observational data in humans, FSANZ also considers the composition of the material (the types and concentrations of substances that consumers would ordinarily be exposed to in the diet), the manufacturing process (in terms of the potential to concentrate any deleterious substances) and any history of safe consumption of the equivalent material outside of Australia and New Zealand.

Nutrients

Nutrients are food chemicals required for human health that must be supplied in the diet because the body cannot manufacture them or can only manufacture insufficient quantities. The adverse effects that result from consuming too little of an essential nutrient over a prolonged period of time are well characterised. Some, but not all nutrients also have adverse effects when intake is excessive (usually over a long time frame). Therefore for nutrients, hazard identification primarily involves an examination of data from human studies, particularly those that involve the target populations, at inadequate or excessive levels of intake. A wide range of data may be examined including epidemiological, clinical, and other studies relating to physiological and biochemical effects and response.

Microbiological agents

Hazard identification of microbiological agents involves reviewing microbiological, clinical and surveillance data, as well as epidemiological information. Scientific information is obtained on the microorganism, its preferred growth conditions, and factors specific to the food and how it is produced (e.g. moisture content, cooking) which may influence the organism's growth, survival or death. Surveillance and epidemiological data may assist in identifying the foods most commonly associated with the organism, the likely level of exposure and mode of transmission, as well as identifying any susceptible population groups. An analysis of the adverse health effects including the nature, severity and causal mechanism of the illness is also considered. Adverse health outcomes may vary from acute, short-term conditions such as gastroenteritis, to serious long-term illness, systemic disease, or may even result in death.

5.2.2 Hazard characterisation

Hazard characterisation seeks to characterise toxicological responses in laboratory animals and/or humans to various levels of exposure (i.e. doses). This is often referred to as a dose-response assessment. Hazard characterisation will identify the critical health effects associated with exposure and, if possible, establish a dose-response relationship.

An important part of hazard characterisation involves assessing relevant studies, including toxicological and epidemiological studies for their quality and relevance.

Chemicals

The hazard characterisation focuses on the most sensitive adverse effect. It is generally accepted that for most chemicals there is a level of exposure, known as a threshold dose, below which adverse health effects do not occur. Hazard characterisation focuses on establishing a 'safe' level of exposure; that is, a level below this threshold level of exposure. This level can be used to establish what is generally referred to as the 'health-based guidance value' (HBGV), which reflects the level of a chemical that can be ingested over a defined time period (e.g. lifetime or 24 hours) without appreciable health risk.

For most chemicals, HBGVs are established on the basis of traditional toxicity studies. These studies use a range of dose levels to identify the highest dose at which adverse health effects do not occur—the no-observed-adverse-effect level (NOAEL). In some cases, and particularly for certain contaminants, agricultural chemical residues and nutritive substances, the NOAEL may be based on human studies. To establish the HBGV based on the NOAEL, 'safety' (or 'uncertainty') factors are applied. A factor of 100 is generally applied when the NOAEL is determined from adequate long-term studies in animals.

However, for some chemicals, such as those considered to be genotoxic and carcinogenic, a threshold of toxicity cannot be readily identified. In such cases, an alternative to the NOAEL approach can be used, which involves dose-response modelling to determine a benchmark dose or BMD. This may also be expressed as the BMDL that is the lower confidence limit of the BMD. The BMD is a level producing a low but measurable adverse response, corresponding to a pre-determined increase (usually 5 or 10%) in a defined adverse effect.

The HBGVs commonly established to take account of long term exposure are the acceptable daily intake (ADI) for food additives or agricultural and veterinary chemical residues and the provisional tolerable (daily, weekly, monthly) intake (PTDI, PTWI, PTMI) for contaminants. For some chemicals, a HBGV is established for short term exposure, usually during one meal or one day, without appreciable risk to the consumer [the acute reference dose (ARfD)].

The HBGVs that FSANZ uses in its risk assessments may be derived from several different sources, depending on the type of chemical under review:

- The Office of Chemical Safety and Environmental Health of the Department of Health assigns ADIs and ARfDs for agricultural and veterinary chemicals[10] [11].

- FSANZ may establish a HBGV based on data provided by external individuals, organisations or companies as part of their application to amend the Code.

