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MANATŪ HAUORA

Methodological framework for the review of Nutrient Reference Values

Australian Government Department of Health

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Glossary

Acronyms	Descriptions
AI	Adequate Intake. The average daily nutrient intake level based on observed or experimentally-determined approximations or estimates of nutrient intake by a group (or groups) or apparently healthy people that are assumed to be adequate (used when an EAR cannot be determined)
AMDR	Acceptable Macronutrient Distribution Range. An estimate of the range of intake for each macronutrient for individuals (expressed as per cent contribution to energy), which would allow for an adequate intake of all other nutrients whilst maximising general health outcomes.
CV	Coefficient of Variation. The ratio of the standard deviation to the mean of a set of measurements, usually expressed as a percentage and measuring the variability of the population relative to the average.
DRI	Dietary Reference Intakes. Nutrient reference values developed by the Institute of Medicine. They provide the scientific basis for developing food guidelines in both the United States and Canada and are intended to provide a guide for good nutrition.
DoH	The Department of Health (named the Department of Health and Ageing prior to 2013)
DoHA	The Department of Health and Ageing (changed to the Department of Health in 2013).
DRV	Dietary Reference Values. The equivalent of DRIs and NRVs in the United Kingdom.
EAR	Estimated Average Requirement. Nutrient level required to meet the needs of approximately half the healthy individuals in a particular life stage or gender group.
EER	Estimated Energy Requirement. The average dietary energy intake that is predicted to maintain energy balance in a healthy adult of defined age, gender, weight, height and level of physical activity consistent with good health.
EURRECA	European Micronutrient Recommendations Aligned. A network of excellence funded by the European Commission to develop methodologies to standardise the process of setting micronutrient recommendations.
EWG	Expert Working Group. Nutrient and other technical experts that will review scientific evidence and develop NRV recommendations.
FSANZ	Food Standards Australia New Zealand. Bi-National Government agency responsible for developing and administering the Australia New Zealand Food Standards Code, which lists requirements for foods such as additives, food safety and labelling.
GRADE	Grading of recommendations, assessment, development and evaluation. Approach used by WHO to assess the evidence base for clinical, health and dietary guidelines.
IOM	Institute of Medicine. An independent non-profit organisation in the US that provides authoritative advice on health to decision makers and the public.
LOAEL	Lowest Observed Adverse Effect Level. Lowest dose at which there is a measurable adverse effect from a test substance in a test subject or population.

Acronyms	Descriptions
NHMRC	National Health and Medical Research Council. Australia's peak body for supporting health and medical research; for developing health advice for the Australian community, health professionals and governments; and for providing advice on ethical behaviour in health care and in the conduct of health and medical research.
NOAEL	No Observed Adverse Effect Level. Highest dose at which there is a measurable adverse effect from a test substance in a test subject or population.
NRV	Nutrient Reference Values. A set of nutritional recommendations, based on current scientific knowledge, used to assess the health status of populations and individuals.
Nutrient	A substance that provides nourishment essential for the maintenance of life and for growth.
NZ MoH	New Zealand Ministry of Health.
PICO	Population, Intervention, Comparison and Outcomes. A table used as part of the WHO GRADE approach to clearly identify the key questions of interest.
Potential for significant harm	Presents an established risk of impairment and/or adverse effects to the health or development of individuals.
RCT	Randomised Controlled Trial. Scientific clinical study designed to determine the efficacy of a potential treatments or medical interventions in a defined group of test subjects.
RDI	Recommended Dietary Intake. The average daily dietary intake level that is sufficient to meet the nutrient requirements of nearly all (97-98%) healthy individuals in a particular life stage and gender group.
SACN	Scientific Advisory Committee on Nutrition. A UK advisory committee of independent experts that provides advice on the nutritional content of food, diet, and nutritional status of people.
SDT	Suggested Dietary Target. A daily average (mean) intake from food and beverages for certain nutrients that may help in the prevention of chronic disease.
TGA	Therapeutic Goods Administration. Australia’s regulatory authority for therapeutic goods.
UL	Upper Level of Intake. The highest average daily nutrient intake level 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.
WHO	World Health Organization.

Summary of the methodological framework

Nutrient Reference Values (NRVs) are a set of recommendations for nutritional intake for individuals and/or population groups based on current available scientific knowledge. Recommendations are used to assess the health status of populations and individuals, advise individuals, and provide a fundamental evidence base for development of health policy.

In 2002, the Department of Health (DoH) (formally the Department of Health and Ageing (DoHA)), in conjunction with the New Zealand Ministry of Health (NZ MoH), commissioned the National Health and Medical Research Council (NHMRC) to review the existing Recommended Dietary Intakes (the only type of nutrient reference values that had been produced at the time). The review resulted in a new set of recommendations known as the *Nutrient Reference Values for Australia and New Zealand (2006)*. To ensure values remain relevant, appropriate and useful, NHMRC recommended that NRVs be reviewed every five years.

As a result, in 2011 DoH, in consultation with the NZ MoH, commissioned a scoping study to determine the validity of, and scope for, undertaking a review of NRVs. Stakeholders consulted during the study argued that a consistent methodology and approach is needed to increase confidence in the recommendations of subsequent reviews. A key finding from the study was that a future review provides the opportunity to improve the rigour of the nutrient review process through:

- greater transparency in the decision making process including clear justification for inclusion of experts and determination of nutrient values
- clear documentation of all underlying decisions, evidence, assumptions and rounding processes
- development of robust methodologies to construct recommendations, particularly for nutrients with gaps in the data for specific population groups.

To realise these objectives, the scoping study recommended the development of a methodological framework to guide future reviews of nutrient values.

In January 2013 DoH, in consultation with the NZ MoH, engaged Nous and a consortium of experts (led by Professor Peter Clifton, and including Dr Andrew Bartholomaeus, Professor Caryl Nowson, Associate Professor Jennifer Keogh, and Kylie Lange) to develop this methodological framework (see Appendix C for qualifications and experience of the expert team).

The framework aims to ensure broad stakeholder support and confidence in the recommendations of subsequent nutrient reviews through inclusion of methodologies and approaches that support the objectives of consistency, transparency and efficiency. Guidance provided in the framework is intended for Nutrient Expert Working Groups (EWGs) appointed by the Steering Group to review specific priority nutrients.

The framework consists of three sections:

- clarification of the conceptual basis and application of NRVs
- process for the review of NRVs
- methods for deriving NRV recommendations.

The framework is intended for application across a range of nutrients (both micro and macronutrients), and provides high level guidance that should not be affected by characteristics unique to individual nutrients.

A summary of the guidance provided in each section of the framework is provided in Table 1.

Note that the development of this framework has been informed by multiple rounds of consultations with relevant stakeholders. This process concluded with an invitation to key stakeholders to provide a written submission on final draft of the framework. Proposed changes in each submission were considered in the final production of the framework (with the results of this analysis provided in a written response to all submission authors).

Table 1: Summary of framework guidance

Clarification of the conceptual basis and application of NRVs

Framework section		Summary of guidance
Terminology of NRVs	*s. 2.1*	• The current suite of NRVs remains appropriate and applicable for future reviews. Neither the concepts, nor their names require change (see NHMRC 2006). • The concept of Adequate Intakes (AIs) remains acceptable and should continue to be used in the absence of sufficient data to establish an EAR (and hence RDI), in order to provide some guidance on adequacy of intakes for individuals or population groups. • A review of the data underpinning recommendations for Acceptable Macronutrient Distribution Ranges (AMDRs) for protein, carbohydrate and fat is needed. • The selective recommendation of Upper Levels of Intake (ULs) remains appropriate for some nutrients, however a range of options for UL descriptors should be developed to reflect the strength of underlying evidence.
Application of values to assess group and individual health status	*s. 2.2*	• Each NRV is intended to be used to assess nutrient intake. In most cases, NRVs can be used at an individual or population level, although the interpretation may be different. • For assessing groups, the EAR is used as a short-cut method to assess the prevalence of inadequate intakes for populations. • For assessing individuals, a comparison of their intake with the EAR provides the best estimate of the likelihood that an individual's usual intake is inadequate. • Recommended Dietary Intakes (RDIs) are only set where an EAR has been set (at EAR + 2 SD). Although RDIs provide a means of assessing if an individual's usual intake has a low probability of nutrient deficiency, RDIs cannot be used for the absolute diagnosis of nutrient deficiency in individuals. RDIs should not be used to assess nutrient intakes for populations. • Adequate Intakes (AIs) are used to assess if an individual's usual intake (where an individual has an intake > AI) has a low probability of inadequacy. For populations, if the median intake> AI, a low prevalence of inadequate intakes is implied. When the AI is based on the median nutrient intake of healthy populations (derived from a previous national nutrition survey) the assessment for an individual or population is made with less confidence. • Clarity of the basis and application for each NRV recommendation is necessary to avoid misuse of values (particularly the RDI). Materials outlining the conceptual basis of EARs and RDIs should be distributed to Nutrient EWGs prior to review.

Framework section		Summary of guidance
Health endpoints, physiological and dietary requirements, and nutrient interactions	*s. 0*	• Where relevant, NRVs should address both nutritional deficiency and chronic disease prevention. Recommendations for deficiency and chronic disease prevention should be clearly separated. • If a meta-analysis shows a convincing association[1] between a nutrient and a primary health outcome, the Suggested Dietary Target (SDT) should be the median of the desirable population intake so that it is analogous to the AI. • Reviews of Vitamin D and Vitamin K should clearly identify separate descriptions of physiological requirements and dietary intake recommendations. • Bioavailability and bioconversion should be taken into account when developing dietary intake recommendations. For vitamins, the concept of equivalents should be continued (e.g. retinol equivalents, niacin equivalents, alpha-tocopherol equivalents). For minerals, a percentage factor should be applied to the physiological requirement to determine the dietary recommendation. • Systematic reviews are needed to investigate the factors to apply for bioavailability and bioconversion where these are applied in developing nutrient values. • Known interactions between nutrients should be taken into account in the assessment of data and development of values. This should include an assessment of the intake of the nutrients or relevant foods in the Australian and New Zealand population.

Process for the review of NRV

Framework section		Summary of guidance
Steering Group	*s. 3.1*	• The Steering Group comprises representatives of DoH and NZ MoH, the two funding bodies. • The Steering Group is responsible for horizon scanning and ongoing monitoring of changes that may trigger the need for a review. • Criteria for prioritising nutrients for review are: (i) changes to and/or developments in NRVs in comparable countries; (ii) emergence of new evidence; (iii) public health priorities; and (iv) lack of methodological rigour in previous reviews.

[1] Where convincing association is consistent with NHMRC's use of the term in the Australian Dietary Guidelines

Framework section		Summary of guidance
Advisory Committee	*s. 3.2*	• The nutrient review requires an expert reference and advisory group that can act as an independent moderator of nutrient recommendations (i.e. an Advisory Committee). • The Committee should be comprised of members with a broad range of expertise, including micronutrients, toxicology, public health, end user needs, research, chronic disease, nutrition and macronutrients. The Committee should include members from both Australia and New Zealand. Food, supplement and drug industry representatives should not be appointed to the Advisory Committee. • All final decisions on NRVs (i.e. whether recommendations from the Nutrient EWG have been accepted or not) should be communicated to Nutrient EWGs, with feedback provided on the rationale for acceptance/ rejection of proposed values.
Nutrient EWGs	*s. 3.3*	• Each Nutrient EWG should include five-six members (including a younger scientist for succession planning). • Each Nutrient EWG should include at least one representative from Australia and New Zealand. For nutrients that are a higher priority in New Zealand, it is essential to include New Zealand representation in the Nutrient EWG membership. • Each Nutrient EWG should consist of (or have access to) a range of expertise, including statisticians, toxicologists, and end users. Representatives from the food, supplement and drug industry should not be included in Nutrient EWGs. • There are several possible models for Nutrient EWG composition. The selected model will depend on: (i) available funding and access to expertise; (ii) the nutrient(s) selected for review; and (iii) the selected area(s) of focus. • The primary responsibility of Nutrient EWGs is the derivation of revised NRVs and an assessment of the implications of proposed changes to NRVs (if any). E.g. whether food fortification or recommendations for supplementation is required. • Nutrient EWGs are required to record all discussions and the rationale for arriving at conclusions.
Develop NRV report	*s.3.4*	• Upon completion of the review, Nutrient EWGs need to provide the draft guideline outlining the recommendations for use in clinical settings and in population assessment. The draft guideline should include a technical report, which provides a record of the evidence review process. • Guidelines need to include: (i) the funding source for the NRV review; (ii) a plain English summary of the recommendations; (iii) the context for use of NRVs; (iv) a brief summary of the scoping study used to assess the 2006 Nutrient Reference Values; and (v) the triggers and rationale for conducting a review.
Public consultations	*s. 3.5*	• Revised NRVs and review data should be made available on a public website and an opportunity for public comment provided on at least one occasion.

Framework section		Summary of guidance
Independent expert reviews	*s. 3.6*	• Before finalisation of NRVs for each nutrient, the NHMRC will initiate independent methodological and clinical expert reviews of the final draft recommendations and approve a protocol for the process of the NRV review.
Submission to NHMRC	*s. 3.7*	• Secretariat is responsible for submission of the draft guidelines to NHMRC, along with the technical report, administrative report, public consultation submissions summary, and dissemination plan. • The NZ MoH is responsible through its internal endorsement processes for adoption of the draft recommendations, after consideration of all relevant reports and consultation processes.

Methods for deriving NRV recommendations

Framework section		Summary of guidance
Define the question	*s. 4.1*	• The first step in the derivation of a new numerical value is to clearly define the issue in relation to the current recommended value(s) and any special issues associated with the nutrient. • After defining the question, Nutrient EWGs need to identify the focus of the review, including: (i) the form of recommendation (e.g. UL, EAR); (ii) the life stage population group of relevance (e.g. infants, children, adults); and (iii) health criteria and outcomes (nutritional deficiency or chronic disease prevention).
Select biomarkers	*s. 4.2*	• The physiological and biochemical indices of a nutrient deficiency state need to be clearly defined, including measurement methods. • Endpoints relevant for the assessment of deficiency status and chronic disease prevention should be clearly defined in advance of selecting the evidence and justified. • Biomarkers used to assess the level of nutrient intake required to reduce chronic disease need to be associated with disease outcomes, modifiable by the nutrient intake that is associated with change in disease risk. . For example, fish intake is associated with less cardiovascular disease, and plasma fatty acids as a marker of fish intake are also associated with the disease outcome and change in response to intake of fish. Biomarkers used as indicators of deficiency states need to be confirmed as being measurable and reliable.

Framework section		Summary of guidance
Select evidence and data	*s. 4.3*	∘ Selection of evidence should be confined to that which will help answer the question(s) formulated about the specific NRV. ∘ Selection of evidence should commence with a review of the recent work on NRVs conducted by the IOM, EURRECA, and the European Food Safety Authority (EFSA). ∘ New studies should be identified through a systematic style search, following NHMRC methods with clearly defined search terms and a priori reasons for inclusion/ exclusion, rather than a selective approach to locating studies. ∘ The most important consideration in assessment of the evidence is consistency across all sources of evidence. ∘ For both prevention of nutrient deficiency and chronic disease, high quality systematic reviews and meta-regressions of randomised control trials (RCTs) and cohort studies should be the primary source of data. In the absence of these studies, double blind RCTs should be used where possible. This evidence should be critically examined in the context of usual population intakes from food (as collected in national surveys) and the impact on population health, utilising longitudinal studies and relevant epidemiological data.
Assess the quality of evidence	*s. 4.4*	∘ As per the NHMRC guidelines, only one approach, either the GRADE (Grading of recommendations, assessment, development and evaluation) approach used by the World Health Organization (WHO) or NHMRC levels of evidence and grading process (referred to as FORM from here on in) approach should be applied. GRADE is the preferred approach as this is internationally recognised and rates studies that have been conducted well more highly than similar types of studies that have been poorly conducted (i.e. not all RCT studies would be graded equally). If FORM is used, evidence should be assessed according to the *NHMRC levels of evidence and grades for recommendations for developers of guidelines* (NHMRC guidelines) (noting that there may be very few level II studies and that only metabolic or factorial studies may be available). ∘ For both macro and micronutrients, the best approach to assess the evidence is to use the GRADE system.

