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RISK ASSESSMENT AND MANAGEMENT IN SETTING FOOD STANDARDS FOR ADDITIVES AND CONTAMINANTS IN AUSTRALIA

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Revision

Introduction

1. The primary task of the National Food Authority (NFA) is to develop food standards and variations to food standards, for the protection of public health and safety (*National Food Authority Act 1991*).

2. This paper summarises how the Authority defines, assesses and manages risk in relation to the setting and varying of food standards in Australia. Risk assessment and management underlie the existing regulatory structures and procedures applying in Australia and these are described more fully in an Authority paper that can be made available to interested parties.

3. A more informed debate about acceptable levels of risk in relation to food can only be achieved through a greater awareness of risk assessment and management practices.

4. Risk assessment and risk management are regarded as two distinct processes and the various aspects of each are discussed in this document.

5. For the purposes of this paper, the following definitions are used:

- *Hazard* is the intrinsic property of a substance to cause harm;

- *Risk assessment* is the process of using available information to evaluate the hazard of a substance and its potential to cause adverse health effects at different levels of exposure;

- *Risk management* is the process of integrating risk assessment results with social, economic and political concerns and, after consideration of alternative strategies, of identifying a strategy to minimize or eliminate the identified risk.

Concept of risk

6. Risk can be defined as the potential for the occurrence of unwanted negative consequences of an event. In relation to food, this is usually interpreted as the potential to cause either immediate or long-term adverse health effects. The concept of "risk", however, has many dimensions, and the probability of adverse health effects, as determined from a scientific viewpoint, is just one. Other

dimensions include psychological factors, social and ethical factors, and political and economic factors. Risk assessment, as performed at the Authority, is defined as the scientific assessment of risk and is performed independently of these other dimensions of risk, although they may contribute to the subsequent risk management decisions.

7. Fundamental to an estimation of risk is the acceptance of a degree of uncertainty. The basis of this uncertainty is two-fold. Firstly, there is uncertainty with regard to the quantity and quality of the information upon which a decision is made. Secondly, there is uncertainty with regard to the validity of the assumptions upon which the prediction of risk is made, such as species extrapolation, dietary modelling or the degree of heterogeneity in the population. Together, these determine the degree of uncertainty in the risk estimation in a particular circumstance.

Food-related risks

8. The protection of public health and safety is the most important of the factors taken into consideration when setting and maintaining food standards. Public health and safety in relation to food refers to all those aspects of the diet which could adversely affect human health either in the short or long term. The two terms, "public health" and "safety" are sometimes used interchangeably because of their close relationship but each have characteristics which differentiate them, such as the timeframe of an effect, definition of the outcome, and individual versus population effects.

9. The risks associated with food are probably best considered from the point of view of the whole diet, although the number of confounding factors make this a difficult task in most cases. More commonly, risks are assessed for a specific food or for an individual component of that food. Chemical factors associated with food-related risks include food additives, cooking and process-related factors, environmental contaminants, food processing aids, marine toxins, mycotoxins, novel food components, packaging migrants, pesticide residues, plant toxins and veterinary chemical residues.

10. The Authority has a responsibility with respect to each of these risk factors. For some, such as food additives, processing aids, and contaminants, the Authority has a major responsibility to establish and maintain food standards where necessary to protect public health and safety. In other areas, such as the risks associated with naturally-occurring toxins and other potentially toxic chemicals formed during cooking and processing, food standards are not generally considered to be the appropriate risk management approach. The Authority may work with other Agencies and organizations to reduce the risks through encouraging better food processing practices or through public education programmes.

11. For agricultural and veterinary chemicals, while maximum residue levels (MRLs) are enforced through the *Food Standards Code* and State Food legislation, MRLs are established largely by other agencies, namely, the National Registration Authority for Agricultural and Veterinary Chemicals (NRA) and the Department of Human Services and Health.

Steps in risk assessment

12. The process of risk assessment can be divided into four distinct steps, namely, hazard identification, hazard characterization, exposure assessment, and risk characterization. The various steps in the scientific assessment of risk are considered below.