- The Joint FAO/WHO Expert Committee on Food Additives (JECFA) sets HBGVs for both additives and contaminants and FSANZ will endeavour to harmonise the HBGVs it uses with these wherever possible.

The HBGVs established during the hazard characterisation step are subsequently used in the risk characterisation step of the risk assessment to compare with the estimated dietary exposure levels.

10 OCS (2012) *Acceptable Daily Intakes for Agricultural and Veterinary Chemicals.*
    http://www.health.gov.au/internet/main/publishing.nsf/Content/ocs-adi-list.htm
11 OCS (2012) *Acute Reference Doses for Agricultural and Veterinary Chemicals.*
    http://www.health.gov.au/internet/main/Publishing.nsf/Content/ocs-arfd-list.htm

Nutrients

Nutrient-related hazards are usually characterised using the HBGVs called Nutrient Reference Values (NRVs) set for Australia and New Zealand by the National Health and Medical Research Council of Australia (NHMRC) and New Zealand Ministry of Health to assess population nutrient intakes[12]. To assess nutrient inadequacy either the Estimated Average Requirement (EAR) or the Adequate Intake (AI) is used, depending on the available evidence for the specific nutrient. These are measures of adequate intake in healthy populations. Macronutrients, including protein, have an Acceptable Macronutrient Distribution Range that provide an upper and lower limit on the range of intake (expressed as a per cent of energy intake) that is advisable. To assess whether population intakes might be excessive, the Upper Level of Intake (UL) is available for some micronutrients and is the highest average nutrient intake likely to pose no adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects increases. A small number of minerals also have a Tolerable Daily Intake (TDI). On occasion, FSANZ might use the TDI rather than the UL for assessing whether intake of these minerals is excessive[13].

There are currently many chemical forms of vitamins and minerals that can be added to food in Australia and New Zealand. If permission to add a new form is sought, its bioavailability must be assessed and compared with the current permitted forms. Bioavailability in a nutritional context is the proportion of the ingested nutrient that is absorbed and utilised through normal metabolic pathways. The bioavailability and bioconversion of different forms of nutrients is usually taken into account in one of two ways. For vitamins, such as folate, niacin, vitamin A or E, there are standard 'equivalence' factors that are applied to different vitamins (i.e. different forms of the vitamin exhibiting proportionally equivalent vitamin activity), or foods, to allow for bioavailability and bioconversion. The equivalents are totalled and compared to NRVs expressed in units of equivalents (e.g. niacin equivalents). For minerals, the NRVs have been increased by a factor to allow for the typical bioavailability in the Australian and New Zealand dietary pattern. As the bioavailability of a nutrient is also influenced by interactions with other nutrients and food components, processing and preparation of food, and host-related intestinal and systemic factors, consideration must be given to various characteristics of the food group intended to contain the added nutrient and the target and non-target populations.

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12 NHMRC (2006) *Nutrient Reference Values for Australia and New Zealand Including Recommended Dietary Intakes.*
   http://www.nhmrc.gov.au/guidelines/publications/n35-n36-n37

13 Codex Alimentarius Commission (2011) *Nutritional Risk Analysis Principles and Guidelines for Application to the Work of the Committee on Nutrition and Foods for Special Dietary Uses.* In: Codex Alimentarius Commission Procedural Manual Ed. 20. Joint FAO/WHO Food Standards Programme, Rome.
   http://www.codexalimentarius.org/procedures-strategies/procedural-manual/

Microbiological agents

The severity of the adverse effect from microbiological hazards can be influenced by the strain and subtype, food production, processing and storage, and the food matrix in which the hazard is present. The food matrix is particularly relevant as it may influence the ability of the microorganism to survive the hostile environment of the stomach. Factors related to the host that need to be considered include underlying conditions that may predispose the host to infection, illness and immune status. A dose-response relationship may exist describing the relationship between the number of microorganisms ingested and the severity and/or frequency of the associated adverse health effects. However, issues such as strain variability and host susceptibility provide an increased level of uncertainty.

The infectious disease process following exposure to a microbiological hazard is multiphasic. Each organism ingested is assumed to have a distinct probability of surviving host barriers (such as the gastric acid of the stomach) to reach a target site for colonisation and cause illness i.e. non-threshold dose-response. Infection may be asymptomatic or, depending on a wide range of virulence and host factors, result in various adverse responses (acute, chronic or intermittent). Although most commonly associated with gastroenteritis, exposure to pathogens can result in long-term illness and, in some cases, death.