Framework section		Summary of guidance
Derive NRV recommendations	*s. 4.5*	◦ Recommendations for deficiency prevention should be derived according to either the factorial or dose-response approach. ◦ The EAR is set at the point at which 50% of the population are deficient according to the selected biomarker/ physiological criteria. ◦ For the prevention of chronic disease, the evidence will be a mix of observational and intervention studies. ◦ Recommendations provided by Nutrient EWGs should be sent to independent experts for review by the Advisory Committee if they are controversial or represent a significant change from previous values. ◦ Recommendations should be tested for coherence, alignment and validity through: (i) comparison with international values; (ii) comprehensive dietary modelling of Australian and NZ populations to assess the consequences of the revised NRVs (i.e. whether the recommendation can be achieved with or without additional fortification or supplementation); and (iii) consideration of whether the new value is sufficiently different from the old value to justify a change, and what the consequences would be if a change was not made (note consideration of the consequences of changing the NRV is the responsibility of the Steering Group and Advisory Committee).
Apply scaling and extrapolation methods	*S .4.6*	◦ Scaling methods should be selected on a case-by-case basis and should consider: (i) the context of the available evidence; and (ii) differences in metabolism, toxicokinetics, and homeostatic mechanisms between adults and children. ◦ The two extrapolation methods used by EURRECA and the IOM are an appropriate starting point.

Determine Upper Levels of Intake	*s. 4.7*	◦ ULs should only be developed when there is strong, high quality evidence supporting the potential for significant harm from realistically achievable dietary intakes (from diet and supplements combined).
		◦ Other options for UL descriptors should be considered when the data supporting adverse effects of high intake is poor in quality; speculative; reliant on biomarkers of uncertain relationship to primary health outcomes; or derived from populations with unusual or deficient diets.
		◦ The four options for UL descriptors are:
		  ◦ Upper Level of Intake (UL)
		  ◦ Provisional UL
		  ◦ Not determined
		  ◦ Not required.

1 Role of the methodological framework in guiding nutrient reviews

Nutrient Reference Values (NRVs) are a set of recommendations for nutritional intake based on current available scientific knowledge. Recommendations are used to assess the health status of populations and individuals, and provide a fundamental evidence base for development of health policy.

This methodological framework has been developed to guide reviews of nutrients included in the *Nutrient Reference Values for Australia and New Zealand (2006).* This section outlines the background to the framework and provides the rationale for its development, including:

- the history and process for the development of current NRVs
- justification for a review of nutrient values and opportunities to improve the future review process
- the purpose and structure of the methodological framework.

1.1 NRVs are used by a diverse range of stakeholders to assess population and individual health

NRVs are a set of recommendations for nutritional intake used by a variety of stakeholders to assess the dietary requirements of population groups and individuals.

Recommendations are intended for use by professionals (rather than consumers), and are applied for a range of purposes, including:

- **Public health** – used by policy makers, epidemiologists and researchers in the assessment of nutrient intake data to support the development of health policies and guidelines
- **Population group health** – used by dietitians to plan menus for institutions and by dietitians and other professionals to assess the adequacy of nutrient intakes in national surveys
- **Risk assessment** – used for population group risk assessment of both nutrient deficiency and toxicity
- **Regulation** – used by Food Standards Australia New Zealand (FSANZ) and the Therapeutic Goods Administration (TGA) for assessments underpinning regulatory decisions, including: (i) voluntary and mandatory food fortification (e.g. iodised salt in bread, thiamin and folic acid in wheat flour for bread making); (ii) food labelling standards and requirements; and (iii) nutrient supplements
- **Food formulation** – used by food manufacturers for formulation, fortification and product labelling as permitted by the Food Standards Code
- **Individual health** – used by health professionals (e.g. doctors, dietitians) for dietary planning and individual risk assessment
- **Education and research** – used in a range of education settings and academic research.

NRVs have been translated for the public into guidelines that describe food intake rather than nutrient intake. Australian and New Zealand guidelines include:

- *Australian Dietary Guidelines* (DoHA, NHMRC, 2013) – provides recommendations for food and nutrition intake, as well as physical activity, breastfeeding, handling and storage of foodstuffs. The recommended foods in this guideline are derived predominantly from epidemiology but it would be expected that these guidelines if followed completely would meet all the NRVs. Similarly the guidelines are designed to provide a food pattern associated with the lowest risk of chronic disease which parallels to specific SDTs in this document.
- *Australian Guide to Healthy Eating* (DoHA, NHMRC, 2013) – provides recommendations for food types that should be included in a healthy diet (and which should be avoided or limited)
- *Food and nutrition guidelines for five life-stages: Background papers for health practitioners and associated health education resources for the public* (NZ MoH 2003-2013) – provides information about the nutritional and physical activity requirements necessary for optimum health amongst individuals at various life stages and ages. Documents in the series specifically address infants and toddlers, children and young people, pregnant and breastfeeding women, adults and older populations.

Note that while the recommendations may have many purposes, they are intended for use amongst healthy populations and may not meet the specific nutritional requirements of individuals with various diseases or conditions, pre-term infants, or people with distinctive genetic profiles that affect absorption, bioavailability, or metabolism of nutrients.

1.2 A major review of nutrient values was conducted in 2006

The current set of NRVs for Australia and New Zealand was developed through a comprehensive and extensive review process.

The process for developing NRVs commenced in 1997 with a workshop with nutrient experts which identified the need for a comprehensive review of the Recommended Dietary Intakes (RDIs) developed in 1991. The following year, a discussion paper titled *Recommended dietary intakes - is it time for a change?* (Cobiac L, Dreosti I, Baghurst K, 1998) addressed a series of issues related to the RDIs, including their appropriateness, the need for reference values that address health issues other than deficiency, and the process for a future review of reference values.

In response, in 2002 the NHMRC (at that time part of the Department of Health and Ageing (DoHA)) reviewed the existing nutrient values in conjunction with the New Zealand Ministry of Health (NZ MoH). The review resulted in a new set of recommendations known as the *Nutrient Reference Values for Australia and New Zealand (2006)*, replacing and expanding the 1991 RDIs.

The nutrient review process extended over four years and involved two main groups of experts:

- A Working Party, consisting of 13 members (including the Chair) was appointed by NHMRC to oversee the review process. Membership included representatives from DoHA, NZ MoH, FSANZ, the Australian Food and Grocery Council, the Commonwealth Scientific and Industrial Research Organisation and academics.
- Expert reviewers were appointed to complete between one and three reviews of nutrient values. Some reviewers were involved in the decision making process, however the Working Party had final responsibility for determining nutrient references.

The starting point for development of NRVs was the US-Canadian Dietary Reference Intakes (DRIs), which were developed by the Institute of Medicine (IOM) between 1994 and 2004. The suitability of DRI values for the Australian and New Zealand context was determined using a template developed by the Working Party which required consideration of a range of factors, including population groups, dietary

patterns, interpretation of evidence, and comparison with values used by other countries and organisations (e.g. the Food and Agriculture Organization and the World Health Organization (WHO)).

Key dates in the nutrient review process are provided in Table 2.

Table 2: Key dates in the development process for the 2006 NRVs

Timeframe	Activity
July 1997	A workshop held with nutrient experts identified the need to revise the 1991 RDIs.
July 1999	A second workshop with experts scoped the recommendations of the 1997 meeting and decided: • a joint review between Australia and New Zealand should be conducted • a set of nutrient recommendations should be developed using the terminology of NRVs • NRVs should be based on the US-Canadian DRIs and concurrent work being conducted in these countries.
2002	DoHA commissioned NHMRC to undertake a scoping study for the review of nutrients. Following this, NZ MoH proceeded by funding the review of two priority nutrients, iodine and selenium.
2002	The Working Party is appointed to oversee the review process.
2002 – 2004	Nutrient expert reviewers completed reviews of 40 priority nutrients.
Dec 2004 – Mar 2005	Draft recommendations were released for public consultation, which included: • Public submissions • Two workshops with health professionals, food industry representatives and end users in Australia and New Zealand.
May 2005	The Working Party received and considered a total of 64 public submissions.
2006	NHMRC endorsed the NRVs for Australia and New Zealand.

There were several key differences between the 2006 NRVs and the 1991 RDIs:

- A range of reference values were developed, including the Recommended Dietary Intake (RDI), Adequate Intake (AI), Upper Level of Intake (UL) and Estimated Average Requirement (EAR). These reference values expanded the range of classifications for the first time and enabled some assessment of dietary adequacy for individuals and groups.
- NRVs were developed for more than 36 different nutrients and energy, compared to the 19 nutrients included in the 1991 RDIs. NRVs were developed for several macronutrients for the first time.
- The review addressed both nutritional deficiency and chronic disease prevention. This involved development of Suggested Dietary Targets (SDT) and Acceptable Macronutrient Distribution Ranges (AMDR) for reducing the risk of chronic disease.
- Age categories for adults were expanded from two to four, life stages for pregnancy and lactation were expanded from one to three, and age categories for children were reduced from eight to six.
- NRVs provided an Estimated Energy Requirement (EER) for different genders, ages and heights, whilst the 1991 RDIs provided a range of energy intakes for any age-gender group.

The final NRVs provided guidance in four different aspects– prevention of deficiency (EAR, RDI, AI), prevention of harm (UL), maintenance of optimum health (EER and AMDR), and prevention of chronic disease (SDTs).

Definitions for the different NRV recommendations are provided in Table 3.

Table 3: Definitions from *Nutrient Reference Values for Australia and New Zealand (2006)*

The following definitions were used in the 2006 review, adapted from the Institute of Medicine definitions:

- **EAR (Estimated Average Requirement)** – A daily nutrient level estimated to meet the requirements of half the healthy individuals in a particular life stage and gender group.
- **RDI (Recommended Dietary Intake)** – The average daily dietary intake level that is sufficient to meet the nutrient requirements of nearly all (97-98%) healthy individuals in a particular life stage and gender group.
- **AI (Adequate Intake)** – The average daily nutrient intake level based on observed or experimentally-determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate (used when an EAR cannot be determined).
- **EER (Estimated Energy Requirement)** – The average dietary energy intake that is predicted to maintain energy balance in a healthy adult of defined age, gender, weight, height and level of physical activity consistent with good health. In children and pregnant and lactating women, the EER is taken to include the needs associated with the deposition of tissue or the secretion of milk at rates consistent with good health.
- **UL (Upper Level of Intake)** – The highest average daily nutrient intake level 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.
- **AMDR (Acceptable Macronutrient Distribution Range)** – An estimate of the range of intake for each macronutrient for individuals (expressed as per cent contribution to energy), which would allow for an adequate intake of all the other nutrients whilst maximising general health outcome.
- **SDT (Suggested Dietary Target)** – A daily average (mean) intake from food and beverages for certain nutrients that will help in prevention of chronic disease.

1.3 A scoping study was conducted to determine the validity of, and scope for, a new review of NRVs

To ensure NRVs remain relevant, appropriate and useful, in 2006 NHMRC recommended that NRVs be reviewed every five years.

As a result, in 2011 DoHA, in consultation with NZ MoH, commissioned a study to investigate the validity of, and scope for, undertaking a review of the 2006 NRVs for Australia and New Zealand. The scoping study concluded that there was sufficient justification for a review given:

- The release of new DRIs (for vitamin D and calcium) by the IOM in 2010 and new findings from international research groups were likely to have implications for the accuracy and appropriateness of current NRVs.
- New evidence on the relationship between nutrients and chronic disease suggested that the chronic disease section was out-dated and required comprehensive review.

- The fortification of the food supply, and the increasing use of supplements, requires regular monitoring of recommendations for nutritional intake, particularly in relation to ULs.

In contrast to the 2006 review, the scoping study advised future reviews of nutrients should be targeted. Nutrients assessed as high priority by the Steering Group should be reviewed immediately, and then other nutrients should be reviewed on a rolling basis as time and funding permit.

1.4 The scoping study identified opportunities to improve the methodological rigour of setting NRVs

Throughout the consultation process associated with the scoping study, stakeholders argued that a consistent methodology and approach (both for assessing the evidence and setting the NRVs) is needed to increase confidence in the recommendations of subsequent reviews.

A number of opportunities to improve the methodological rigour of future nutrient reviews were identified, including:

- Reviews should be conducted in a consistent manner across the different nutrients.
- A future review should ensure adequate documentation of underlying decisions, evidence, assumptions and rounding processes to aid interpretation of values by users. This was cited as being particularly important for the derivation of ULs.
- The decision-making process needs to be more transparent, and include the rationale for inclusion of experts and determination of NRVs.
- Recommendations for NRVs for particular population groups (e.g. children, infants and the elderly) with gaps in the data need to be developed based on robust and coherent methods (e.g. construction of ULs through extrapolation of adult values to children based on body weight).
- Comprehensive dietary modelling should be conducted to ensure recommendations can be translated into dietary advice. The modelling also needs to take into account the current use of supplements and the potential for the new recommendation to increase the number of people exceeding the UL.
- The document outlining NRVs should be more user-friendly, and should support consistent implementation and interpretation of values amongst users.

As a result, the scoping study proposed that a new review begin with the development of a methodological framework that outlines the overarching principles, methodologies, and approaches that will ensure consistency of application and transparency in the review process across nutrients.

1.5 This methodological framework aims to ensure ultimate confidence in the recommendations for NRVs

This framework has been developed through consultations with technical experts, and drew on recent work conducted in comparable international jurisdictions. In particular, the framework recently developed by the European Micronutrient Recommendations Aligned (EURRECA) between 2007 and 2012 was used as a starting point for development of the methodological framework.

Development of the framework included the following activities:

- Research and document reviews – a review was conducted of: (i) the EURRECA framework for establishing micronutrient values; (ii) methodologies used by the IOM to derive DRIs between

1994 and 2004; and (iii) documentation from the Australian and New Zealand 2006 nutrient review process

- Literature review – a high level literature review of nutrients with recommendations was conducted to identify idiosyncrasies and characteristics of different nutrients that may impact guidance provided in the framework
- Consultations with technical experts – two workshops (one in Australia and one in New Zealand) were conducted to provide technical experts with the opportunity to contribute to development of the framework (note the opportunity for written feedback was provided to technical experts unable to attend the workshops).

The methodological framework aims to ensure broad stakeholder support and confidence in the recommendations of subsequent nutrient reviews by focussing on three objectives:

1. **Consistency** – provides a set of principles, methodologies and approaches to ensure the method and approach for the review is consistent: (i) across nutrient review teams; and (ii) irrespective of the timing of reviews. The framework needs to ensure consistency in method, whilst being flexible enough to accommodate the differences between individual nutrients. The inclusion of scientifically sound and rigorous methodologies (free of preconceptions or philosophical influences) should enable independent experts examining the same data to arrive at very similar conclusions (at a minimum).
2. **Transparency** – provides a practical set of principles, methodologies, and approaches for reviewing evidence and setting nutrient levels in a transparent manner. For example, all discussions are documented and fully justified, and a full case is supplied where a change is made.
3. **Efficiency** – simplifies the review process without compromising the rigour of nutrient reviews. The framework can be adapted across a range of nutrients (including both micro and macronutrients).

Guidance provided in the methodological framework is intended for Nutrient Expert Working Groups (EWGs) appointed to review specific priority nutrients.