Hazard Identification

13. Hazard identification is *the qualitative evaluation of the adverse health effects of a substance(s) in animals or in humans*. For chemicals, hazard identification establishes the toxicity of a substance and may identify the set of inherent properties which make it capable of causing an adverse effect.

For new chemicals, this is established through a consideration of: (i) the structure and associated physiochemical properties; (ii) the metabolism and toxicokinetics of the substance; and (iii) the results of a series of toxicity tests conducted both in animal models and in *in vitro* systems. The extent of the toxicity tests required is determined on a case-by-case basis, and will be dependent on the nature of the substance and the anticipated level of human exposure. Animal toxicity studies are designed to investigate the major biological systems and would include acute toxicity, reproductive toxicity, genotoxicity, embryotoxicity, teratogenicity, carcinogenicity, organ toxicity, and sometimes other specific studies such as neurotoxicity or immunotoxicity.

14. For existing chemicals, toxicology data may also be available from published papers although the quality of this data is variable. In some cases, human toxicology data may be available. This could include: (i) case studies of adverse effects; and (ii) results of epidemiological studies. Individual case studies may not by themselves be highly significant, but a pattern may emerge over a period of time with increasing numbers of reports of adverse effects.

Hazard Characterization

15. Hazard characterization is *the process of estimating the relationship between the dose of a substance(s) and the incidence of an adverse effect*. For chemicals, hazard characterization involves a consideration of the results obtained in the hazard identification phase in relation to the dose levels used. The outcomes should be: (i) identification of the major toxicological endpoints and the dose levels at which they occur; (ii) an estimate of the dose level below which the observed toxicity does not occur; (iii) some understanding of the metabolism and kinetics of the substance in a mammalian system; and (iv) in some cases, information on the mechanism of action of the observed toxicity.

Exposure Evaluation

16. Exposure evaluation is *the evaluation of the magnitude and duration of actual or anticipated human exposure, and the number of persons affected*. For chemicals, exposure evaluation involves estimating the level and extent of human intake of a particular substance in the whole diet. When the exposure evaluation is based on estimated or anticipated exposure, the process is sometimes referred to as dietary modelling. Where survey data is available, more accurate exposure evaluations for specified population groups can be made. In general, exposure estimates are based on known or anticipated dietary information for particular foods together with an estimate of the level of the chemical in particular commodities.

Risk Characterization

17. Risk characterization is *the process of estimating the probable incidence of an adverse health effect to humans at various exposure levels, including a description of the uncertainties involved*. Risk characterization brings together the information of the previous steps in order to provide a practical estimate of risk for a given population. It is on the basis of this determination that the risk management strategy is formulated. The degree of confidence in the final estimation of risk will depend on the uncertainty factors identified in previous steps.

18. For chemicals, risk characterization might be expressed in terms of a margin of safety between the acceptable level of intake of an additive or contaminant, based on the known hazard, and the known level of human exposure via the diet.

General concept of risk assessment

19. Chemical risk assessment depends, firstly, on an ability to predict potential adverse health effects in humans and, secondly, on the fact that there is a direct relationship between the level of exposure and the effect(s) observed. The prediction of potential adverse effect in humans generally relies on evaluation of toxicity tests in animals or, in more limited cases, the results of epidemiological studies. While complete toxicological testing on all chemicals might be the ideal, such an approach to assessing hazard is impractical and indeed unnecessary. In many cases, other information is available on which to assess potential hazard, including information on the structure of the chemical, its metabolites, its rate of metabolism and its history of use. The extent of toxicity testing which might be desirable can generally be established after consideration of these factors.

20. Animal models are selected on the basis of their sensitivity for the particular biological parameter being measured. In assessing safety, the conservative assumption is made that humans will be at least as sensitive as the most sensitive animal species. In some circumstances, the animal model may not be suitable or may be inappropriate to predict effects in humans. There is also increasing use of in vitro systems to study general toxicity and to explore mechanisms of action. The Authority provides guidance on the type of toxicity studies considered appropriate to assess hazard and to address the question of potential risk in particular circumstances.