For a limited number of pathogenic microorganisms, dose-response data has been gathered from human-feeding studies. These studies usually involve exposing healthy adult volunteers to high numbers of microorganisms and measuring the response (infection and/or illness). Mathematical models are then fitted to the data to estimate the response at much lower doses. The use of adults for developing dose-response models leads to uncertainty about the suitability of the dose-response models for application to children or other population sub-groups. Alternatively, dose-response data may be based on epidemiological studies, in vitro studies or animal studies. Epidemiological studies have been used to determine adjustments in the dose-response models to account for population sub-groups.

5.2.3 Exposure assessment

FSANZ generally undertakes dietary exposure or nutrient intake[14] assessments, though in some cases may consider other sources of exposure. An exposure assessment seeks to provide an estimate of the magnitude, frequency and duration of exposure to the hazard or, the magnitude of nutritional intake found in the diet.

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14 For nutritional risk assessments the term *intake* is used instead of *exposure*, however for the purpose of this section the term exposure covers chemical, nutritional and microbiological dietary assessments.

Chemical exposure assessments (including nutrients)

FSANZ estimates dietary exposures using dietary modelling—a technique, supported by a customised computer program, to combine food consumption data with food chemical concentration data to estimate dietary exposure to food chemicals such as food additives, processing aids, contaminants, novel food ingredients, agricultural and veterinary chemical residues and nutrients.

FSANZ uses methods for calculating dietary exposure that are used internationally. A detailed description of FSANZ's dietary exposure assessment methodologies is provided in the *Principles and Practices of Dietary Exposure Assessment for Food Regulatory Purposes*[15].

Food consumption data for dietary modelling purposes is most commonly derived from the most recent Australian and New Zealand National Nutrition Surveys (NNSs). These surveys collected data on food and beverage consumption amounts using a 24 hour recall method over one or two non-consecutive days. From time to time, FSANZ may also commission consumption and consumer behaviour surveys to fill evidence gaps and to confirm behavioural assumptions. This is particularly important when new products have entered the market since the NNSs were carried out or where the NNS contains limited data for use in specific dietary exposure assessments.

Data on the concentration of chemicals and nutrients in food is derived from different sources depending on the purpose of the assessment and the nature of the chemical. Food additive, processing aid, novel food or other ingredient concentrations can be derived from manufacturers' actual or proposed use levels or analytical survey data. In the absence of other data, the maximum permitted levels specified in the Code might be used to estimate dietary exposure noting this would tend to overestimate the concentration in food because actual levels present in the food may be lower. For agricultural and veterinary chemical residues, maximum residue limits from the Code can also be used to estimate dietary exposure, or alternatively, data from agricultural trials of the chemical on crops or in animals or analytical surveys. Data on food contaminant concentrations can be sourced from monitoring surveys, including total diet studies. Data on the concentration of nutrients in food are available from Australian food composition databases compiled by FSANZ, New Zealand food composition databases, or directly from specific analytical surveys.

15 FSANZ (2009) *Principles and Practices of Dietary Exposure Assessment for Food Regulatory Purposes.* http://www.foodstandards.gov.au/science/riskanalysis/exposure/documents/Principles%20_ %20practices%20exposure%20assessment%202009.pdf

Food consumption and chemical and nutrient concentration datasets are often incomplete, variable in quality or inadequate for use in a dietary exposure assessment. When limitations are identified, assumptions about the data are made and additional information may be available to underpin these, all of which is documented in the risk assessment. The data may include market share data for foods, both across the food supply or in a specific food category. Information on food consumption, chemical concentration or market share data from other comparable countries can also be used where there may already be a permission for, or history of use of, a specific food, ingredient or chemical.

Nutrient concentration data should comprise both naturally occurring forms of the nutrient and that added as fortificants. In addition, nutrient concentrations of complementary medicines (as defined in Australia) and dietary supplements (as defined in New Zealand) may be needed in some situations to allow total nutrient intakes from food and these other sources to be calculated.

Bioconversion might be an important consideration in some cases. If bioconversion from another compound occurs, then both the form of the chemical present in the food and its precursor(s) need to be included in an exposure assessment. For example, a dietary exposure assessment of vitamin A would include beta-carotene and retinol. The form must also be taken into account for many non-nutrient chemicals, for example organic arsenic versus inorganic arsenic.