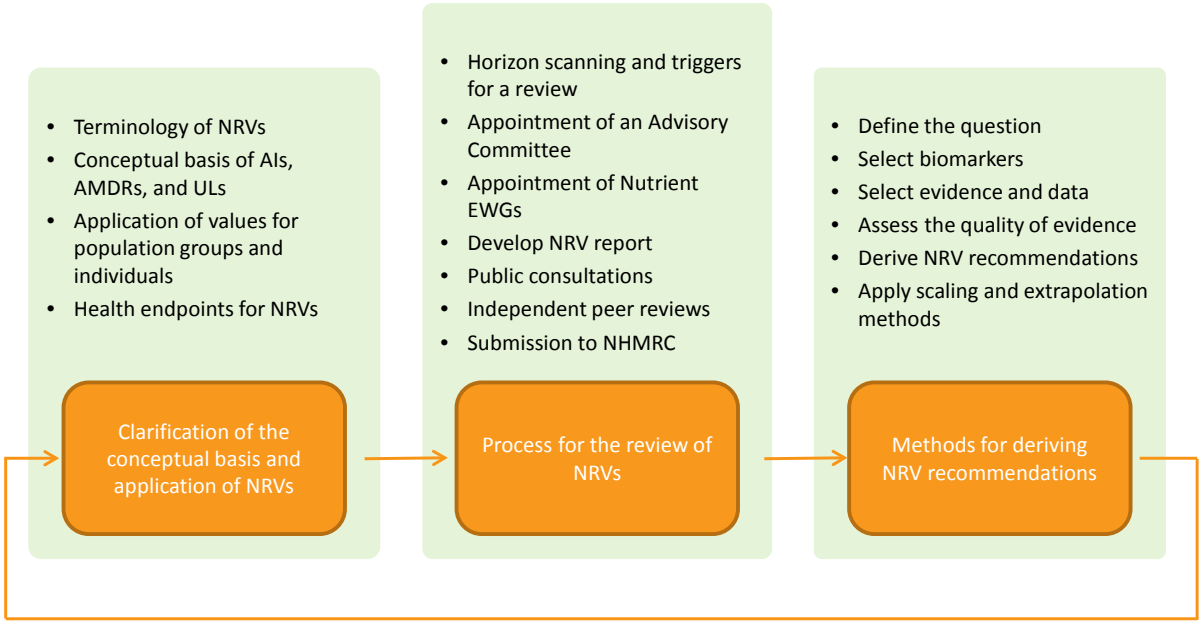
The framework is designed for application across a range of nutrients (both micro and macronutrients), and hence provides high level guidance that should not be impacted by characteristics unique to specific nutrients.

The framework consists of three sections:

- **Clarification of the conceptual basis and application of NRVs**– provides guidance on the terminology and conceptual basis underpinning NRV recommendations, and application of recommendations for assessment of population group and individual health status
- **Process for the review of NRVs** – outlines the process for the review of NRVs
- **Methods for deriving NRV recommendations –** provides specific methodologies and approaches to guide Nutrient EWGs in the assessment and derivation of NRVs.

The structure of the methodological framework is shown in Figure 1.

Figure 1: Structure of the methodological framework



2 Clarification of the conceptual basis and application of NRVs

Guiding principles

- Members of Nutrient Expert Working Groups have a clear and consistent understanding of the conceptual basis underpinning NRVs (particularly AIs, AMDRs and ULs[2]).
- Stakeholders, as listed on page 16, use NRVs accurately and consistently for the assessment of population and individual health status (particularly EARs, RDIs and AIs).
- Values for deficiency status and chronic disease prevention are derived consistently[3] across nutrient reviews.

The methodological framework provides the opportunity to address a number of issues associated with the derivation and application of NRVs.

A key concern identified by stakeholders was the appropriateness of current terminology, and the validity of the conceptual basis underpinning AIs, AMDRs, and ULs. Some stakeholders questioned whether it would be more appropriate to harmonise NRV terminology with international values.

Selection and application of values for assessment of the dietary adequacy of individuals was also identified as problematic. Lack of understanding about appropriate application of values has led to common misuse of values, particularly the RDI. Technical experts indicated that greater clarity about the application of EARs ad RDIs for the assessment of individual health status is required.

Additionally, the methodological framework provides the opportunity to clarify a number of conceptual issues underpinning nutrient reference values. Three issues were identified as being particularly contentious and in need of clarification: (i) the use of deficiency and chronic disease prevention as health endpoints; (ii) development of physiological versus dietary requirements; and (iii) consideration of the interactions between nutrients.

The following sections clarify each of these issues identified by stakeholders.

2.1 The current terminology and definitions for NRVs remain appropriate for future nutrient reviews

Technical experts consulted during development of the methodological framework indicated that consideration should be given to international harmonisation of NRVs.

The current terminology used for NRVs differs to international values, for example:

- Average Requirements (AR) are used by EURRECA as the equivalent of EARs (note Population Reference Intakes 50 (PRI 50) are the equivalent of ARs)

- Population Reference Intakes 95 (PRI 95) are used by EURRECA as the equivalent of RDIs (note under some circumstances PRIs can also be set at other levels (e.g. PRI 80)).

Some technical experts argued that international harmonisation of terminology would provide greater clarity of the purpose and application of values, whilst others indicated that a change in terminology would lead to considerable confusion amongst Australian and New Zealand users.

Although the current terminology of NRVs differs to international values, the definitions and underlying concepts remain largely similar. A comparison of the terminology used in Australia and New Zealand and internationally is provided in Table 4.

As a result, it was determined that the current terminology for NRVs remains largely appropriate and applicable for future nutrient reviews (see Table 3 for current definitions).

Note that this framework supports consistency in the derivation and conceptual basis of NRVs by drawing on methodologies and approaches used by both EURRECA and WHO (where relevant and appropriate).

The basis for development of AIs, AMDRs, and ULs was identified as more contentious than other nutrient values. These three values are discussed in detail below.

Adequate Intakes (AIs)

AIs were established during the 2006 review when there was insufficient data to set an EAR (and hence a RDI). AI values were based on either experimental evidence, or adopting the most recently available population median intake and assuming Australian and New Zealand populations were not deficient.

As a result, AIs are determined based on lower levels of certainty and require a higher level of judgement when they are being used than the RDI. A number of stakeholders expressed concern that the difference in the strength of evidence underpinning the EAR and AI was not well understood and needs to be more clearly communicated. Additionally, differences in the use of EARs and AIs are not well understood by a number of stakeholders.

The concept of AIs remains acceptable and should continue to be used in the absence of sufficient data to establish an EAR in order to provide some guidance on the probability of inadequate intakes for individuals. An alternative name may make the derivation and purpose of the AI clearer for users.

An AI should only be defined as the median intake of the nutrient in question in an apparently healthy population, and could be used to guide dietary recommendations for an individual. Nutrients with unique characteristics (e.g. vitamin D, vitamin K, and sodium) may be an exception.

Consequently, the AIs for the following nutrients (which are currently based on data from experimental studies), will need to be redefined:

- fatty acids
- potassium, sodium
- chromium, copper, fluoride
- biotin and choline.

For these nutrients the future AI will be higher than the (unknown) RDI because: (i) there is no evidence that the Australian and New Zealand population has any level of deficiency; and (ii) the CV of intake typically exceeds the CV of requirement.

End-users should interpret AIs with caution, and recognise that AIs cannot be used to clearly define inadequate dietary intake.

Acceptable Macronutrient Distribution Ranges (AMDRs)

The concept of AMDRs was adopted from IOM values and has generally not been widely supported. There is limited understanding amongst stakeholders about how they have been derived, and revision of the US Dietary Guidelines in 2010 presented evidence suggesting that AMDRs may be unnecessary for carbohydrate and fat and potentially misleading (particularly in the context of a high rate of overweight and obesity).

A review of the data underpinning recommendations for acceptable ranges of protein, carbohydrate and fat is required.

Following the initial review of nutrients, it may be appropriate to abandon the concept of a range. If the concept of a range is retained, it may be appropriate to change the name to avoid the implication that intakes outside the nominated range are unacceptable (e.g. it may be more suitable to name them Optimal Macronutrient Distribution Ranges).

Upper Levels of Intake (ULs)

ULs are important for dietitians in clinical practice with patients taking supplements or on unusual diets.

Current guidance for ULs has not been widely supported for several reasons:

- The process and principles underpinning ULs are less established than other NRVs and vary between regulatory and advisory bodies. As a result, no single source provides a suitable model or basis (in isolation) for developing ULs for Australia and New Zealand.
- The current process for setting ULs is based on the approach used for chemical additives and contaminants in food. ULs are frequently extrapolated to either adults or children. There is a recognised need that if consideration was given to checking normal dietary exposure compared to the exceeded extrapolated value set this would improve the process. This means that some current UL values are overly precautious.
- Prescriptive ULs have significant potential impacts upon regulatory bodies (e.g. FSANZ, TGA, Medicines and Medical Devices Safety Authority (Medsafe) and public health initiatives).
- Establishment of ULs based on poor quality data (or application of excessive precaution or conservatism) can result in discordance between regulatory determinations, which are contestable at the Administrative Appeals Tribunal.

Provision of UL recommendations for Australian and New Zealand populations remains appropriate for some nutrients. A range of options for UL descriptors should be developed however to reflect the strength of underlying evidence. Details about the different options are provided in Section 4.7.

Table 4: Comparison of international nutrient recommendations

Recommendation type	Australia/ New Zealand	EURRECA	US-Canada	World Health Organization	UK (SACN)	European Food Safety Authority
	Nutrient Reference Values (NRV) 2006	Dietary Reference Values (DRVs) 2013	Dietary Reference Intake (DRI) 1994 - 2004	Vitamin and mineral requirements in human nutrition 2004	Dietary Reference Values (DRV) 1991	Dietary Reference Values (DRV) 2010
Deficiency	Estimated average requirement (EAR)	Average requirement (AR)	Estimated average requirement (EAR)	Estimated average requirement (EAR)	Estimated average requirement (EAR)	Average requirement (AR)
	Recommended dietary intake (RDI)	Population reference intake (PRI 95)	Recommended dietary allowance (RDA)	Recommended nutrient intake (RNI)	Reference nutrient intake (RNI)	Population reference intake (PRI)
	Adequate intake (AI)	~	Adequate intake (AI)	~	Safe intake	~
Safety	Upper level of intake (UL)	~	Upper level of intake (UL)	Upper level of intake (UL)	Upper level of safe intake (UL)	Upper level of safe intake (UL)
Optimum Health / Chronic Disease Prevention	Suggested Dietary Target (SDT)	~	~	~	~	~
	Estimated energy requirement (EER)	~	~	Energy requirement (ER)	Estimated average requirement (energy) (EAR)	Average Requirement (Energy) (AR)
	Acceptable macronutrient distribution range (AMDR)	~	Acceptable macronutrient distribution range (AMDR)	Some macronutrients (e.g. protein) assigned EAR and RNI values Dependent upon evidence	~	Macronutrients (e.g. protein) assigned AR and PRI values

Reference: King J, Garza C et al. 2007

2.2 Although terminology remains appropriate, the application of some recommendations requires clarification

Deriving dietary reference requirements needs to be recognised as a difficult task. Estimated values are approximations, and often lean on the side of caution rather than precision. Additionally, recommendations reflect the limited data that is often available, and the need for inductive extrapolation of data from small groups of individuals to large, heterogeneous populations. These methods of extrapolation are often unreliable due to the lack of information about the population distribution of requirements (assumed to be Gaussian but is probably skewed and influenced considerably by homeostatic mechanisms) (Aggett et al, 1997).

Each nutrient recommendation has different levels of nutritional adequacy:

- **Estimated Average Requirement (EAR)** – Nutrient level is adequate for 50% of the population (i.e. it is median requirement). Studies that test a dose that leads to more or less than 50% of subjects being inadequate do not identify the EAR. However a scaling could be derived based on the body of evidence using appropriate statistical methods which would allow the EAR to be calculated.
- **Recommended Dietary Intake (RDI)** – Nutrient level is adequate for 97.5% of the population because it is two standard deviations above the EAR (CV is assumed to be 10% of the mean unless evidence suggests otherwise).
- **Adequate Intake (AI)** – Nutrient level is derived from less robust data than the EAR. The AI may be derived from the median intake of apparently healthy populations (but may be based on observed or experimentally derived approximations). However, it is also defined in some literature (but not in the 2006 NRV document) as a level expected to meet the needs of essentially all members of the population. In these circumstances the AI is closer to a RDI than an EAR. The AI is only established when an EAR cannot be determined (usually due to insufficient levels of high quality data).
- **Upper Level of Intake (UL)** – Daily nutrient intake that under most circumstances should not be exceeded over longer periods of time, but, dependent on the nutrient and the nature of the effect on which it is based, might be safely exceeded over a shorter period of one to several days. I.e. for some nutrients, the average intake over one to three months may be more important than intake over a single (or several) days.

Each of the specific types of nutrient recommendation (EAR, AI, UL etc.) can be used to assess individual nutrient status, and/or group nutrient intake. However, not all nutrient recommendations are appropriate for application to both individuals and populations, and the use may vary depending on whether an assessment of individuals or groups or menu planning is being conducted.

For example, users intending to assess the nutritional status of a population may calculate the proportion with inadequate intakes using either the EAR cut-off method or the full probability approach for nutrients which have an EAR. However, for these same nutrients the RDI is typically used for menu planning for individuals in institutions and for individual diets to ensure nutritional adequacy (although the EAR and its CV can be used for a detailed examination). Assessment of population or individual intakes against the AI for nutrients which have this value is more limited, and in this case the population median is compared to the AI.

Stakeholders indicated that greater clarity about the use of EARs and RDIs for assessment of individual versus population health is required. In particular, determining the right value for assessment of dietary adequacy of individuals is problematic. Although by definition EARs will be correct 50% of the time, it might be appropriate to choose a higher level for greater certainty of adequacy (e.g. a value one

standard deviation above the EAR such as a population reference intake of 84). Selection of this level may depend on the height, age, and body weight of the individual.

Application of different NRV recommendations for individuals and groups is outlined in Table 5 below.

Table 5: Application of NRVs for assessment of individuals and groups (NHMRC 2006)

NRV	Application for individuals	Application for groups
Estimated Average Requirement (EAR)	Use to examine the probability that usual intake is inadequate.	Use to estimate the prevalence of inadequate intakes within a population group.
Recommended Dietary Intake (RDI)	Can be used to assess the intake of individuals. Usual intake at or above this level has a low probability of inadequacy.	Do not use to assess intakes of groups.
Adequate Intake (AI)	Usual intake at or above this level has a low probability of inadequacy. When the AI intake is based on median intakes of healthy populations, this assessment is made with less confidence.	Mean usual intake at or above this level implies a low prevalence of inadequate intakes. When the AI is based on median intakes of healthy populations, this assessment is made with less confidence.
Upper Level of Intake (UL)	Usual intake above this level may place an individual at risk of adverse effects from excessive nutrient intake.	Use to estimate the percentage of the population at potential risk of adverse effects from specified levels of nutrient intake and to establish the nature and severity of the effects.
Suggested Dietary Targets (SDTs)	Where a chronic disease nutrient relationship is shown, a suggested value for the individual to achieve is based on the mean of the desirable population intake.	Where a chronic disease nutrient relationship is shown, a suggested value for the population is based on the mean of the desirable population intake.

Specific guidance about the use of EARs, RDIs, AIs and SDTs for the assessment of individual dietary adequacy is provided in the sections below.

Estimated Average Requirement

The EAR and the CV should be used to assess individual risk. The EAR and the CV provides the best estimate for an individual's unknown requirement, defined as the median requirement of a nutrient for a given life stage and gender group (IOM, 2000).

To ensure a consistent understanding of EARs (and avoid further misuse of RDIs), materials outlining the conceptual basis of these values should be distributed to Nutrient EWGs prior to nutrient reviews.

Recommended Dietary Intake

RDIs indicate the intake levels of essential nutrients considered to be adequate to meet the known nutritional needs of practically all healthy people.

The RDI value is derived based on the EAR plus two standard deviations. This value theoretically meets the requirements of 97.5% of the population (if the requirement is normally distributed). The Coefficient of Variation (CV) (defined as the standard deviation/ EAR) is usually assumed to be 10% unless there is direct evidence of a higher value. This means that only 95% of individuals have requirements between

80% and 120% of the EAR (± 2 standard deviations). For some nutrients, the CV of the requirement distribution may be higher (e.g. vitamin A).

The IOM states that Recommended Dietary Allowances (RDAs) (the US term equivalent to RDI), cannot be assumed to indicate that an individual's intake is inadequate. The RDA, by definition, exceeds the actual requirements of all but 2-3% of the population, so many people with usual intakes below the RDA may be meeting their individual requirements. The likelihood of nutrient inadequacy, however, increases as the usual intake falls further below the RDI until it reaches the EAR (at which point there is a 50% chance of sufficiency and a 50% chance of deficiency).

It is important to recognise that RDIs exceed the actual nutrient requirements of practically all healthy persons and are not synonymous with requirements. Although they provide a means of assessing the probability that individual members of a population are vulnerable to nutrient deficiency, RDIs cannot be used for the diagnosis of nutrient deficiency in individuals.

Adequate Intake

If there is no EAR and only an AI is available, it is still possible to determine whether an individual's usual intake is above the AI with a level of confidence. No conclusions can be drawn, however, when usual intake is below the AI.