21. The concept of a dose-response relationship is fundamental to establishing the safety of chemicals in food. Animal studies may be useful, firstly, to identify the target organs for toxicity and perhaps gain some information on the mechanism of action of the observed toxicity and, secondly, to estimate the dose level below which the adverse effect does not occur. This dose level is referred to as the no-observable-effect-level (NOEL). In order to compensate for the uncertainty in this figure as a measure of safety, the NOEL is generally adjusted by means of so-called "safety factors" to arrive at a safe level of intake for humans. The safety factor (or "uncertainty factor") used may vary from 10 to 2000 depending on the confidence in the available data. For food additives, a safety factor of 100 is generally used which comprises a factor of 10 to account for the species differences between experimental animals and humans, and a factor of 10 for the variation in the human population. If the NOEL is based on human data, a safety factor of 10 may be considered adequate, while on the other hand, if the NOEL is based on less than lifetime studies, a higher safety factor (1000-2000) may be applied. The acceptable daily intake (ADI) is determined by applying the safety factor to the NOEL. For food additives, the ADI is used as the basis for establishing the safe level of human lifetime exposure.

22. While this approach is applicable for the majority of chemicals which are specifically added to food, there are classes of chemicals where a different approach may sometimes be necessary. This includes genotoxic carcinogens, some naturally-occurring chemicals, environmental contaminants, nutrients and traditionally-used food additives and processing aids.

23. Carcinogenic chemicals which are also genotoxic present a particular problem with regard to safety assessment. Because of their ability to produce DNA damage at very low dose levels, a NOEL cannot easily be established for such chemicals. In general, the approach has been to disallow the use of such chemicals in food. When their occurrence in food is unavoidable, either because they are naturally-occurring or are produced during processing, levels should be kept to a minimum. Carcinogenic chemicals which are not genotoxic can generally be regulated in a similar manner to other chemicals with the establishment of a NOEL and an ADI.

24. Environmental contaminants cannot be regarded in the same way as food additives since they are not intentionally added to food and the levels cannot necessarily be controlled to provide the same margin of safety which can be achieved with a food additive. Thus, assessments must be done on

the basis of the lowest achievable level. Maximum permissible concentrations (MPCs) are generally established on the basis of the lowest achievable levels of contamination which are consistent with protecting public health and safety.

25. For many traditionally used food additives and processing aids, there is little toxicity data upon which to base an assessment of risk. Many such chemicals have a long history of use in foods or are members of chemical classes known to be safe. For some chemical groups, standard toxicity tests may be inappropriate to assess hazard. Generally, safe levels of intake are determined using a combination of toxicity data, information on traditional food use, structure/activity relationships and metabolism and toxicokinetic data.

Sources of uncertainty

26. Risk assessment contains a degree of uncertainty which is dependent on the quality of information available and assumptions used in the assessment process. Factors which may affect the degree of confidence in the assessment outcome are discussed below.

Quality of the toxicity data

27. Data quality is a significant factor in providing confidence in the determination of hazard. Poor data can often lead to misleading conclusions which are not supported by subsequent studies. Quality control measures such as Good Laboratory Practice (GLP) have contributed significantly to improvements in data quality. In some cases, this source of uncertainty is taken into account in the choice of safety factors used to determine the ADI. For many chemicals found in food, data is available from various sources and needs to be analyzed critically before conclusions can be drawn regarding potential hazard.

Species specificity

28. The choice of animal model is an important consideration in interpreting toxicity data in relation to human risk assessment. In some cases, even with the most appropriate animal model, toxicity studies can lead to results which are specific to that species only. Recognition of such an effect can significantly influence the interpretation of data and subsequent assessment of risk. In some cases, limited testing in humans may be desirable to obtain more relevant toxicity information. This might be particularly relevant for chemicals or novel foods which potentially affect bioavailability of nutrients.