The nature of the food chemical and the hazard it poses will determine whether a chronic dietary exposure estimate is required (exposure over time) or an acute estimate (exposure over a meal or one day). Depending on the purpose of the assessment, dietary exposure to a chemical may be estimated for the whole population, for consumers of the food only, for high consumers and/or for specific population sub-groups.

When undertaking a dietary exposure assessment, FSANZ may use a tiered or stepped approach, particularly where data and resources are limited. Initial estimates of dietary exposure tend to be very conservative and serve to identify those cases that warrant a more detailed assessment. A more refined and accurate dietary exposure assessment, using more detailed consumption data, improved or more concentration data and more sophisticated dietary modelling techniques, is conducted where initial estimates indicate HBGVs may be exceeded. Generally, FSANZ uses a 'semi-probabilistic' dietary modelling approach which combines the detailed food consumption data from NNSs with single point chemical concentration data. A distribution of exposures for a population is derived and population statistics (mean and various percentiles of dietary exposure) are reported. Occasionally, where further refinement and characterisation of the dietary exposure assessment is required, and where suitable data is available, FSANZ may conduct a probabilistic dietary exposure assessment. Probabilistic modelling combines detailed food consumption data

from the NNSs with a range of chemical concentration data and derives a probability, or likelihood, of a level of exposure for a population sub-group.

When there are significant uncertainties in the data used in an assessment, FSANZ will apply conservative assumptions. When determining exceedances of the HBGVs, the use of conservative assumptions will help ensure that the dietary exposure is not under-estimated. Similarly, when determining whether the intake of nutrients is sufficient, as compared to the relevant NRV, the use of conservative assumptions will ensure that the dietary exposure is not over-overestimated.

The dietary model is often run multiple times. The first model describes the baseline situation. Subsequent models predict the dietary exposure in the population under other scenarios, as a result of possible changes to the Code. For food components such as nutrients that have beneficial as well as adverse effects, the focus of the iterative dietary exposure assessment might be on obtaining an acceptable level of intake by the target population while ensuring intake by the non-target population is not at excessive levels that have the potential to cause adverse effects.

Microbiological exposure assessments

An assessment of exposure to microbiological hazards takes into account the ability of a pathogen to grow, survive or be inactivated in the food. Various factors need to be considered including: data on the prevalence and level of hazard in the food, the amount and frequency of the food consumed, the population consuming the food, the characteristics of the hazard and the effect that food production, processing and handling has on the hazard (actual levels as well as the likelihood of the hazard being present). Food consumption data can be sourced from two areas: food production statistics and food consumption surveys like those discussed above.

Data on the prevalence and level of hazard in the food at various stages of the food supply chain also needs to be gathered. This may be problematic as there may be little or no data available. Sometimes unpublished information can be obtained from government laboratories, the food industry or other regulatory agencies. In some cases, it may be necessary to undertake microbiological surveys of food to obtain appropriate information. Data also needs to be gathered on the food, how it is produced and stored and how these factors may influence the level of hazard present in the food at the time of consumption.

FSANZ may develop predictive mathematical models to predict the growth, inactivation and survival of a microbiological hazard throughout the food chain, taking into account the impact that factors such as food processing and storage and the amount of food consumed have on the level of exposure. Different quantitative models may be developed depending on the amount of data and resources available. Deterministic models produce single

outputs from single sets of data, while stochastic, or probabilistic models, use frequency distributions to cover a range of possible values. Probabilistic models incorporate variability and uncertainty into model inputs and provide a range (distribution) of possible exposure levels. Probabilistic models therefore seek to better represent the variability and randomness of events observed in the natural environment, which can assist with identifying steps in the exposure pathway that have most influence on risk.

The type of model used will depend on many factors such as what information is needed to make a risk management decision, the availability and quality of relevant data and the urgency for requiring the risk assessment outputs (recognising that developing complex quantitative models often requires significant resources and time to complete).