Adequate Intakes (AIs) are used to assess if an individual's usual intake (where an individual has an intake > AI) has a low probability of inadequacy. For populations, if the mean intake > AI, a low prevalence of inadequate intakes is implied. When the AI is based on the median nutrient intake of healthy populations (derived from a previous national nutrition survey) the assessment for an individual or population is made with less confidence.

Suggested Dietary Targets

SDTs are to be used when a chronic disease nutrient relationship is shown, with the same quality of evidence required as that used to determine Australian Dietary Guidelines (DoHA, NHMRC, 2013).

Note that the establishment and use of SDTs is somewhat contentious. In part this is because they are not widely used in international guidelines, although the United States' ADMRs are a form of SDTs.

2.3 NRVs should address both nutritional deficiency and chronic disease prevention

The conceptual basis underpinning NRVs is broadly accepted amongst stakeholders. The most controversial issue identified as requiring clarification is the appropriateness of using nutritional deficiency and/or chronic disease prevention as the health endpoint for NRVs.

The conceptual basis for deriving NRVs can focus on either nutrient deficiencies (their original function) or the relationship with chronic disease. In comparable OECD countries the criteria for setting NRVs appears to be mixed – whilst deficiency prevention is the basis for most nutrients, disease prevention is also used for some e.g. calcium and vitamin D values are set for osteoporosis prevention as well as achievement of a normal peak bone mass and prevention of rickets. Another good example is the WHO report on sodium and potassium intakes in 2013 and on free sugars in 2015. These are clear nutrient based recommendations to minimise chronic disease.

The shift in scope from deficiency to chronic disease prevention was driven by: (i) gains in scientific knowledge regarding links between nutrition, chronic disease and optimum health; and (ii) the low prevalence of nutrient deficiency and changing dietary patterns in developed countries. As a result, values for chronic disease prevention were first developed as part of the UK Dietary Reference Values in 1991, and the US-Canadian Dietary Reference Intakes between 1994 and 2004.

NRVs developed by the Australian 2002-2006 Working Party used the concept of adequate physiological or metabolic function and/or avoidance of deficiency states as the basis for developing EARs and RDIs. The relationship between chronic disease and food intake patterns, rather than individual nutrient intake, made assessment of nutritional requirements for chronic disease prevention problematic. As a result, chronic disease was dealt with separately through development of two additional reference values (SDTs and AMDRs) when sufficient evidence was available (NHMRC, 2006).

Although some of the original SDTs in 2006 were based on epidemiology and interventions with intermediate biomarkers which ultimately proved not to be related to disease outcomes, it is entirely possible that further randomised controlled trials will show changes with nutrients (both positive and negative) in biomarkers that have been proven to robustly relate to disease outcomes. Blood pressure, LDL cholesterol and glucose would be regarded as biomarkers that are related to disease outcomes but more biomarkers may be proven over the next 10 year review period. If a nutrient is required to be given as a supplement rather than as a food this is acceptable if the evidence is derived from HIGH GRADE studies.

To ensure appropriate use of values and avoid confusion between the use of NRVs for avoidance of a deficiency syndrome and reduction of chronic disease, evidence should be assessed separately for both deficiency status and prevention of chronic disease. The terminology used for recommendations depends on the strength of evidence:

- If there is strong evidence for both chronic disease prevention and deficiency (e.g. randomised placebo controlled double blind trials), two different values should be set to cover deficiency and disease prevention (note a term other than EAR will need to be used for the value derived for chronic disease prevention). This value should be the median of the desirable population intake so that it is analogous to the AI, which is different to the current definition of SDTs which is at the 80^{th} percentile.
- If the evidence for chronic disease prevention is relatively weak (e.g. NHMRC Level III grade evidence) but there are several studies with the same results and also a metabolic rationale, consideration should be given to development of a Suggested Dietary Target (as per 2006 NRVs).

In determining appropriate recommendations for deficiency and/or chronic disease prevention, stakeholders identified two conceptual elements that require greater clarification:

- establishment of NRVs based on separate descriptions of physiological or dietary requirements for nutrients with non-ingested sources (i.e. vitamin D and vitamin K); and
- the interaction between different nutrients within foods and across the food matrix.

These two concepts are discussed in the following sections.

Physiological versus dietary requirements

There are two micronutrients that have non-dietary sources of intake – Vitamin D and Vitamin K.

Review of these two nutrients requires consideration of whether NRVs should be set based on: (i) physiological requirements of individuals (regardless of the source of intake); or (ii) dietary requirements following consideration of the non-dietary contribution to the physiological intake.

Nutrient reviews should clearly identify the basis for setting nutrients and ensure:

- Studies selected in the development of values are consistent in focus (i.e. dietary or physiological requirements)
- If values are developed based on dietary requirements, both physiological and dietary reference values are provided

- Recommendations clearly identify appropriate comparison and use of values (e.g. it is inappropriate to make comparisons between population vitamin D intakes with an AI that assumes minimal sunlight exposure).

Consideration should be given to development of an AI for vitamin D levels in Australia and New Zealand that takes into account some minimal degree of sunshine exposure in all regions.

Interaction between nutrients

Since nutrients are not consumed in isolation, interactions between different nutrients (both within foods and across the food matrix) are likely to impact nutritional status and health outcomes.

As a result, there has been a shift from assessment of single nutrients towards evaluation of whole diets and dietary patterns in chronic disease prevention. This was the approach adopted during the 2013 review of NRVs.[4]

Nutrient reviews should take into account any known interactions between nutrients in the assessment of data and development of values.

Further reading:

Part I of the IOM's Dietary Reference Intakes provides a comprehensive description of the conceptual basis of nutrient values. These chapters should be read prior to commencement of the review.

Reference for review:

Otten J, Pitzi Hellwig J, and Meyers, L. (2006) *Dietary Reference Intakes: Essential Guide to Nutrient Requirements*

[4] Also note that dietary patterns where considered in the 2006 review of NRVs for the optimising diets for lowering chronic disease risk section

3 Process for the review of NRVs

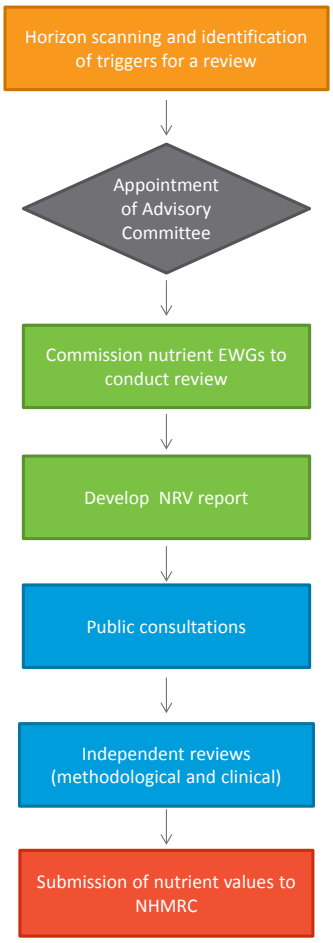
Guiding principles

- The process for nutrient reviews is transparent and provides stakeholders with adequate opportunity to contribute to the development of recommendations.
- The process for nutrient reviews is efficient and warrants the investment of time and resources.
- Selection of members of the Advisory Committee and Nutrient EWGs is transparent, and members have appropriate levels of knowledge, expertise and independence.
- The decision making process is highly transparent, with all discussions and the rationale for arriving at conclusions clearly recorded.

Nutrient reviews will be conducted on a rolling basis to ensure NRVs remain relevant and appropriate.

The Steering Group will oversee the nutrient review process and will be responsible for all strategic, funding and technical decisions of the review. The Steering Group consists of representatives from both funding agencies, namely the DoH and NZ MoH. The overall review process is shown in Figure 2.

Figure 2: Process for the review of nutrient values



The process follows requirements for meeting the 2011 NHMRC standard for clinical practice guidelines. NHMRC requirements should be reviewed by all individuals involved in the review process prior to commencement of each nutrient review.

Reference for review:

NHMRC (2011). *Procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines.*

Each step of the review process is discussed in the sections below.

3.1 Horizon scanning and identification of triggers for a review

The review process commences with horizon scanning for new evidence, international developments, or relevant changes in government policy that would warrant a future nutrient review.

The Steering Group is responsible for ongoing monitoring of triggers for a new review, and ensuring nutrient reviews are conducted in a timely manner.[5]

There are four criteria for prioritising a specific nutrient for review[6]:

1. *Changes to and/or developments in NRVs in comparable countries* – changes have been made to recommendations for specific nutrients in comparable Organisation for Economic Cooperation and Development (OECD) countries (e.g. changes to values developed by the IOM)
2. *Emergence of new evidence* – the emergence of significant new evidence suggests the current NRV may be inappropriate for the population
3. *Public health priority* – fortification or widespread supplement use (due to the perceived need for a particular nutrient by the public) may require a review of nutrient recommendations
4. *Methodological rigour* – there are concerns regarding the strength and/or consistency of the methodology and evidence underpinning the current nutrient recommendations.

Nutrients that are part of a mandatory fortification program should be reviewed every five to seven years to assess whether: (i) there is still a need for fortification; and (ii) there are any toxicity concerns that may require changes in ULs and fortification levels.

When decisions are made to commence a review, the Steering Group will publish relevant details on its website, including which nutrients are to be reviewed, and the timeline for completing the review.

The increased transparency and rigour in the process for reviewing NRVs increases the resources required to undertake the review. Before confirming that a review is required, the Steering Group should consider whether the likelihood of a NRV recommendation changing as a result of the review warrants the investment of time and resources. As a general guide, it is expected that a partial review of a NRV may take between four to six months, and a full nutrient review may take up to 12 to 15 months.

The Steering Group will make all decisions on the requirement for a nutrient review based on expert advice, and consult as required to guide the discharge of its responsibilities.

3.2 Appointment of the Advisory Committee

Once the need for a review has been confirmed, the Steering Group is responsible for appointment of an Advisory Committee. The Advisory Committee is intended as an expert reference and advisory group, and acts as an independent moderator of recommendations for NRVs.

[5] It is anticipated that each nutrient would typically be considered for review every five to ten years.

[6] Criteria for prioritisation of nutrients for review were identified by stakeholders as part of the scoping study. These should be considered as guiding the prioritisation process rather than requirements that must be satisfied before a review is triggered.

The Advisory Committee should be comprised of members with a broad range of expertise, including experts in the areas of micronutrients, toxicology, public health, end user needs, research, chronic disease, nutrition and macronutrients. The Advisory Committee should include representatives from both Australia and New Zealand.

Food, supplement and drug industry representatives should not be appointed to the Advisory Committee and all members are required to complete Conflict of Interest declarations.

Key responsibilities of the Advisory Committee include:

- Provide expert advice to the Steering Group on priority nutrients for review, including whether the nutrient adequately meets the criteria for triggering a review[7,8]
- Advise on the expert composition of Nutrient EWGs (although the Steering Group is responsible for the final composition of Nutrient EWGs)
- Maintain lines of communication between the Steering Group and Nutrient EWGs
- Chair the Nutrient EWG meetings
- Provide periodic advice and guidance to EWGs on review processes and NRV development as required
- Review outcomes from the nutrient reviews
- Provide advice on the risks associated with NRV recommendations.

All final decisions on NRVs made by the Advisory Committee (e.g. outcomes from public consultations) should be communicated to Nutrient EWGs, with feedback provided on the rationale for acceptance or rejection of proposed NRVs.

3.3 Commission Nutrient EWGs to conduct the review

The Steering Group (with the advice of the Advisory Committee), is responsible for commissioning Nutrient EWGs to conduct the nutrient reviews. Nutrient EWGs are primarily responsible for examining scientific evidence and establishing nutrient values.

Nutrient EWGs should consist of five-six members and should include appointment of a junior scientist for future succession planning. In addition, each Nutrient EWG should have access to adequate research assistance.

Food, supplement and drug industry representatives should not be appointed to a Nutrient EWG and all members are required to complete Conflict of Interest declarations.

It may be appropriate for Nutrient EWGs to review more than one nutrient (which should be clustered in natural groups e.g. all minerals under consideration at the time).

Where possible, each Nutrient EWG should include at least one representative from Australia and New Zealand. For nutrients that are a higher priority in New Zealand than Australia, it is essential to include New Zealand representatives in the Nutrient EWG.

The responsibilities and required experience of EWG members are outlined in Table 6.

[7] If it is unclear whether a new review is warranted, the Advisory Committee should advise the Steering Group to commission a short literature review to determine the probability of a new review resulting in changes to the NRV recommendation.

[8] The Advisory Committee may need to consult with nutrient experts to determine priority nutrients for review.

Table 6: Skills and responsibilities of Nutrient EWGs

Requirements	Details
Specific responsibilities	Specific responsibilities of Nutrient EWGs include: • apply the methodological framework to establish revised NRVs (including defining the scope of the review and selecting, grading and examining the evidence) • provide advice on the implications of the NRV recommendations (e.g. increased fortification) • produce the report with revised NRV recommendations.
Required skills and experience	All members should have general nutrition knowledge, and at least one representative from each Nutrient EWG should have some experience in setting NRVs. Nutrient EWGs should be comprised of (or have access to) a broad range of expertise, including a relevant mix of: • experts in the nutrient being reviewed • experts in infants, children, pregnancy and lactation, adults and the elderly • statisticians with broad expertise, including modelling capability • end users (e.g. dietitian or FSANZ user) • toxicologists to examine upper levels (consideration should be given to appointing the same toxicologist across Nutrient EWGs) • experts in monitoring nutritional status in population groups • members with group/ project management skills • experts in implementation of NRVs into relevant public health policy.

The composition of each Nutrient EWG will vary depending on: (i) available funding and access to expertise; (ii) the nutrient(s) selected for review; and (iii) the area(s) of focus for the review.

As a result, there are several different models for the Nutrient EWG teams. Two example models are outlined below. EWG teams should resemble one of the following two models (or some combination/ variation of the two models) depending on the specific nutrient, the number of reviews conducted and the expertise/ resources available.

Model 1: A team of specialists is established to undertake the review of a specific nutrient, with support from people with more general skills

In this case, the EWG is:

- led by a team of experts in the specific nutrient under review (which should include a toxicologist if the review focusses on ULs)
- supported by a (typically full-time) research assistant with the required skills in literature searches, data analysis, study design, and grading evidence, and able to undertake most of the technical writing
- supported by a competent technical writer (if the research assistant is unable to undertake the majority of the technical writing)
- able to access more general advice (if the relevant expertise is not present in the EWG) including statisticians, toxicologists, and experts in the review methodology (possibly established as a 'panel' to support a number of EWGs).

Model 2: A core team is established to undertake one or more of the reviews, accessing specialist expertise as required

In this case, the EWG is:

- led by one or more skilled nutritionists (but not necessarily specialists in the nutrient(s) under review)
- competent in the general skills required to successfully complete a review (e.g. literature searches, data analysis, study design, and grading evidence), includes a competent technical writer, and has a good grasp of the application of the methodological framework
- able to access advice from experts in the nutrient(s) under review, and from other experts (e.g. toxicologists, statisticians).

Representatives from the food, supplement and drug industry should not be included in Nutrient EWGs. Additionally, persons with known agendas on the need for policy change in the specific nutrient should not be included. All members should declare their current and previous involvement with relevant industries and policy processes and are required to complete the NHMRC Conflict of Interest declarations. Research interests should also be declared. The Steering Group should ensure that composition of the final Nutrient EWG team provides a balance of views to prevent bias in experience and perspectives.

Consider including one person (e.g. an Advisory Committee representative) in several Nutrient EWGs to ensure consistency of process across nutrient reviews and continuity of experience across newly established groups.

Nutrient EWGs are required to record all discussions, with reasons for inclusion/ rejection of evidence and the rationale for arriving at a final conclusion. This includes documentation of all assumptions, rounding approaches, and justification for selection of methods. Documentation of decisions is of particular importance when underlying evidence is weak or thin.

Any decisions to deviate from the guidance provided in this framework should be clearly documented and justified.

Secretariat support for Nutrient EWGs is essential for ensuring accurate documentation of decisions.

The Steering Group should ensure Nutrient EWGs have adequate levels of support throughout the review process. This includes effective channels for communication and access to guidance, for example:

- teleconferences with the Advisory Committee to seek guidance and advice
- face to face meetings between Nutrient EWG members
- methods for Nutrient EWGs to share information between groups (if multiple reviews are being conducted).