Determination of the ADI

29. One of the criticisms of the ADI approach is that the value of the NOEL is dependent on the dose levels chosen for the study and, in some cases, an overly conservative ADI may result. This uncertainty factor is difficult to correct except by repeating the experiment at different dose levels, but needs to be considered when questions of safety arise for chemicals for which the intake is approaching the ADI.

Toxic effect upon which the ADI is based

30. The nature of the toxic effect upon which the ADI is based is important when considering the health implications of a dietary intake above the ADI. This may be an important consideration when concern is expressed regarding excessive intake. Chemicals which cause, for example, a neurotoxic effect or a retinal disorder, should be monitored more closely in relation to the ADI than those which cause a slight liver weight increase.

Use of safety factors

31. Safety factors (or uncertainty factors) are one way of dealing with the uncertainty arising from, firstly, species extrapolation of toxicity studies and, secondly, human heterogeneity with regard to response to the toxicity of chemicals, and are designed to protect the more sensitive members of the population. If the toxicity to humans is known, and also the most susceptible groups within that population can be identified, the safety factors can be smaller.

Dose-response relationships and thresholds

32. The advantage of the ADI approach to establishing a safe level of exposure is that it avoids extrapolation of the dose-response curve beyond the dose levels used in the study. Where no threshold dose level is evident to establish a NOEL, it may be necessary to extrapolate to a so-called virtually safe dose level. While mathematical models are available to perform such extrapolations, these are not considered particularly reliable since they themselves make assumptions regarding the shape of the dose-response curve. The only situation where it may be necessary to consider extrapolation to a virtually safe dose level is for the naturally-occurring genotoxic chemicals in food.

Measurement of exposure

33. Uncertainty in the measurement of dietary exposure to chemicals can be due to lack of knowledge in a number of areas; firstly, variable dietary consumption of particular foods by different groups of the population; secondly, information on the level of the chemical in the different food commodities; and thirdly, information regarding the level of absorption from the gastrointestinal tract and its distribution in the body prior to excretion.

Chemical risk management

34. There are a number of approaches to managing the risks associated with the presence of chemicals in food, including: (i) restricting the level of the chemical in food, if necessary; (ii) appropriate labelling to indicate the presence of the chemical and, (iii) an education programme to make the public aware of potential risks associated with excessive consumption. The general principle of minimizing unnecessary exposure to chemicals underlies each of the above approaches.

35. The most prohibitive approach to an unacceptable risk is total restriction of use. This approach may be taken for: (i) chemicals which should not enter the food supply, (ii) chemicals for which there is no toxicity information, (iii) for certain agricultural chemicals which are no longer in use, and (iv) certain botanicals which are not considered suitable for use in food.

36. The most common management approach with chemicals is to establish a permissible upper level in food. The basis on which this permissible level is established will depend on the nature of the chemical and the type of food in which it occurs, as discussed below. Labelling of food is used to identify the presence of food additives and may also be used to highlight the potential for adverse reactions to particular foods or food components.

37. Unrestricted use may be suitable for chemicals of very low toxicity, and for some chemicals which have been traditionally used in foods with no evidence of adverse health effects. This is similar to the US "generally regarded as safe" or GRAS classification. Unrestricted use of a chemical may or may not also need to be accompanied by a public education programme. Chemicals for which better understanding of the risk associated with their consumption is needed are: (i) the naturally-occurring toxic chemicals in food, e.g. pyrrolizidine alkaloids; and (ii) those potentially hazardous chemicals which are formed during cooking or food processing, e.g. heterocyclic amines.

38. Whether the presence of a chemical is restricted or not, surveys, such as the Australian Market Basket Survey, can be useful tools for monitoring actual levels in food, as consumed. Such information can then be combined with food consumption data and used to estimate the level of dietary intake of chemicals for different population sub-groups. This information is important to reassure the public regarding the safety of the food supply.