5.2.4   Risk characterisation

Risk is a function of both the hazard and the level of exposure to that hazard. For this reason, both elements are equally important in determining the level of risk of an adverse effect in consumers. Risk characterisation—the last step in risk assessment—seeks to integrate information from the hazard and exposure assessments to generate a risk estimate. For chemicals and nutrients, this often involves comparing the dietary exposure estimates for different population groups with the HBGVs and, for nutrients, the NRVs, noting in some cases other sources of exposure may also be considered. For microorganisms, there are generally no set values; therefore, a range of methods including qualitative, semi-probabilistic and probabilistic modelling may be used to best describe the risk to consumers.

The risk characterisation may apply to the whole population or for a specific population sub-group, depending on the nature of the adverse health effect and the pattern of dietary exposure. Specific risk characterisation information for at risk groups e.g. infants, pregnant or lactating women, the elderly, immuno-compromised or individuals with special dietary needs, may need to be considered separately in the risk assessment.

The risk characterisation may be repeated numerous times for each of the different risk management scenarios that have been identified. These scenarios might relate to differences in the concentration of the hazard in the food.

Chemicals

Different approaches are used for risk characterisation of chemicals depending on the nature of the chemical and whether a toxicity exposure threshold can be identified from animal or human studies.

A threshold approach can generally be used in most cases where there is a non-cancer endpoint. Whether a threshold of toxicity can be identified or not, the ALARA principle should apply, whereby exposure to the chemical in question should be as low as reasonably achievable without withdrawing the food completely from the market.

When a threshold of toxicity is evident, the risk characterisation involves comparing the dietary exposure estimates for consumers at the mean and high levels of consumption to an appropriate HBGV. According to current generally accepted definitions for HBGVs (see Section 5.2.2), exposure below the HBGV is considered to be *without appreciable health risk* for a food additive, novel food ingredient or pesticide and veterinary drug residue and to be of low risk and *tolerable* for a food contaminant.

When a threshold of toxicity is not evident, risk characterisation may involve a margin-of-exposure (MOE) approach to provide an estimate of relative risk. The MOE approach compares the BMD [or the lowest-observed-adverse-effect level (LOAEL), if the BMD is not available] with estimated dietary exposure to the chemical. While a large MOE (e.g. >10,000) generally indicates a low risk, the MOE is not a quantification of risk, and needs to be accompanied by some narrative to describe the way in which it has been derived and the limitations of this approach.

Occasionally, estimated dietary exposures may exceed the HBGVs for food contaminants or older chemicals (food additives, pesticide and veterinary drug residues) that may have a long history of apparent safe use, but which were not assessed against current regulatory standards. In this scenario, a detailed case-by-case approach involving a re-examination of both the hazard and exposure assessments, together with any new scientific information, is needed.

A small or transient dietary exposure above a HBGV does not necessarily mean the exposed population is at significant additional health risk as a result of that exposure. However, if the risk characterisation indicates there is an exceedance of a HBGV that may pose a health risk, FSANZ will adopt a conservative approach to ensure the protection of public health and safety, reflecting FSANZ's low overall risk appetite. The approach may include regulatory or non-regulatory actions proportionate to the identified risk, to reduce dietary exposure to the substance.

Nutrients

Risk characterisation of nutrients must consider both food safety and health aspects for all population groups. Good quality evidence in humans is required to accurately characterise any risks and benefits to health of nutrients. Corroborating evidence from in vitro and animal studies of potential adverse effects (and to a lesser extent potential beneficial health effects) is also used to strengthen the evidence. Evidence of a plausible biological mechanism associated with consumption of the nutrient and the health effect is also considered in the totality of evidence.

Estimating the proportion of the population with nutrient intakes below the EAR, where it exists, can be used to estimate the proportion of the group whose usual intake is inadequate. Estimates of intakes that are above the UL, where it exists, or TDI, where it exists for minerals,

are used to assess the probability of excessive intakes and potential risk of adverse effects. For population nutrient intake assessments that indicate a small proportion of intakes below the EAR or above the UL, there is little likelihood of any adverse health effects.

The risk characterisation must also consider the variability in population food intakes and therefore nutrient intakes (also see Section 5.5). For example, the dietary intakes for one group in a population might be inadequate while at the same time, a substantial proportion of a different group in the same population might have intakes exceeding the UL. This could become problematic when considering possible food fortification options. If exceedance of the UL is likely, the extent and duration of the exceedance needs to be considered based on the proposed level of addition of the nutrient to various foods. Further assessment of the basis for the UL can also be undertaken to determine if the endpoint on which the UL is based is relevant for the population group with the high intakes and also to assess the nature of the risk associated with an exceedance of the UL. As with other chemicals and food contaminants, where an exceedance occurs, FSANZ will adopt a cautious approach that aims to protect public health and safety.