Selection of appropriate communication channels for Nutrient EWGs requires consideration of the associated workload and cost-effectiveness.

3.4 Develop NRV report

Although NRVs are reference values, they are assessed against NHMRC standards for externally developed guidelines.

As a result, at the completion of the review process Nutrient EWGs need to provide:

- **The draft guideline** – outlines the recommendations for use in clinical settings and in population assessment, and includes:
- **A technical report** – provides a record of the evidence review process.

Detailed guidance about information for inclusion and the style of these documents can be found in the *NHMRC procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines* (see Appendix B) and should be reviewed prior to commencement of the review.

The detailed structure and content of each NRV report will vary between reviews depending on the nutrient selected and area(s) of focus.

All guidelines need to include the following:

- a brief summary of the NRV recommendations in plain English
- a statement about the source of funding for the nutrient review
- the context for the use of NRVs
- a brief summary of the scoping study used to assess the 2006 Nutrient Reference Values
- the triggers and rationale for the review (e.g. emergence of new evidence).

As a general guide, each NRV report should follow the structure provided in Figure 3. Nutrient EWGs should discuss proposed changes to the report structure with the Advisory Committee to ensure consistency across the Nutrient EWGs.

Figure 3: Proposed structure of revised reports for Nutrient Reference Values

GUIDELINE HIGH LEVEL STRUCTURE

1. **TITLE PAGE**

2. **TABLE OF CONTENTS**

3. **EXECUTIVE SUMMARY**

4. **SUMMARY OF RECOMMENDTIONS IN PLAIN ENGLISH**

5. **INTRODUCTION**

Includes:

- Details about the source of funding for the review
- Context for the general use of NRVs
- Summary of the scoping study used to assess the 2006 NRV guidelines
- Triggers and rationale for the review.
- Background information for the specific nutrient

6. SCOPE AND PURPOSE

7. EVIDENCE REVIEW (TECHNICAL REPORT)

a. Selection of biomarkers

Includes:

- Description of the biomarkers selected for the review
- Rationale for the selection of biomarkers

b. Selection of evidence

Includes:

- Data used during the review
- Methods
- Assumptions and limitations
- Rationale for decisions

c. Review of evidence

Includes:

- Methods used
- Results

8. GUIDELINE RECOMMENDATIONS

Includes:

- Rationale for any changes to previous values
- Validity of recommendations

9. APPENDIX – MEMBERSHIP OF GROUPS AND COMMITTEES INVOLVED IN THE DEVELOPMENT PROCESS

10. GLOSSARY

11. REFERENCES

Upon completion of the review, EWGs are required to submit the draft reports with revised NRV recommendations to the Advisory Committee for review.

If funding permits, the Steering Group should organise a one or two day workshop to:

- enable EWG members to present and discuss their findings with the Advisory Committee
- provide EWG members with the opportunity to learn from the other nutrient reviews (if multiple reviews are being conducted)
- identify key learnings that will help shape the process for future nutrient reviews.

3.5 Public consultation on proposed NRVs

Revised nutrient values and review data should be made available on a public website and an opportunity for public comment provided on at least one occasion (allowing adequate and appropriate time for responses).[9]

The public consultation process should include engagement with an appropriate consumer group.

If nutrient reviews have considered issues specific to particular population groups (e.g. Aboriginal and Torres Strait Islander peoples, Maori groups or culturally and linguistically diverse populations), the public consultation process should ensure engagement with appropriate socio-cultural consumer groups.

A summary of collated public consultation submissions should be developed and include:

1. Dates of consultations and where details of the public consultation were published
2. An overview of the submissions received, including: (i) the number of submissions; (ii) the types of individuals or organisations from whom submissions were received; and (iii) recurring themes in submissions (including any potential contentious issues and how they were addressed)
3. An overview of the main decisions taken in response to submission comments.

A list of submissions and corresponding responses and decisions should be organised thematically or according to the structure of nutrient reviews. Any responses (including nil responses) where advice has been sought from relevant authorities and key organisations should be documented and clearly highlighted in the public consultation document.

Public consultation submissions should include the authority or organisation name in the table of submissions, but not individual names. Submissions made independent of an organisational affiliation should be listed as 'individual'[10].

3.6 Independent expert reviews

Before finalisation of nutrient values, NHMRC will initiate independent methodological and clinical expert reviews of the final draft recommendations. The two review processes are described below.

3.6.1 Independent methodological review

The purpose of the independent methodological review is to determine whether the process undertaken to develop the new NRV recommendations meets the requirements of the NHMRC standard for clinical practice guidelines.

NHMRC is responsible for selection of methodological reviewers (who should not have any association with the guideline development process).

3.6.2 Independent clinical expert review

The purpose of the independent clinical expert review is to evaluate the appropriateness of the nutrient reference values, based on an overview of the body of evidence. Specifically, clinical expert reviewers will consider whether:

[9] Note that the public consultation process will be aligned with procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines.

[10] This is subject to requirements of the Australian Freedom of Information Act and the New Zealand Official Information Act.

- Appropriate evidence has been identified and reviewed in line with the scope and clinical questions outlined in the 2011 NHMRC standard for clinical practice guideline.
- Risks and potential harms of recommendations have been fully considered in the context of clinical practice and public health policy.
- Any conflicts arise with recommendations provided in other existing relevant guidelines (including Australian, New Zealand, and other international guidelines). In the instance where conflicts are identified, expert reviewers will consider whether the new recommendations are justified by current evidence and their rationale is clearly explained.

NHMRC may request amendments, clarification or further documentation either during or following completion of the expert review.

DoH and NZ MoH are responsible for nominating six potential clinical expert reviewers, however final selection of reviewers will be made by NHMRC.

3.7 Submission of nutrient values to NHMRC

After independent reviews of nutrient values, the Steering Group is responsible for submission of final nutrient recommendations and associated documentation to NHMRC for consideration by the Council and CEO.

The following documents need to be submitted with the final draft guideline:

- The technical report
- The administrative report
- The public consultations submissions summary
- The dissemination plan (and implementation plan if developed).

Details about each of these documents can be found in the *NHMRC procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines* and should reviewed prior to commencement of the review.

The NZ MoH is responsible through its internal endorsement processes for adoption of the draft recommendations, after consideration of all relevant reports and consultation processes.

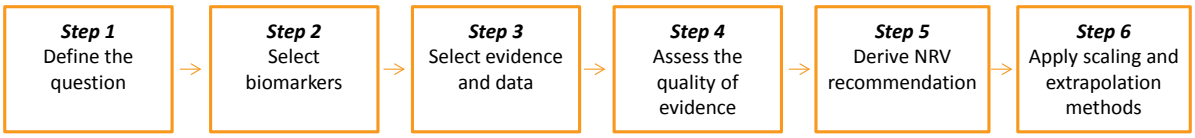
4 Methods for deriving NRV recommendations

Guiding principles

- Methodologies for deriving nutrient recommendations are applied consistently and support efficiency across the nutrient review process.
- The process for examining evidence across all nutrients is consistent, transparent and robust, with enough flexibility to accommodate issues specific to individual nutrients.
- The broad implications of revised NRVs for Government policy agencies, regulatory authorities, dietitians, universities, the food industry, consumers and the population are considered in their development.

The third stage of the framework defines the different methods used to derive nutrient recommendations. There are six steps to this stage of the framework, as shown in Figure 4.

Figure 4: Steps for the derivation of nutrient recommendations



Due to the unique characteristics and special considerations of ULs, derivation of ULs is considered separately in section 4.7.

A checklist of key issues that should be considered by Nutrient EWGs during each step is provided in Appendix A.

4.1 Define the question

The first step in the derivation of revised NRVs is to clearly define the question for the current NRV.

Each of the following questions requires consideration, and responses should be documented by Nutrient EWGs before commencing the review.

1. Is there a problem with the current NRV for any particular age group? (note inappropriate values for specific age groups may require evaluation even in the absence of new data)
2. Why is it important for the nutrient to be reviewed now? Are there special issues for this nutrient?
3. Have any significant issues arisen since 2006 that may influence the nutrient reference value?
4. Does a large proportion of the population currently not meet the EAR or exceed the UL? If so, is this considered to reflect a problem in: (i) the EAR or UL (ii) the food supply; or (iii) population behaviour?
5. Is there accurate information about the nutritional status of the population available?
6. Should publication of revised NRVs for a nutrient wait for release of results from the Australian Health Survey and/or relevant New Zealand surveys?
7. Is there any relevant new evidence that needs to be considered? (e.g. WHO, IOM, EURRECA, UK review of energy recommendations (Scientific Advisory Committee on Nutrition 2010), German/Swiss/Austrian Nutrition Societies review of recommendations for vitamin D 2012)
8. Is any new information about toxicity available from existing population data or other studies?

Selection of NRV recommendations for review

The four criteria for selecting a nutrient for review – changes and developments in comparable countries, emergence of new evidence, public health priorities and methodological rigour – may only justify review of a specific form of NRV recommendation.

After defining the problem with the NRV, Nutrient EWGs need to determine the focus of the NRV review:

1. **Form of recommendation** – for each nutrient, the complete set of recommendations or only a specific form of NRV may require review. For example, Nutrient EWGs may decide that a review is only required for ULs, without reconsidering the need for an EAR.
2. **Life-stage population groups** – for each nutrient, it may only be necessary to review the recommendations for a specific life stage (i.e. infants, children and adolescents, adults, pregnancy or lactation). For example, a review may be conducted of the EAR or RDI across all age groups or only for one specific age group.
3. **Health criteria and outcomes** – for each nutrient, the review may focus on nutritional deficiency, prevention of chronic disease, or both.

Nutrient EWGs should confirm the focus of the NRV review with the Advisory Committee prior to commencement of the nutrient review. Advice provided by the Advisory Committee will need to be considered by the Steering Group before the review commences. Table 7 below provides an example of a PICO table which would help determine the search strategy for both micro and macro nutrients.

Table 7: Example PICO table

Question: How much excess iodine is required to influence thyroid function in iodine replete, euthyroid adults

Items (PICO)	Description
Population	Groups of euthyroid adults (18 years and older) with spot median urinary iodine concentration >100ug/L
Intervention(s)	Dose(s) of iodine 100ug/day or greater in addition to usual diet
Comparator	Placebo (dose of iodine=0) in addition to usual diet
Outcome	Thyroid stimulating hormone level

Helpful information can be found in the World Health Organization Handbook for Guideline Development.

Reference for review:

World Health Organization (2009). WHO Handbook for Guideline Development.

4.2 Select biomarkers

Prior to selecting biomarkers, the physiological and biochemical indices of a nutrient deficiency state need to be clearly defined.

Status biomarkers are varied and include plasma concentration, enzymes levels and activities, and a range of biochemical and functional indicators.

To determine the level of intake necessary to prevent deficiency, robust biomarkers that identify the link between dietary intake and nutritional status should be selected.

Additional biomarkers may need to be selected to characterise the link between nutritional status and chronic disease (which may not have been captured by markers used to estimate levels of intake required to prevent nutrient deficiency).

In the selection of biomarkers, Nutrient EWGs should ensure:

- End points relevant for the assessment of deficiency status and chronic disease prevention are defined in advance of selecting the evidence.
- Biomarkers used as indicators of deficiency states are confirmed to be measurable and reliable.
- Biomarkers used to assess the level of nutrient intake required to reduce chronic disease are associated with primary health outcomes, modifiable by nutrient intake which is associated with change in disease risk (note changes in the biomarker should be clearly associated with reductions in disease incidence). Information on the minimal duration to maximise the change is also required.
- Consideration is given to the use of multiple biomarkers, as measurement of multiple biomarkers that are key components central to the maintenance of health, metabolic, oxidative, inflammation and psychological processes may enable a more integrated approach to the assessment of micronutrient status.

EURRECA has done significant work in the identification of new indicators and the evaluation of traditional indicators for micronutrients. This work provides helpful guidance for Nutrient EWGs in determining appropriate selection of biomarkers.

Reference for review:

Harvey L, Colling R et al. (2011). *Best Practice Guidelines for Status Markers.*

4.3 Select evidence and data

Identification and selection of evidence and data for the development of NRVs should use a systematic approach that accounts for the specific nutrient, population group, and health outcome or endpoint being considered.

The process for examining evidence should be documented ***prior*** to commencing the selection of evidence to ensure a robust and consistent approach. This includes criteria for inclusion of a study, acceptable levels of evidence, and guidance for following international studies with different population contexts. The matter of animal studies or level III evidence should also be clarified upfront.

Selection of evidence should commence with a review of the recent work on NRVs conducted by the IOM, EURRECA and the European Food Safety Authority (EFSA). Nutrient EWGs should take into account the most recent conclusions from these groups and modify (where relevant) the findings based on more recent evidence. If there is serious doubt about the conclusions reached by these groups, Nutrient EWGs should consult the earlier literature.

Additionally, new clinical trials since the last trials considered by the IOM process should also be examined as part of the nutrient review.

New studies need to be identified through a systematic search, following NHMRC methods, with clearly defined search terms (including trials, cohort studies and mechanistic studies) and a priori reasons for inclusion/exclusion, rather than a selective approach to locating studies.

Nutrient EWGs need to clearly document the search strategy, search terms and databases searched. It is recommended that Nutrient EWGs include the following databases and websites in their systematic searches:

- Databases – Medline, Cochrane database, Embase
- Websites – FSANZ, EFSA, Food Standards UK, IOM.

Nutrient EWGs should: (i) document how many papers are taken from each database and website; and (ii) develop a flow diagram with the number of papers identified and the number used in the development of NRV recommendations (this should include the rationale for rejection of any papers).

Nutrient EWGs should refer to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and flow diagram for guidance on reporting search strategies and outcomes.

To set numerical values, literature which addresses the following areas may be required:

- describes the dose-response relationship between the nutrient and the selected biomarker (studies meeting pre-defined minimum duration criteria). Note that while at least two different doses are required to estimate an EAR, more studies would ensure greater validity of the estimate.
- investigates the duration of study required to permit the selected biomarker to reach its maximum value
- investigates the variability in response to inform decisions about whether there is evidence for using a CV other than 10% when deriving the RDI from the EAR
- investigates the bioavailability, or bioconversion, of the nutrients or different vitamins.

In the selection of relevant evidence for review[11], Nutrient EWGs should consider and address the following:

- Control groups should be included in studies where possible, and Nutrient EWGs should endeavour to be as consistent as possible in their selection of evidence.
- Where appropriate, intervention studies with suitable outcomes and duration should take priority over “calculated” factorial studies or short term balance studies (although these studies will still require consideration).
- Consistency of evidence is important across all sources of evidence and between each EWG.
- If a comprehensive review is deemed as necessary, the search should cover all studies (including those prior to 2002).
- Epidemiology should be considered (especially negative epidemiology where nutrient intake levels are not associated with disease outcomes). Positive epidemiology for micronutrients requires confirmation with randomised controlled trials before it can be used to alter EAR and RDI levels, however, it may be used for softer values such as SDTs for both macro and micronutrients.
- Evidence from animal studies may be required to assist in setting ULs, however, extrapolation is difficult.
- Duration of trials need to be sufficient to maximise changes in selected biomarkers. Trials of short duration should be clearly identified and the evidence treated as weaker than trials of longer duration.

[11] Refer to NHMRC guidelines for full guidance on how to appropriately extract data and assess literature.

Nutrient EWGs should note that the inclusion criteria for the duration and design of a study may vary across different nutrients. For example, red blood cell folate studies require a minimum of 120 days duration to provide robust evidence, whilst for other nutrients shorter timeframes may be adequate.

If review of a specific nutrient has not been conducted by EURRECA or another relevant international body (and if deemed necessary by the Nutrient EWG), a systematic review and meta-regression may need to be conducted. The purpose of the meta-regression is to identify the point at which 50% of the population are deficient (when defining the EAR). This will need to be done after consultation with the Advisory Committee and Steering Group.

EURRECA designed and adopted a standardised systematic review process for the identification of data relevant to the derivation of dietary recommendations. This process provides useful guidance for Nutrient EWGs in the selection of evidence and data.

Reference for Review:

Dhonukshe-Rutten R, Bouwman J et al (2013). *EURRECA – Evidence-Based Methodology for Deriving Micronutrient Recommendations pp.16-17.*

4.3.1 Selection of evidence for deficiency status

Physiological and biochemical end points relevant for the assessment of deficiency status should be defined in advance of selecting evidence.

