Dietary reference values for phytochemicals?

ML Wahlqvist, N Wattanpenpaiboon, A Kouris-Blazos, P Mohandoss, GS Savige

Monash University Department of Medicine, Monash Medical Centre, Clayton, VIC, 3168

Summary

Dietary Reference Values (DRV) and the categories of recommendations that accompany these values do not currently extend to the area of phytochemicals. Phytochemicals have a relatively greater multifunctionality than is understood for the currently accepted nutrients and would appear, in many cases, to be essential if not desirable for optimal health. It is likely that phytochemicals contribute to optimal health, and their deficiencies, in some cases, may be associated with disordered physiology, ill health and even frank disease. An excessive intake of phytochemicals from either food or non-food sources may have unintended and unfavourable health consequences. A variety of food sources of phytochemicals is likely to be the safest strategy for intake. An Index of Preferred Phytochemical Intake (IPPI) could be one that is food based as this would have the advantage that it would reflect the several members of a class of phytochemicals, with complementarity, synergy or modulatory effects. Data sources are needed to develop such an index and would include food compositional data, observational data about the intakes and their health relationships, and intervention data. Biologically active compounds in bodily fluids or tissues also need to be identified and measured along with their kinetics. These values will be useful in determining preferred levels of specific food intakes and related phytochemical status.

Food components

There has been a recent appreciation that many food components, whether of animal (zoochemical), plant (phytochemical) or microbial (notably mycochemical) origin, have the potential to affect human biology, for better or worse. This has stimulated interest in the definition, at least of the preferred levels of intake, if not the degree of essentiality or desirability or the need for exclusion or undesirability of food components previously not covered by Recommended Dietary Intakes (RDIs), statements of safe and adequate ranges of intake (ESADDI), or upper limits of intake. In the US the National Academy of Sciences recently released a report that dropped the term RDA in favour of Dietary Reference Intakes (DRIs) which include four categories of recommendations: recommended dietary allowance (RDA), adequate intake (AI), estimated average requirement (EAR), and tolerable upper intake level (IUL) (1). The larger area of concern here is that of phytochemicals.

Essentiality, RDIs and estimated safe and adequate intakes (ESADDIs)

Even those nutrients for which RDIs or ESADDIs (estimated safe and adequate daily dietary intakes) are presently nominated are not necessarily essential in the short-term. This may depend on whether they are made in the skin (as with vitamin D) or gut (vitamin K, biotin, folic acid), substituted for by other nutrients with similar direct or indirect functions (vitamin E, selenium), what the storage and kinetics are, or what the conditioning factors (like metabolic stress for glutamine, PUFA intake for vitamin E) are.

It also may be a matter of survival or optimal health, or the time to survival without the nutrient. A good example of nutrient essentiality over the long term compared with the short term is dietary fibre in the prevention of large bowel cancer (2); dietary fibre in the short term has more to do with optimal health rather than survival as illustrated by its importance in bowel function and avoidance of constipation (3).

Phytochemicals may fit any one of these definitions of essentiality, depending on the component and its function. However, one of the impressive differences between currently accepted nutrients and phytochemicals is that phytochemicals have a relatively greater multifunctionality based on the present evidence (4).

Physiological and health protective functions

The question might be asked as to whether enough consideration has been given to food component contributions to bodily functions and to health protection as we currently understand it. Such food component contributions would raise the possibility that many areas of food-component deficiencies are yet to be defined. For example, menopause is not prevented by the intake of essential nutrients and is not recognised as a deficiency disorder. One of the changes associated with menopause (vaginal-cell maturation index), however, has been improved with the intake of phytoestrogens (5-7) and in some studies, phytoestrogens appear to have a favourable effect on hot flushes (8, 9) and bone density (10). Therefore, menopausal symptoms might result from a phytochemical deficiency (11).

Another general problem of the physiology of nutrients is that those functions currently described may be only part of the story, such as is the case with vitamin D. Vitamin D previously was thought to have a limited role in bone, but now is known to play a role in gene expression, cell differentiation, immune function, and possibly other functions. To date the RDI for vitamin D has been predicated on only one or two functions; thus the general dilemma of matching food components and function. If phytochemicals were to have RDIs they would need to be under constant review as the science rapidly unfolds.

Classification of phytochemicals

This may proceed in accordance with plant source, chemistry, or functions. No one classification will be satisfactory because plants will be sources of various chemical and functional classes of compounds, the chemistry is complex and the compounds myriad. The functions of phytochemicals have to be considered in context as their functions may be underestimated if viewed in isolation. What has become clear is that one class of phytochemicals may have several functions, ie multifunctional compounds. On the other hand, a particular function may be provided by more than one class of phytochemicals. The interactions between the compounds is also likely to be considerable and complex, as certain components could synergise or conversely mask the effect(s) of other food components.

Phytochemicals may fall into any one of several categories: carotenoids, flavonoids and isoflavonoids, polyphenols, catechins, isothiocyanates and indoles, allyl sulphinates, terpenoids, phytosterols, curcumins, salicylates, L-dopa and non-digestible oligosaccharides [Table 1]. These categories are now being considered and actively investigated for their biological and health properties.