Microbiological agents

Risk characterisation of microbiological hazards integrates dose-response and exposure information to provide an estimate of illness and other adverse health effects that may occur in a given population (general or sub-population).

Risk estimates may be expressed either qualitatively i.e. in a descriptive manner such as a risk ranking or descriptive categorisation (high, medium or low) or quantitatively i.e. expressed mathematically. Mathematical expressions of risk may describe the likelihood of illness for an adult or a child from a single meal. It may also be expressed in terms of the probability of illness per 100,000 individuals or the predicted annual incidence of human illness in a total population.

Determining a risk estimate, whether it is qualitative or quantitative, depends on many factors including the initial scope of the problem as determined by risk managers, the selection (and rejection) of scientific and other data and the exposure pathways (i.e. a pathogen present in a raw product may be consumed in a number of different types of food). The risk estimate must be viewed with knowledge of all factors affecting the determination of the final result, the associated data sources and assumptions, and taking into account any uncertainties/limitations.

The microbiological risk characterisation also identifies factors in the food chain that reduce the risk to consumers. In the case of a quantitative risk assessment, the cost of introducing additional control measures can be readily assessed against the benefit of reductions in human illness. The best interventions, that minimise costs and maximise the benefit, can then be determined.

5.3 Special risk assessment cases

5.3.1 Bovine spongiform encephalopathy

The risk to human health associated with the prion responsible for bovine spongiform encephalopathy (BSE) has historically been difficult to assess due to the high level of uncertainty around many aspects of the disease and its science. When initially recognised as a potential foodborne disease, the nature of the BSE agent and its infectivity was to a large extent unknown. However, it is now clear that the BSE agent is only spread to cattle through the feeding of contaminated ruminant protein and does not naturally spread between cattle. The human form of the disease, variant Creutzfeldt-Jakob disease (vCJD) was acquired when people consumed BSE-contaminated meat products, and although rare has also been acquired through blood transfusion. Uncertainties that still exist in the understanding of these types of diseases include the mode of action of prions in causing BSE and vCJD in humans, the dose-response relationship, and the existence of a threshold dose level. There is now, however, better information on the characterisation of prions, the relative susceptibility of various species, the identity of those animal tissues containing the highest concentration of BSE and, therefore, a better understanding of the foods that potentially may pose a risk of containing BSE. There is now also solid evidence that controls, if implemented effectively across the cattle/beef supply chain, can be successful in eliminating BSE from animal herds and preventing contamination of food. Therefore, the approach is to assess the BSE risk status of a country by examining its through-chain controls for the production and processing of meat and meat products, as well as surveillance of cattle herds.

5.3.2 Allergenic foods

Food allergies are adverse reactions that involve the immune system of some individuals. A small number of foods are responsible for most food allergies in the population. Milk, egg, wheat, soy, peanut, tree nuts and fish are some of the allergenic foods widely consumed around the world. In allergic individuals, proteins in these foods trigger various symptoms ranging from mild to severe. Assessment of the risk associated with allergenic foods has unique features due to the nature of allergy itself, in that the risk from allergenic foods is specific to allergic individuals. Also, allergic individuals vary widely in their sensitivity in the amount of allergenic food that triggers an allergic reaction (allergen thresholds). However, clinical evidence on allergen thresholds is being developed internationally to support risk assessments in this area. This is particularly relevant to assessing the risk from ingredients and products derived from allergenic sources, and from the unintended presence of allergens in food products.

5.3.3   Special purpose foods

The ingredients of special purpose foods generally require premarket approval, as these foods are intended for vulnerable populations as a sole source of nutrition (e.g. infant formula products) or to supplement the normal diet (see Section 2.3.4). The safety and composition of these products is assessed with a particular focus on the target population and the intended special purpose of the food. Specific data relevant to the particular population group will be required, such as that described for nutrients above. In general, an even more cautious and conservative approach is taken in relation to the acceptable level of risk for foods in this category i.e. the level of uncertainty must be low (see Section 5.5) or the risk(s) capable of being easily managed (see Chapter 6). If the consumer of a special purpose food is well defined, and the products are unlikely to be consumed by a non-target audience, assessing risks in the non-target population group is likely to be less of a concern, than when nutrients are added to general purpose foods.