Selection of evidence should apply the following guidance:

1. High quality systematic reviews and meta- regression of well-conducted RCTs and cohort studies should be the primary source of data. The quality of the meta- regression needs to be scrutinised as it may be of low quality (despite being published).
2. In the absence of quality systematic reviews and meta- regressions, well-conducted single or multiple double blind randomised controlled trials should be used where possible.
3. Evidence needs to recognise the grading up of studies with large effects (e.g. vitamin A and xeropthalmia).
4. Results of double blind randomised controlled trials (and meta-regressions derived using them) need to be viewed in the context of the level of nutrient intake in the population. The incidence of deficiency disease and the level of agreement between the dose of nutrient used in the RCT, current dietary intake and deficiency rates should be assessed.
5. For nutrients with limited available evidence and few (if any) randomised controlled trials, the studies should be characterised by:
    - the dose
    - the form of supplement/fortification
    - the analytic method
    - the sample populations
    - the longest duration intervention that elicits a response in the biomarker following a change in status.

Nutrient EWGs should develop a Population, Intervention, Comparison and Outcomes (PICO) table for all nutrients. An example of a PICO table is provided in section 4.5.2.

Note EURRECA has a complete list of all studies included in their recent reviews available online.

Reference for Review:

EURRECA (2013). *Systematic reviews: methods and main results*

4.3.2 Selection of evidence for chronic disease prevention

The most important consideration for selection of evidence for chronic disease prevention is a clear definition of the question being asked, the primary outcome and secondary outcomes. A PICO table should be developed for each identified question.

Selection of evidence for macronutrients should apply the following guidance:

1. High quality systematic reviews and meta analyses should be the primary source of data where possible (these may need to be commissioned if necessary).
2. If quality systematic reviews and meta analyses are unavailable, double blind randomised controlled trials should be used where possible with validated biomarkers.
3. Prospective cohort studies with disease outcomes are acceptable forms of evidence for reviews of macronutrients (see the WHO guide on consideration of evidence).[12] Cross-sectional and case control studies in general should be avoided unless there is no other evidence available.

4.4 Assess the quality of evidence

Each study identified for inclusion in the literature search should be assessed for quality and graded according to either the GRADE or FORM methodology.

As per the NHMRC guidelines, only one approach, either GRADE or FORM, should be used to analyse the literature. All future nutrient reference value reviews are encouraged to use GRADE for both micronutrients and macronutrients. If the NHMRC guidelines are updated in the future, the framework will be updated according to any changes to the guidelines.

A checklist to guide Nutrient EWGs in the examination of evidence is provided in Appendix B, which provides guidance on key factors that need to be recorded to ensure compliance with the NHMRC Guidelines.

The GRADE and FORM approaches are discussed below.

GRADE approach

The GRADE approach ranks the support (or otherwise) of a body of evidence for relationships into four categories – high, moderate, low, and very low.

The quality of evidence for a relationship is based initially on the design of the studies used to assess the relationship. However studies can be carried out in a flawed manner, and so the starting GRADE is down-GRADED and modified to take into account flaws. In addition, there are certain characteristics of a relationship that make it more certain that it exists and so a body of evidence can be up-GRADED based on this.

For example, a body of evidence based on RCTs starts with a high GRADE but can be down-GRADED. Similarly, a body of evidence based on observational studies (including interrupted time series, quasi-experimental design, cohort studies, case control studies, case series and case reports) starts with a low GRADE but can be up-GRADED.

The criteria for increasing or decreasing the GRADE are outlined in Table 8 below.

[12] See: https:www.who.int/elena/about/guidelines_process/en/

Table 8: Criteria for increasing or decreasing the GRADE of a body of evidence (Balshem et al, 2011)

Criteria	Description
Criteria for decreasing the grade*	• Serious or very serious limitation to study quality • Important inconsistency • Some or major uncertainty about directness • Imprecise or sparse data • High probability of reporting bias
Criteria for increasing the grade	• Strong evidence of association – significant relative risk of >2 (<0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1) • Very strong evidence of association – significant relative risk >5 (<0.2) based on direct evidence with no major threats to validity (+2) • Evidence of a dose response gradient (+1) • All plausible confounders would have reduced the effect (+1)

* **Note:** Each quality criteria can reduce the quality by one or (if very serious) by two levels

Under the GRADE approach (or any other grading system) it may not be possible to give a relationship for a nutrient more than a low GRADE (or the equivalent). For example, even if all studies comprising a body of evidence are trials, there may not be many of them. As a result, the body of evidence might be down-GRADED for imprecision or sparseness.

The interpretation of the GRADE hierarchy for a body of evidence for a nutrient-biomarker/outcome relationship is provided in Table 9 below .

Table 9: Interpretation of GRADE quality descriptors for a body of evidence (Balshem et al, 2011)

Evidence quality	Description of evidence grade
High	The guideline development group is very confident that the true effect lies close to that of the estimate of the effect
Moderate	The guidelines development group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect
Very low	The group has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

Finally, the recommendation (i.e. the EAR, UL etc.) derived from the body of evidence for the relationship needs to be GRADED as either strong or weak. Depending on the amount and quality of evidence for the relationship with the identified biomarker, the recommendation under the GRADE system may be assessed as 'weak' rather than 'strong'.

Nutrient EWGs should review the resources below about the GRADE system prior to grading the evidence.

Reference for review:

Balshem et al (2011). *GRADE guidelines: 3. Rating the quality of evidence*.

GRADE working group (2005-2014). *Frequently asked questions.*

World Health Organization (2009). *WHO Handbook for Guideline Development pp.37-45*

GRADE development group (various) (2010) *GRADE guideline series. Journal of Clinical Epidemiology*

FORM approach (NHMRC levels of evidence and grading process)

NHMRC evidence levels are determined based on the strength of the study design, with systematic reviews of randomised controlled trials considered Level I evidence. A summary of the NHMRC hierarchy for study assessment is provided in Table 10 below.

Table 10: NHMRC hierarchy for study assessment

Level	Description of level of evidence
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group

Level	Description of level of evidence
III-3	Evidence obtained from comparative studies without concurrent control and with historical control, two or more single arm studies, or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test/post-test outcomes

The NHMRC overall grades of recommendations are intended to indicate the strength of the body of evidence underpinning the recommendation. To determine the overall grade of recommendation, Nutrient EWGs should apply the grades provided in Table 11 to the value selected for the NRV (not the relationship that is being assessed).

Table 11: Definition of NHMRC grades of evidence

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Source: Merlin T, Westin A et al,(2009) NHMRC additional levels of evidence and grades for recommendations for developers of guidelines Page 8.

To ensure compliance with NHMRC standards, Nutrient EWGs are required to rate the evidence base, consistency, clinical impact, generalisability and applicability of the evidence.

An evidence statement needs to be completed as part of this process. Nutrient EWGs should refer to NHMRC resources on the grading system, and the evidence template, prior to grading the evidence (see reference below).

Reference for review:

Sang Z, Wang PP, et al (2011). *Exploration of the safe upper level of iodine intake in euthyroid Chinese adults: a randomized double-blind trial.*

Merlin T, Westin A et al (2009). *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines.*

Note: For some nutrients it may be difficult to grade evidence according to the NHMRC levels of evidence because there are few truly double blinded, randomised controlled trials. For example, although balance studies are interventions, they are not randomised, blinded or controlled. Although balance studies may only be level IV evidence at best, they may be the only evidence available for the selected nutrient and will need to be used to derive the NRVs. A similar situation may arise with fortification studies.

The example above about iodine toxicity provides an example of a randomised trial that can be easily assessed using NHMRC grading systems.

4.5 Derive NRV recommendations

A different approach should be applied for derivation of recommendations for prevention of nutritional deficiency and prevention of chronic disease (both for micronutrients and macronutrients).

For prevention of nutrient deficiency, micronutrients should follow either the factorial or dose-response approach.

For the prevention of chronic disease (both micro and macronutrients), the evidence will be a mix of epidemiology and intervention studies.

To derive the final NRV recommendations, Nutrient EWGs may need to make decisions about prioritisation of different issues. For example, Nutrient EWGs may need to address: (i) inconclusive statistical findings; (ii) conflicting findings from international frameworks; or (iii) low levels of evidence.

In the absence of more conclusive dose response trial data Nutrient EWGs should give preference to physiological and factorial approaches in the decision making process for final NRV recommendations.

For both chronic disease prevention and nutritional deficiency, a Population, Intervention, Comparator, Outcomes (PICO) table should be developed to help form the search strategy for evidence. An example is provided in section 4.5.2. Ranking the importance of health outcomes (as per GRADE) should occur once the PICO questions have been established.

Recommendations developed for prevention of nutritional deficiency and/or chronic disease prevention should test for coherence, alignment and validity as follows:

- **Comparison with international values** – after selection of methods for derivation of reference values, comparisons should be made with methods used to develop international values in order to identify opportunities to leverage existing work or potential errors in the derivation of values.
- **Coherence within and across nutrient reviews** – comprehensive dietary modelling should be undertaken[13] by an independent reviewer prior to finalisation of recommendations to assess; (i) the impact of the new EAR; and (ii) whether it is possible to achieve the new EAR with or without fortification or supplementation.
- **Validity of recommendations** – following derivation of recommendations, Nutrient EWGs should consider whether the new value is sufficiently different from the old value to justify a change, and the consequences of not changing the NRV. This should include consideration of: (i) who uses the NRV recommendation; (ii) the accuracy of the underlying evidence; and (iii) the impact of rounding findings.

All decisions regarding the basis of EARs (prevention of deficiency or prevention of chronic disease) need to be clearly recorded and communicated to final end-users.

If final recommendations differ substantially to international values or do not align with FSANZ regulatory nutrient reference values, Nutrient EWGs should record the rationale for difference in findings.

If recommendations provided by Nutrient EWGs are considered controversial or represent a significant change from previous values, the Advisory Committee, in consultation with the Steering Group, should consider sending the recommendations to independent experts for review.

Methods for derivation of recommendations for prevention of nutritional deficiency and chronic disease are provided below.

[13] Suggest this modelling be performed in accordance with the dietary modelling approach used during the review of the Australian Dietary Guidelines if appropriate (DoHA, NHMRC, 2013)

A checklist with specific considerations for derivation of NRVs is provided in Appendix A.

4.5.1 Derivation of recommendations for nutritional deficiency

Derivation of nutrient recommendations for the prevention of nutrient deficiency should use the factorial or dose-response approach (as per the EURRECA framework). Note NRVs do not cover the treatment of a deficiency disease.

The decision about whether to use the factorial or dose-response approach is based on the availability of data, as well as the types of studies, methodological principles and designs:

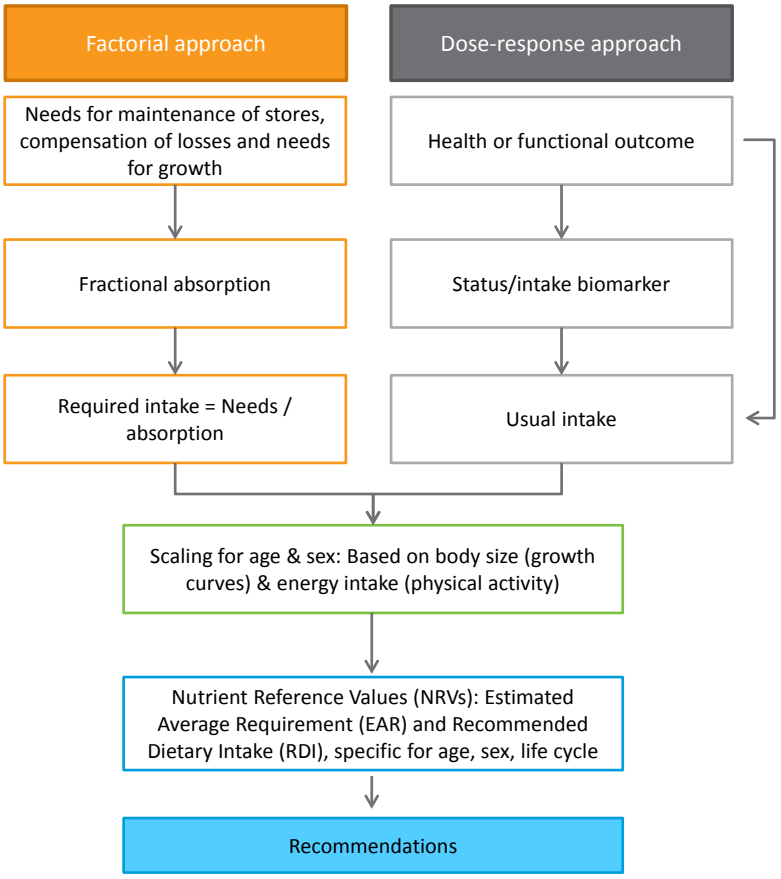
- **Factorial approach** – depends on physiological data related to micronutrient losses in balance with absorption. This approach measures the various (exchanges between) body pools to estimate losses and needs for maintenance and growth. Factorial approaches are usually combined with estimates of bioavailability and are used during periods of growth and development. Derivation of reference values for micronutrients through the factorial approach often requires application of a bioavailability factor to convert the physiological requirement into a dietary intake value (Fairweather-Tait, Collings R., 2010).
- **Dose-response approach**[14] – is based on the prediction of a physiologically relevant outcome (e.g. measurement of an accepted micronutrient status biomarker in response to dietary intake, or assessment of clinical disease endpoints in relation to intake or status). This approach provides evidence for the adult population on optimal nutrition in relation to specific health outcomes and endpoints, and is usually based on RCTs and epidemiological studies.

Both approaches need to be collectively analysed to determine an intake cut point where 50% of the population achieve the desired end point with that level of intake (i.e. a meta-regression). This may require sophisticated statistical modelling.

The factorial and dose-response approach use by EURRECA is shown in Figure 5.

[14] Estimation of the dose response requires at least two doses to be tested in controlled trials. Large doses (in which 100% of the population reach the required level of the biomarker) are not particularly helpful, as it is unknown how low the dose could be reduced and still produce a 100% response. Similarly, to test a dose that only makes 20-30% of the population replete might require depletion/ repletion experiments which are not physiologically the same as maintenance experiments (in which the majority of the population are replete). For example, iron absorption increases dramatically in iron deficiency compared with iron repletion, however only the latter absorption rate is relevant to calculation of the EAR.

Figure 5: Assessment of prevention of deficiency disease (adapted from EURRECA framework[15])



Details about application of the factorial and dose-response approach are provided in EURRECA framework for micronutrient recommendations. This should be reviewed by Nutrient EWGs prior to the derivation of nutrient values.

References for review:

Dhonukshe-Rutten R, Bouwman J et al (2013). *EURRECA – Evidence-based methodology for deriving micronutrient recommendations, p.p. 9-16.*

Fairweather-Tait and Collings R (2010). *Estimating the bioavailability factors needed for setting dietary reference values, pp.249-256.*

4.5.2 Derivation of recommendations for chronic disease prevention

Recommendations for chronic disease prevention should be derived based on the WHO Handbook for Guideline Development. This methodology was recently applied in the development of new recommendations for the reduction of non-communicable diseases in most adults and children.

There are four key steps involved in the development of recommendations to prevent chronic disease:

1. Identification of priority questions and outcomes (including development of a series of questions related to the Population, Intervention, Comparator, Outcomes (PICO)).

[15] Dhonukshe-Rutten R, Bouwman J, Brown KA et al. (2013) EURRECA – Evidence-based methodology for deriving micronutrient recommendations. Critical Reviews in Food Science and Nutrition (accepted).

2. Retrieval of evidence appropriate to the Australian and NZ populations (e.g. sedentary Western populations)
3. Assessment of the quality of the evidence and synthesis of the evidence from different study types (e.g. interventions examining biomarkers as well as epidemiology)
4. Formulation of recommendations from the totality of evidence.

4.6 Apply scaling and extrapolation approaches

NRVs will need to be defined for population groups for which there is currently no experimental research data (e.g. infants and children). Various methods of scaling (both interpolation and extrapolation) can be used to define values for these sub-groups based on known data for other populations (e.g. adults).

Scaling methods can be determined based on energy requirements, body weight, or metabolic body weight[16]. The appropriate scaling method for a particular nutrient needs to be selected on a case-by-case basis, and should consider:

- the context of the available evidence; and
- differences in metabolism, toxicokinetics, and homeostatic mechanisms between adults and children.

Nutrient EWGs need to ensure selected scaling methods are appropriate for each nutrient (e.g. body weight or BSA scaling for minerals and metabolic weight scaling for B vitamins).

If possible, Australia and New Zealand should use the current nutrient reviews as an opportunity to develop their own set of standardised bodyweights from recent health surveys. In the meantime, the body weights used in the 2006 NRVs should continue to be used.

The EURRECA framework selected the two most frequently used methods of extrapolation – one based on body surface area, and one based on metabolic body mass and growth needs.

1. Metabolic turnover

This method is based on body surface area (BSA), calculated as $BSA = \sqrt{Weight\ (kg) * Height(cm)/3600}$

Extrapolation is based on:

$$AR_{child} = AR_{adult} * \frac{BSA_{child}}{BSA_{adult}} = AR_{Adult} * \sqrt{\frac{Weight_{child} * Height_{child}}{Weight_{adult} * Height_{adult}}}$$

Although the NRVs produced in the 2006 review used energy intake for some nutrients, the difference between BSA and energy intake based equations would be marginal as there are no reliable estimates of activity factors in each age group.

2. Metabolic body mass and growth needs (*used by the IOM*)

This method expresses maintenance needs relative to metabolic body weight. There is an extra term for growth based on protein needs, which is applied for all nutrients.

Extrapolation is based on:

[16] For example, see Appendix 1 in 'Scientific opinion on principles for deriving and applying Dietary Reference Values', EFSA Panel on Dietetic Products, Nutrition, and Allergies. EFSA Journal 2010; 8(3): 1458.

$$AR_{child} = AR_{adult}\left(\frac{Weight_{child}}{Weight_{adult}}\right)^{0.75} * (1 + growth\ factor)$$

All methods, assumptions and underlying scientific evidence should be clearly documented.

4.7 Determine Upper Levels of Intake

Previous reviews had difficulty deriving UL recommendations due to the use of a "formula" or specific process, rather than adapting and contextualising the approach to the issue being addressed. Inherent differences between nutrients and chemicals (the typical subject of risk assessments) mean the normal chemical assessment paradigm that the literature reports can only provide a starting point for the assessment of NRVs.

Nutrients have benefits and risks (at both the individual and population level), and as a result the high degree of conservatism which is adequate for agricultural or industrial chemicals is not appropriate for nutrient ULs. Development of UL values that are not supported by adequate evidence places substantial constraints on FSANZ in responding to public health issues or specific applications for the addition of nutrients to food products.

As a result, if the data is not strong enough to provide trusted evidence in support of a UL, then it is recommended that the Nutrient EWG does not set one.

The steps for deriving UL recommendations are largely similar to other nutrient values. The five steps for deriving ULs are outlined in the sections below:

1. Define the question (see section 4.1)
2. Select evidence and data
3. Assess the quality of evidence
4. Develop options for UL descriptors
5. Apply scaling and extrapolation approaches.

Note: A detailed description and explanation about how to develop ULs is provided in the supporting document "General principles for establishing safe upper levels (ULs) of intake for micronutrients".

4.7.1 Select evidence and data

Due to limited levels of data often available for ULs, consideration of studies of lesser strength than RCTs may be required. The following should be considered in the selection of data for ULs:

- Extrapolation of dose levels from animals to humans for nutrients is highly problematic and generally not appropriate. Relatively low quality studies in humans will generally provide a more reliable basis for establishing a UL than well designed animal studies.
- *In vitro* experiments, in isolation, are an unreliable source of evidence of either hazard or dose response relationships and do not provide an adequate basis for establishing a UL. In instances where clear evidence of an effect in humans is available, well designed *in vitro* or *ex vivo* studies may provide supporting information on mechanism and in some specific circumstances where validation against human *in vivo* data is available, dose response.
- Establishment of a UL is unlikely to be appropriate in the absence of evidence of adverse effects from a high level of consumption in humans. This does not equate to a conclusion that a nutrient is safe at any intake but intake at reasonably achievable levels has not resulted in such effects.

4.7.2 Assess the quality of evidence

ULs are intended for the general healthy population and exclude sub populations with genetic disease or other conditions that predispose them to adverse effects at levels below the general population. Potentially sensitive sub populations should be identified, where possible, and discussed when evaluating the evidence base for the establishment of ULs.

Identification of the dose at which adverse health effects are observed should consider the following:

- Where possible, benchmark dosing methodology (dose response modelling) rather than the Lowest Observed Adverse Effect Level (LOAEL)/ No Observed Adverse Effect Level (NOAEL) approach should be used for all nutrient risk characterisation. This approach may allow for a more robust UL to be established.
- A key consideration for identifying a point of departure is discrimination between the two responses to high chemical/ micronutrient load – adverse and adaptive, or non-adverse physiological. An effect that increases with dose can be adverse at some doses and benign (or beneficial) at lower doses. Biologically and/or statistically significant observations are not necessarily clinically significant or adverse. The nature and significance (both clinical and health) of the effect on which a UL is to be considered require careful evaluation and discussion in order to discriminate between these scenarios.
- In some circumstances, a high nutrient intake may unmask pre-existing sub clinical disease. This does not necessarily form a reasonable basis for establishment of a UL.

Application of uncertainty factors (safety or adjustment factors) for ULs should address specifically identified and characterised uncertainties. The magnitude of the factor should be clearly justified against the level of uncertainty.

The definition of ULs as the maximum daily intake for each age group may not always be appropriate or sufficient to describe or predict toxicological endpoints. For some nutrients, consideration of the duration and intermittency of exposure is required to account for characteristics such as rapid excretion, bioaccumulation, adaptive pharmacokinetics or saturable detoxification.

Development of ULs should consider the relationship between the adverse effects and the time course of exposure. Where appropriate, this relationship should be incorporated into the expression of the UL.

4.7.3 Develop guidance options for upper ranges of intake

ULs should only be developed when there is strong, high quality evidence supporting the potential for significant harm from realistically achievable dietary intakes (from diet and supplements combined).

In the case where an UL cannot be set (or it is inappropriate to set), there may be merit in indicating the upper range of intake in the normal healthy population (i.e. not known to be associated with adverse effects of the nutrient). This will provide guidance on known safe upper levels of intake without inferring any adversity from higher intakes in the absence of data to that effect.

Less prescriptive forms of guidance than ULs should be used when data supporting adverse effects of high intake is:

- poor in quality;
- speculative in nature;
- reliant on biomarkers of uncertain relationship to primary health outcomes; or
- derived from populations with diets that are unusual in the Australian or New Zealand context, are nutrient deficient, or only applicable to aberrant levels of intake.

A range of options should be considered for describing the appropriate upper range of nutrient intake and the underlying available evidence (including evaluation results, strengths and limitations). Proposed options are outlined in Table 12.

Table 12: Options for descriptors of Upper Levels of Intake

Option	Criteria	Frequency
Upper Level of Intake	Good evidence of an adverse effect in humans at realistically achievable intakes; AND Sufficient data to support establishment of a dose response relationship.	Expressed per day, week or month as appropriate for individual nutrients.
Provisional UL	Sufficient evidence of adverse effects in humans at realistic levels of intake; AND Nature or extent of the evidence is insufficient to determine a point estimate of the safe upper level with reasonable confidence.	Expressed per day, week or month as appropriate for individual nutrients
Not determined	An absence of evidence of hazard; OR Some evidence of potential adverse effects at high intake levels well above that normally achievable in the diet; OR The evidence is insufficient to support the determination of a UL with any confidence.	N/A
Not required	Good quality evidence demonstrating no adverse outcomes from nutrient intakes well above amounts normally achievable from the diet.	N/A

If the quality of evidence does not permit establishment of a UL, an indication of the highest observed intake not associated with adverse effects (either through direct experimental evidence in human subjects and/ or through a calculation of dietary intake in high consumers) may be appropriate.

If the data is robust and supports derivation of a UL, Nutrient EWGs need to consider the following key issues associated with development of the UL:

1. Establish a robust point of departure (i.e. where toxicity starts to become apparent in the available evidence).
2. Establish the slope of the dose-response curve (note if a dose response cannot be established, any UL will be readily open to challenge).
3. Ensure the value(s) reflect the broader community, rather than a susceptible subset that requires a separate value.
4. Avoid the use of data from populations that do not reflect (or are of uncertain relevance) to Australia and New Zealand.
5. Differentiate between the endpoints that reflect the initiation of pathology and subclinical pre-existing disease.

6. Use uncertainty factors that accurately reflect the level and nature of uncertainty and are not excessively precautionary (i.e. estimate the direction and quantum of each point of uncertainty based on a reasonable evidence base appropriate for each aspect of the uncertainty).
7. Test the UL value against actual intakes in the community that have not been recognised as leading to discernible adverse outcomes across the various sub-populations that can be modelled.

If the development of a UL is considered appropriate, and a tentative value has been determined, a series of tests should be applied to determine the plausibility and defensibility of the value (prior to finalising the recommended value). Nutrient EWGs should compare the derived UL for each sub-population against:

- all relevant human studies with a safety component to their design. This will enable assessment of how many studies (and of what quality) included doses above the UL with no evidence of the proposed pivotal adverse effect.
- the proportion of each subpopulation likely to exceed the postulated UL at current intakes.
- actual levels of intake for high consumers in each population sub-group for which values have been set (where applicable, this should be inclusive of intake from supplements and, for minerals, drinking water). In the situation where actual intakes for a population group exceed calculated ULs for the group (without evidence of adverse effects), the derivation and need for a UL should be reconsidered.
- the upper range of the intake benefit curve. If the UL is close to or below the upper intake range for a benefit, it may be warranted to compare the nature (and likely incidence) of the adverse effect with the nature and likely incidence of the benefit (note this comparison should include consideration of the relative strengths and weaknesses of the data supporting the benefit and adverse effect).
- the postulated mechanism underlying the adverse effect and the plausibility of the dose response for that effect extending down to the proposed UL.

Note that clashes between Drinking Water Guidelines/Standards and NRVs should be avoided (which may occur as water supplies derived from artesian or ground water sources can have substantial levels of various minerals). If a clash is unavoidable, explicit advice about how to manage the different guidance levels should be provided. If a population is exposed to drinking water with minerals above the UL with no apparent ill-effect, consideration should be given to the validity of a derived UL value.

Additionally, derived ULs should be compared with pre-existing values established by Australian, New Zealand and international authoritative bodies, and the basis for any discrepancies should be discussed. Relevant authoritative bodies include FSANZ, the Joint FAO/WHO Expert Committee on Food Additives (JECFA), EURRECA, IOM, the Australian Drinking Water Guidelines Committee, and Drinking Water Standards for New Zealand.

4.7.4 Apply scaling and extrapolation approaches

Selection and adjustment of scaling algorithms for ULs should be based on: (i) the physiological role of the nutrient; and (ii) the relationship of its disposition to the metabolic rate or measures of body mass of the various age groups.

The scaling algorithms used by EURRECA and the IOM are a suitable starting point for scaling ULs between adults and children (see 4.6 of this document).

Appendix A Checklist for deriving nutrient reference values

The following checklist provides a series of criteria that should be considered by Nutrient EWGs in the derivation of nutrient values.

Criteria should be considered both prior to, and at completion, of each step of the review process.

Step 1: Define the question

- ☐ Is there a problem with the current NRV for any particular age group?
- ☐ Why is it important for the nutrient to be reviewed now? Are there special issues for this nutrient?
- ☐ Have any significant issues arisen since 2006 that may influence the nutrient reference value?
- ☐ Does a large proportion of the population currently not meet the EAR or exceed the Upper Level? If so, is this considered to reflect a problem in: (i) the EAR; (ii) the food supply; or (iii) population behaviour?
- ☐ Is there accurate information about population status available?
- ☐ Should publication of revised NRVs for a nutrient wait for release of results from the Australian Health Survey and/or relevant New Zealand surveys?
- ☐ Is there any relevant new evidence that needs to be considered that would substantially alter the conclusion?
- ☐ Is any new information about toxicity available from existing population data or other studies?
- ☐ Is it clear that previous data has been misinterpreted?

Step 2: Select biomarkers

- ☐ Does the nutrient address the prevention of deficiency, chronic disease prevention, or both?
- ☐ What are the physiological and biochemical indices of the nutrient deficiency state?
- ☐ What is the health outcome being measured?
- ☐ Are there any special issues of consideration for the nutrient, such as the bioavailability of nutrients?
- ☐ Does the nutrient review address bioavailability or absorption?
- ☐ Are there multiple indicators that can be used to measure this health endpoint?

Step 3: Select evidence and data

- [ ] Has the nutrient been reviewed by EURRECA, IOM, or a similar international body?
- [ ] What are the key questions being addressed during the studies (Population, Intervention, Comparator, outcomes)?
- [ ] What study design is most appropriate?
- [ ] What duration of study is appropriate to maximise changes in the selected biomarkers?
- [ ] Has the criteria for selection of studies been consistently applied?

Step 4: Grade the quality of evidence

- [ ] What is the study design (cross-sectional, prospective cohort, intervention)?
- [ ] How consistent is the evidence? Is there a body of contrary evidence that makes firm conclusions impossible?
- [ ] How generalisable is the evidence?
- [ ] How applicable is the evidence to Australia and New Zealand?
- [ ] What is the clinical impact of the evidence in Australia and New Zealand?
- [ ] How does the strength of the evidence for deficiency compare to the strength of evidence for chronic disease?

Step 5: Derive nutrient recommendations

- [ ] Are values impacted by bioavailability differences for different population groups (e.g. vegetarian populations)?
- [ ] Does genetic variation have any impact upon the proposed values? If so, should the CV be increased to more than 10% so that the RDI does cover almost the whole population?
- [ ] Do recommendations appropriately account for different body sizes, fat levels, and levels of physical activity? Should the CV be increased to account for this if the data suggests a significant effect?
- [ ] How do draft recommendations compare to the average population intake? Can the proposed value be achieved without the use of supplements or fortification? If not, should the data be re-examined to check assumptions behind the values (e.g. the CV may be set too high and the data may support a lower CV)?
- [ ] How do draft recommendations compare to international values (if applicable)?
- [ ] Has the risk assessment approach of the IOM been considered in the review process? (i.e. there is a risk of deficiency disease if the NRV is not correct, as well as a risk of toxicity if the UL is exceeded for a prolonged period).
- [ ] What are the consequences of not changing the NRV recommendation? (for example, who uses the recommendation, what is the accuracy of the underlying evidence, and what is the impact of rounding findings).

Step 6: Apply scaling and extrapolation approaches

- ☐ What is the difference in metabolism, toxicokinetics, and homeostatic mechanisms between adults and children for this nutrient (if known)?
- ☐ Is it more appropriate to use weight scaling or metabolic weight scaling for the nutrient?

Appendix B Checklist for NHMRC standards

The following checklist outlines key considerations for Nutrient EWGs in the examination of evidence, documentation of decision-making and development of guideline recommendations. It applies to requirements necessary for development of the technical report and guideline.

Nutrient EWGs need to address each item to ensure compliance with the 2011 NHMRC standard for clinical practice guidelines. Nutrient EWGs should also review the NHMRC requirements prior to examination of the evidence.