5.3.4   Other nutritive substances

Other nutritive substances that are not essential nutrients, such as some amino acids, might be added to food with the intention of achieving a beneficial health effect. Characterising risks associated with these substances will depend on whether the hazard assessment has found any beneficial or adverse effects and whether a HBGV can be established against which dietary intakes can be compared.

In cases where risks or threshold effects are found, then FSANZ may need to identify or establish a HBGV. Intakes can then be compared to the HBGV for beneficial or adverse effects, as described in Section 5.2.4. It may be necessary to conduct separate risk assessments for the target and non-target populations. When a HBGV cannot be established, an estimate of dietary intake may be provided for information purposes only.

The focus remains on assessing the likelihood of adverse effects occurring in the target and non-target populations and the likelihood of the beneficial health effects occurring in the target population at the estimated levels of consumption. This can be assessed empirically by pooling and analysing the results of various studies or by assessing the strength of the evidence to support the true existence of a beneficial health effect or the likelihood of a risk. As is the case for nutrients, good quality evidence from studies in humans as well as in vitro and animal studies is required to accurately characterise any risk and benefit to health of these nutritive substances.

5.3.5 New technologies

Food irradiation

Irradiation of foods produces some minor chemical and nutrient changes in foods depending on the dose used. Risk assessments of irradiated foods are undertaken on a case-by-case basis and include consideration of the following:

- the history of safe consumption of irradiated foods in other countries

- conclusions from previous assessments by expert committees, the WHO, other regulatory agencies and safety assessments conducted by FSANZ

- an assessment of the technological need to irradiate foods and data on the safety of irradiated foods that has become available since the previous assessments

- compositional (nutrient) data on irradiated foods compared to their non-irradiated counterparts and the level of consumption of those foods (and nutrients) in Australia and New Zealand.

Genetically modified foods

The safety assessment of genetically modified foods is based on the concept that their safety can be assessed, to a large extent, by comparison to the conventional counterpart having a history of safe use, and taking into account both intended and unintended changes. The objective is to identify new or altered hazards relative to the conventional counterpart. Any identified hazards then become the focus of further assessment. The objective of further assessment is to determine if there is any risk associated with any of the identified hazards under the intended conditions of use; and if any new conditions of use are needed to enable safe use of the food.

The safety assessment is characterised by:

1. case-by-case consideration of GM foods—this is necessary because the key issues requiring consideration will often depend on the type of food being evaluated and the nature of the genetic modification

2. consideration of both the intended and unintended effects of the genetic modification

3. comparisons with conventional foods having an acceptable standard of safety.

The goal of the safety assessment is not to establish the absolute safety of the GM food but rather to consider whether the GM food has all the benefits and risks normally associated with the conventional food.

The safety assessment relies on: (i) consideration of the molecular characterisation of the genetic modification; (ii) phenotypic characterisation of the new organism, compared with an appropriate comparator; (iii) assessment of novel substances, including proteins, that may be expressed in the food; and (iv) compositional analysis of the new food or the specific food product.

Nanotechnology

The use of technologies such as nanotechnology to produce nanoscale materials provides an opportunity for innovation in various areas of the food sector including production, processing, preservation and packaging. However, the use of nanoscale materials may also potentially lead to a new or increased risk in food.

FSANZ considers that its risk assessment framework is generally sufficient for assessing new or novel nanoscale materials. Assessment of the safety of a new material—nanoscale or non nanoscale—generally includes an evaluation of the toxicokinetics and metabolism of the substance as well as the toxicity of the substance as determined through studies in animals and, where available, humans. When ingested orally, soluble or biodegradable nano particles are understood to behave differently than those that are poorly soluble and non-biodegradable, especially those that remain particulate in nature in the final food. Therefore, pharmacokinetic studies following oral ingestion that allow the differentiation of solubilised material from particulate material will be particularly useful in conducting a health and safety assessment of nanoscale materials in food products or food contact materials.