Reference for review:

NHMRC (2011). *Procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines.*

A. Governance and stakeholder involvement

Mandatory requirements – the guideline/ development process must meet all the following conditions:

	NHMRC Requirement	Description	Documented in:
✓	**A.1**	The organisation/s responsible for developing and publishing the guideline is/are named.	Guideline
✓	**A.2**	Sources of funding for guideline development, publication and dissemination are stated.	Guideline
✓	**A.3**	A multidisciplinary group that includes end-users, relevant disciplines and clinical experts is convened to develop the purposes, scope and content of the guideline, and the process and criteria for selecting members are described.	Guideline
✓	**A.5**	A complete list of people involved in the guideline development process is provided, including the following information for each person: (i) name; (ii) profession or discipline; (iii) organisational affiliation; and (iv) role in the guideline development process.	Guideline
✓	**A.7**	A list of organisations formally endorsing the guideline is provided.	Guideline

B. Scope and purpose

Mandatory requirements – the guideline/ development process must meet all the following conditions:

	NHMRC Requirement	Description	Documented in:
✓	**B.1**	The purpose of the guideline is stated, including the clinical questions, issue or problems the guideline addresses	Guideline (Technical Report optional)

	NHMRC Requirement	Description	Documented in:
✓	**B.2**	The health care setting to which the recommendations apply is described, including the health system level (e.g. primary care, acute care) and clinical stage (e.g. whether the guideline covers prevention, screening, assessment, treatment, rehabilitation or monitoring).	Guideline
✓	**B.3**	The intended end users of the guideline are clearly defined, and any relevant exceptions are identified.	Guideline
✓	**B.4**	The population to which the guideline recommendations will apply is defined (e.g. children, adolescents, adults or older adults) and population subgroups for which specific information is required are identified and described.	Guideline
✓	**B.5**	Issues relevant to Aboriginal and Torres Strait Islander peoples (such as particular risks, treatment considerations or sociocultural considerations) are identified and described.	Guideline

Desirable requirements – the guideline/ development process should meet the following conditions, where applicable:

	NHMRC Requirement	Description	Documented in:
✓	**B.5.1**	Issues relevant to special-needs groups such as culturally and linguistically diverse communities or groups with low socioeconomic status (e.g. particular risks, treatment considerations or sociocultural considerations) are identified and described.	Guideline

C. Evidence review

Mandatory requirements – the guideline/ development process must meet all the following conditions:

	Requirements	Description	Documented in:
✓	**C.1**	Clinical questions addressed by the guideline are stated in a structured and consistent format to define the boundaries of the topic – i.e. by specifying the relevant population, intervention/s (e.g. treatment/s or diagnostic test/s), comparator/s and outcomes measured.	Technical report Guideline
✓	**C.2**	Systematic searches for evidence are undertaken and the search strategy is documented, including the search terms and databases searched.	Technical report
✓	**C.3**	The population groups specified in the search strategy include Aboriginal and Torres Strait Islander peoples and any population subgroups that have been identified	Technical report
✓	**C.4**	The publication period covered by the searches is stated, and the latest date is within 12 months of the first day of public consultation and within 20 months of submission of the final draft guideline to NHMRC for approval.	Technical report
✓	**C.5**	The inclusion and exclusion criteria used to select studies for appraisal are described.	Technical report

	Requirements	Description	Documented in:
✓	**C.6**	For each clinical question, there is an evidence table which summarises the systematic assessment and critical appraisal of all studies that meet the inclusion criteria (i.e. the body of evidence on which a recommendation will be based). Each evidence table should include information on study design, outcomes, level of evidence, the findings of meta-analysis (if performed) and other relevant information.	Technical Report
✓	**C.7**	There is an evidence statement form for each clinical question. The form documents the synthesis and evaluation of the body of evidence to determine the grade of each recommendation (according to a NHMRC-approved method).	Technical report
✓	**C.8**	An evidence summary is provided for each recommendation. For each clinical study used to develop the recommendation, the evidence summary states: (i) the outcomes of the clinical study; (ii) the level of evidence; and (iii) the reference details.	Guideline
✓	**C.9**	A recommended date for future update of the guideline is identified.	Guideline

Desirable requirements – the guideline/ development process should meet the following conditions, where applicable:

	Requirements	Description	Documented in:
✓	**C.3.1**	The population groups specified in the search strategy include groups such as culturally and linguistically diverse communities or other groups for whom specific sociocultural factors (including ethnicity, gender, age, disability, socioeconomic status and location) in treatment or prevention outcomes should be considered.	Technical report
✓	**C.3.2**	Search strategies include search terms to identify evidence related to consumers' perceptions and experiences.	Technical report
✓	**C.3.3**	Dependent on the guideline scope, the search strategy is designed to identify evidence for all relevant alternatives for screening, prevention, diagnosis or treatment of the condition addressed by the guideline, including relevant complementary and alternative medicine approaches.	Technical report
✓	**C.3.4**	Search strategies include search terms to identify evidence related to cost effectiveness and resource implications of practice.	Technical report
✓	**C.8.1**	If gaps in the evidence are identified during the evidence review, these are described in the guideline and areas for further research are noted.	Guideline

D. Guideline recommendations

Mandatory requirements – the guideline/ development process must meet all the following conditions:

	Requirement	Description	Documented in:
✓	**D.1**	The wording of recommendations is specific, unambiguous, clearly describes the action/s to be taken by users and matches the strength of the body of evidence.	Guideline
✓	**D.2**	The wording of recommendations is written in plain English and is consistent throughout the guideline.	Guideline
✓	**D.3**	For each evidence-based recommendation, the supporting references are listed and the grade of recommendation is indicated according to an NHMRC-approved method (NHMRC grades for recommendations or GRADE).	Guideline
✓	**D.4**	Recommendations formulated in the absence of quality evidence (where a systematic review of the evidence was conducted as part of the search strategy) are clearly labelled as such. The preferred term for this type of recommendation is a consensus-based recommendation.	Guideline
✓	**D.5**	Any further recommendations included in the guideline, where the subject matter is outside of the scope of the search strategy, are clearly labelled as such. The preferred term for this type of recommendation is a practice point.	Guideline
✓	**D.6**	The method used to arrive at consensus-based recommendations or practice points (e.g. voting or formal methods, such as Delphi) is documented.	Guideline
✓	**D.7**	Areas of major debate about the evidence and the recommendations are identified and the various significant viewpoints are outlined in the guideline text (even if the guideline development working group members eventually reached a decision).	Guideline
✓	**D.8**	The strengths and limitations of the body of evidence reviewed are described in the guideline text and areas of uncertainty are acknowledged.	Guideline
✓	**D.9**	The guideline acknowledges current national guidelines approved by NHMRC or endorsed by major authorities, and any deviations from these are explicitly noted in the guideline text and the rationale provided.	Guideline
✓	**D.10**	Where a guideline makes any recommendation/s specifying intervention/s that are not available or restricted in Australia, the text clearly indicates this, and the developer has consulted the relevant authority/ies	Guideline
✓	**D.11**	Any evidence that identifies Aboriginal and Torres Strait Islander peoples or other population groups as having specific treatment or prevention outcomes is clearly identified and considered in the formulation of recommendations.	Guideline
✓	**D.12**	The harms (risks or side effects) and benefits of each recommended intervention and its alternatives are described, with an explanation provided for the rationale of the recommendation.	Guideline
✓	**D.13**	Any safety, legal, or potential misuse issues related to clinical recommendations are identified and described in the guideline text.	Guideline
✓	**D.14**	The potential impact of reach recommendation on clinical practice or outcomes is described.	Guideline

Desirable requirements – the guideline/ development process should meet the following conditions, where applicable:

	Requirement	Description	Documented in:
✓	**D.2.1**	Recommendations are formulated using consistent grammar, syntax and wordings, so they can readily be adapted for electronic implementation strategies (e.g. electronic decision support systems and automatic data collection).	Guideline
✓	**D.8.1**	Recommendations that are likely to be affected by new evidence after the guideline has been approved (e.g. major clinical trials underway at the time of guideline publication) are identified and the implications for the guideline recommendations are explained in the guideline text.	Guideline
✓	**D.9.1**	Clinical recommendations that deviate from current practice are identified.	Guideline
✓	**D.9.2**	The resource implications and cost effectiveness of any recommended practice, compared with current or established practice, are explicitly stated in the guideline.	Guideline
✓	**D.11.1**	Where evidence is identified showing that sociocultural factors (including ethnicity, gender, age, disability, socioeconomic status and location) affect treatment or prevention outcomes, this evidence is clearly identified and considered in the formulation of recommendations.	Guideline
✓	**D.12.1**	Absolute measures of both efficacy and harm are stated for each management option where evidence is available (e.g. expressed as number needed to treat, number needed to screen, or number needed to harm, as relevant to the recommendation).	Guideline
✓	**D.13.1**	Ethical issues are considered when formulating the recommendations and any such issues identified and described.	Guideline
✓	**D.16**	If evidence for complementary and alternative medicine options is identified, the risks and benefits of these are stated in the guideline text and appropriate recommendations included.	Guideline
✓	**D.17**	If there is a lack of rigorous evidence for a complementary and alternative medicine/ therapy commonly used in practice, this is explicitly stated in the guideline text.	Guideline
✓	**D.18**	Recommendations that consider consumer self-management options are included (where relevant).	Guideline
✓	**D.19**	Recommendations emphasise consumer and carer involvement in treatment and care decisions (where relevant).	Guideline

E. Guideline structure and style

Mandatory requirements – the guideline/ development process must meet all the following conditions:

	Requirement	Description	Documented in:
✓	**E.1**	The guideline includes a title page listing: • The date of publication • The authorship (organisation or individuals) • The publisher • Copyright information including the copyright holder • Address for requesting permission to reproduce material in the text • The ISBN number • A preferred citation for the guideline publication.	Guideline
✓	**E.2**	The guideline is easy to navigate and includes a table of contents.	Guideline
✓	**E.3**	The guideline includes a brief (e.g. 1-page) plain English summary.	Guideline
✓	**E.4**	The guideline includes an executive summary that lists all recommendations and their grade using an NHMRC-approved method (NHMRC grades for recommendations or GRADE)	Guideline
✓	**E.5**	A glossary of technical terms, acronyms and abbreviations is provided, and terms are used consistently throughout the entire guideline.	Guideline
✓	**E.6**	Where medicines are mentioned in the guideline, generic names are used and brand names are avoided	Guideline
✓	**E.7**	The document design and layout enables recommendations to be identified easily within the text.	Guideline
✓	**E.8**	References in the text are clearly identified and the citations clearly listed. For electronic references, the source location (e.g. website address) and date accessed is stated.	Guideline
✓	**E.9**	Chapter and heading levels are consistent, clearly distinguishable by the document design and layout, and assist with the navigation throughout each topic of the guideline.	Guideline
✓	**E.10**	The guideline information is sequenced in a logical manner which is applicable to the intended end user.	Guideline
✓	**E.11**	The technical report is either: (i) included in the guideline document; or (ii) provided in a readily accessible location, such as a website (which is indicated in the guideline).	Guideline
✓	**E.12**	The administrative report is either: (i) included in the guideline document; or (ii) provided in a readily accessible location, such as a website (which is indicated in the guideline).	Guideline

Desirable requirements – the guideline/ development process should meet the following conditions, where applicable:

	Requirement	Description	Documented in:
✓	**E.2.1**	An index is included.	Guideline
✓	**E.2.2**	If the guideline is published in PDF format, bookmarks are provided to facilitate navigation.	Guideline
✓	**E.2.3**	If the guideline is published as a web page, hyperlinks are provided to facilitate navigation.	Guideline
✓	**E.3.1**	Plain English is used for all guideline text.	Guideline
✓	**E.4.1**	A summary of recommendations is available as a separate document and the guideline text states where to obtain this document.	Guideline
✓	**E.7.1**	The design of the guideline (printed or electronic) is suitable for people with visual impairment.	Guideline

Appendix C Expert team

Table 13 below outlines the experience and qualifications of members of the expert team involved in development of the methodological framework. Peter Clifton from Baker IDI led the expert team.

Table 13: Experience and qualifications of the expert team

Professor Peter Clifton

Professor of Nutrition , University of South Australia, Research Fellow Baker IDI Heart and Diabetes Institute

Experience

Professor Peter Clifton is Professor of Nutrition, University of South Australia, Research Fellow Baker IDI Heart and Diabetes Institute. He is an internationally respected leader in the field of cardiovascular disease, nutrition and health. To date, Peter has contributed to informing scientific opinion through publication of 164 journal articles, more than 100 of these in the last 10 years, 6 book chapters and many scientific presentations. Peter actively contributes to the provision of scientific leadership to the food industry sector and has positively influenced the health of Australians through his high profile in publications such as the Total Wellbeing Diet whilst at CSIRO and more recently the Diabetes, Diet and Lifestyle Plan (Penguin 2011).

Qualifications

- MBBS, Melbourne University 1975
- B Med Sci, Melbourne University 1972
- Diploma of Histology while undertaking B Med Sci 1973
- Fellowship Royal Australasian College of Physicians 1986
- Membership Royal College of Physicians (UK) 1979
- PhD Department of Medicine, Flinders University of South Australia 1988

Dr Andrew Bartholomaeus

CEO, BartCrofts Pty Ltd, Scientific Services

Experience

Andrew Bartholomaeus is CEO of BartCrofts Scientific Services, a consultancy providing technical and strategic science support to industry and government in the areas of preclinical toxicology, Phase I clinical trials, human safety assessment and chemicals and pharmaceuticals regulation. He is also Adjunct Professor at the University of Queensland Medical School, Adjunct Professor of Toxicology and Pharmacy at the University of Canberra, and was a member of the ILSI IFBiC Steering Group. Andrew has over 20 years' experience working as a toxicologist across a broad range of chemical regulatory areas including agricultural, veterinary and industrial chemicals, complementary medicines, and gene technology products. Prior to retirement he was the General Manager of the Risk Assessment Branch of FSANZ.

Qualifications

- Doctor of Philosophy (RMIT, Toxicology)
- Bachelor of Pharmacy (University of Sydney)
- Introductory Viticulture (CIT)
- Certificate III in Agriculture (CIT)
- Explosives Supply Management (RAAF)
- Medical Officers Nuclear Biological and Chemical Warfare Defence (RAAF)

Professor Caryl Nowson

Professor of Nutrition and Ageing, Deakin University

Experience

Caryl Nowson is Professor of Nutrition and Ageing at Deakin University's School of Exercise and Nutrition. She teaches at undergraduate and postgraduate level and also supervises higher degree students. Caryl is a member of the Centre for Physical Activity and Nutrition Research (C-PAN) and has a specific focus on reducing risk of cardiovascular disease and osteoporosis through preventive strategies that extend throughout the lifespan. Caryl's research primarily centres on nutrition related to hypertension and bone health. In addition to conducting a range of dietary and lifestyle intervention studies, she has recently focused on informing and changing policy to reduce risk of chronic disease, specifically cardiovascular disease and osteoporosis.

Qualifications

- Diploma of Evaluation, University of Melbourne
- Doctor of Philosophy (Physiology), University of Melbourne "The role of dietary minerals and electrolytes in the control of blood pressure"
- Diploma of Education, University of Melbourne
- Diploma of Nutrition & Dietetics, University of Sydney.
- Bachelor of Science (Nutrition, Deakin University

Assocciate Professor Jennifer Keogh

Associate Professor Dietetics and Nutrition, University of South Australia

Experience

Associate Professor Jennifer Keogh is an accredited practising dietitian who is a nationally respected leader in dietetics. Jennifer is a member of the Population Health and Nutrition Concentration in the Sansom institute for Health Research and is a Fellow of the South Australian Cardiovascular Research Development Program. She has published 90 journal articles, has an H-index of 27 and more than 2200 citations. She is leading research on the effects of dietary sodium and potassium on vascular function and cardiovascular disease risk. She is also researching strategies for weight loss and weight maintenance.

She has held leadership roles in dietetics overseas and is now the senior academic in dietetics at the University of South Australia. She contributes to dietetic education and the provision of scientific leadership to the nutrition and dietetic community. Jennifer has recently co-authored a best-selling book on Diet and Blood Pressure published by penguin.

Qualifications

- MBBS, Doctor of Philosophy, University of Adelaide "Nutrition and Vascular Health"
- MSc (Research), University of Melbourne "Bone Mass and Body Composition in Adults: Effects of Liver Transplantation"
- Accredited Practising Dietitian (APD) and Accredited Nutritionist (AN), Dietitians Association of Australia
- Diploma in Dietetics, College of Technology, Dublin, Ireland.

Kylie Lange

Biostatistician, NHMRC Centre of Research Excellence, University of Adelaide

Experience

Kylie Lange is a biostatistician with the NHMRC Centre of Research Excellence (CRE) in Translating Nutritional Science to Good Health (previously the Centre of Clinical Research Excellence [CCRE] in Nutritional Physiology, Interventions and Outcomes) in the Discipline of Medicine, at The University of Adelaide. She is also a visiting Scientist at the Commonwealth Scientific and Industrial Research Organisation (CSIRO), Division of Animal, Food and Health Sciences. With a Mathematical & Computer Sciences degree with honours in Statistics (1999), she has been working in academic research continuously since 2002.

- B Mathematical & Computer Sciences with honours in Statistics (1999)

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