5.4   Impacts on consumers' behaviour

The addition of some substances to foods may precipitate changes in consumers' behaviour with consequential health and safety risks. This may need to be considered as part of the risk assessment, whereby the risk characterisation is repeated for each possible risk management scenario.

The potential to precipitate changes in consumers' behaviour is usually related to functional and nutritive substances, where the new addition is signalled to consumers through labelling and product marketing. Changes in dietary behaviour may occur when consumers adopt new sources of the substance in place of traditional sources of the same substance, and in that change may lose other nutritional benefits from the traditional source. Changes in broader dietary and physical activity outcomes may occur through compensatory consumption behaviour based on beliefs about the new substances. These broader behavioural aspects are typically explored through surveys and experiments. The *FSANZ Application Handbook* also requests data and information on these types of behavioural impacts.

5.5 Variability and uncertainty in food risk assessments

Variability and uncertainty are inherent in the risk analysis process. Variability refers to the differences within a particular parameter (e.g. in concentrations of haemoglobin in people, in the concentration of a particular additive in different samples of the same type of food, or differences in infectivity and virulence between strains of microorganisms). Uncertainty is the lack of perfect knowledge (i.e. data) to define the true value of the parameter (e.g. determination of the absolute NOAEL for a chemical). Variability cannot be reduced but can be better understood and described. In contrast, uncertainty can be reduced (though never completely eliminated) through additional and more accurate data. Risk assessors implicitly deal with variability and uncertainty as part of their scientific decision-making. While it is unnecessary and impractical to document every single aspect of variability and source of uncertainty in a risk assessment, it is important to consider both in the context of the impact on the overall risk characterisation.

Variability

Some examples of how variability is dealt with include: parameter measurements (e.g. toxicology endpoints, food chemical concentrations) which are described statistically with an indication of variability (standard deviations or error); chemical assays including limits of detection and quantification; in setting HBGVs, 10-fold inter and 10-fold intra-species safety factors are typically applied to the NOAEL to account for inter and intra-species variation and dietary intakes are determined for different population groups to take into account variability in the total human population. For microbiological hazards, an additional source of variability is the effect of the food vehicle and its environment on the rate of growth of the microorganism, which can be incorporated into the models underpinning quantitative risk assessments.

Uncertainty

Uncertainty is commonly dealt with in a risk assessment by making conservative assumptions in both the hazard and exposure assessments. Such a conservative approach is commensurate with our low overall risk appetite. For example, there may be insufficient data to confirm the relevance to humans of an adverse effect observed in laboratory animals. Consideration would therefore need to be given as to whether it is appropriate to derive a HBGV from such data. Under this scenario, a conservative assumption would be that the adverse effect *is* relevant to humans. In an exposure assessment, the assumption might be that the substance of interest, say a proposed new food additive such as a high intensity sweetener, will replace *all* existing sweeteners. In the absence of other information, such an assumption will result in a conservative risk estimate.

It is important that the level and nature of uncertainty, and any conservative assumptions that may have been applied, are articulated in the risk assessment. The uncertainty needs to be understood by the risk manager and be fully considered in risk management decisions. Typically, the uncertainty is documented in risk assessments by including descriptive text. However, not all potential sources of uncertainty (or data gaps) will have a large impact on risk estimates and an assessment of the relative importance is also included. A quantitative approach may be possible in some cases.

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5.6   Risk assessment outputs

It is important that the outputs of the risk assessment provide information in a way that facilitates risk management decision-making. For chemicals and nutrients, where it is possible to compare dietary exposure estimates (typically derived using a semi-probabilistic modelling approach) with HBGVs, outputs will generally be quantitative. For microorganisms, where there are generally no set values and often only limited data available, outputs are more likely to be qualitative.

Irrespective of the format in which the risk assessment outputs are presented, the results of the risk assessment are one of a number of considerations informing risk management, others being public health policy guidance, consumer behaviours and economic and regulatory inputs. Risk assessment outputs therefore need to be considered and interpreted within the context of other available information.

While the separation of risk assessment and risk management is an important principle in risk analysis, in reality the risk analysis process is iterative and cooperative. At FSANZ, risk assessors and risk managers work together to develop risk management goals and objectives and the options to achieve these goals and to formulate the risk assessment questions (see Section 6.2.1). By working this way, risk managers are aware and understand the limitations of the risk assessment and how to interpret the risk assessment outcomes.