Index of Preferred Phytochemical Intake (IPPI)

At present, a case could be made for a IPPI for some phytochemicals, like phytoestrogens given the level of evidence about biological effects and the epidemiological data which provide guidance on safety. Such as index could be one that is food based, aggregating foods known to be good sources of phytochemicals in question. This would have the advantage of recognising that there may be several members of a class of phytochemicals, with complementarity, synergy or modulatory effects. To speak only about particular isoflavones like genistein or diadzein, for example, as phytoestrogens neglects the lignans and coumestans and the way in which they interact with each other. It also disregards the limits on intake imposed when food is their source. A food based IPPI provides for caution about intake insofar as potential toxicity is concerned. Furthermore, physiological levels of biologically active compounds in bodily fluids or tissues need to be identified and measured. These values may be useful in determining the level of specific food intake and phytochemical status.

Table 1. Phytochemicals and their possible roles in health

Phytochemicals	Some important food sources	Possible roles in health
Carotenoids	orange pigmented and green leafy vegetables, eg carrots, tomatoes, spinach	antioxidants antimutagen anticarcinogen immuno-modulating
Polyphenols	cranberry, raspberries, blackberries rosemary, oregano, thyme	antioxidant antibacterial reduce urinary tract infection
Catechins	green tea	antimutagen anticarcinogen anticariogen
Flavonoids and saponins	green leafy vegetables and fruit, eg parsley, celery, onions, apple, tea	antioxidant anticarcinogen oestrogen-like
Isoflavonoids	soy bean and soy products	anti-angiogenic immuno-modulating
Lignans	linseed, chickpea	oestrogen-like
Isothiocyanates and Indoles	cruciferous vegetables, eg broccoli, cabbage	antimutagen
Allyl sulphinates	garlic, onions, leeks	anticarcinogen antibacterial cholesterol lowering
Terpenoids including limonene	citrus, caraway seeds	anticarcinogenic against mammary tumours
Phytosterols, eg β-sitosterol	pumpkin seeds	reduce symptoms of prostate enlargement
Curcumin	tumeric	anti-inflammatory
Salicylates	grapes, dates, cherries, pineapple, oranges, apricots, gherkins, mushrooms, capsicums, zucchini	protective against macrovascular disease modulation of gene expression
L-dopa	broad bean	treatment of parkinson's disease
Non-digestible carbohydrates	artichoke, chicory root murrnong, maize, garlic, oats, fruit, legumes and vegetables	stimulate growth of microbial flora cholesterol lowering

This list is not exhaustive for phytochemicals.
Adapted from Wahlqvist *et al.* (11)

Data sources needed to assess IPPI include food compositional data, observational data about intakes and health relationships and intervention data. Available data sources may include information gathered from studies published in the literature. Studies on garlic and its phytochemical components will be used as an example.

Observational studies

Garlic (*Allium sativum* L.) is believed to have originated from central Asia and appears to have been used by human civilization since the Neolithic age. It has been employed for thousands of years in virtually all cultures in the prevention and treatment of a wide variety of ailments. Evidence from ecological studies suggest that there is an inverse relationship between allium consumption and coronary heart disease mortality rates (12). Sainani and colleagues (13) conducted a local Indian community survey and observed that serum lipid levels were lowest in those consuming the most garlic, and lipid levels increased stepwise and were highest when garlic was no longer part of the diet. Fifteen cohorts from the Seven Countries study comprising 11,579 men aged between 40-59 were followed for a 15 year period (14). The authors reported a marked north-south gradient in coronary heart disease in Europe, which roughly corresponds to an inverse pattern of garlic consumption (15). The highest European coronary disease rates are in the North (Finland) and the lowest in the South (Crete).

Intervention studies

Intervention studies have focussed on known classical risk factors for coronary heart disease (CHD). The beneficial effects of garlic in reducing the risks associated with CHD, such as lowering cholesterol levels, reducing blood pressure, have varied in relation to the oral garlic preparation (16, 17). The daily dose of garlic powder has ranged from 0.6 - 0.9 g/day, equivalent to 1.8 - 2.7 g of fresh garlic. The hypolipidaemic effect of dried powder preparations seems to increase between one and three months with the maximum effect in one trial occurring at six months (18). The six month study reported by Lehmann (19) used 0.6 - 1.2 g of standardised garlic powder with minimum 3-6 mg allicin release but did not report how many subjects needed the larger 1.2 g dose to achieve a change in lipid profile. The minimal dose required to achieve total cholesterol reduction is not clear and high-dose regimens are therefore still argued (20). Recent studies of both oil-based garlic and a powder have not demonstrated a significant effect on lowering lipids (21, 22). However, cardiovascular protection by garlic, may yet be medicated via non-classical pathways such as through endothelial function and vascular reactivity (23).

One of the problems associated with these types of studies is that garlic is not consumed as part of the food culture, but consumed in its isolated form such as garlic powder or garlic oil (24).

The risks and benefits of phytochemicals ingested in isolation from food

Caution will be required where a large amount of a particular food source of phytochemicals is being ingested for a therapeutic effect, because toxic levels of the compound of interest may be reached along with those of other companion compounds, about which less is known.

The dose-response relationships for some phytochemicals, notably biogenic amines and salicylates may be steep for some individuals, leading to 'food sensitivity' (25). Tolerance may be greater in a varied diet characterised by snacking rather than large meals, since the intakes are in smaller aliquots and can be modulated by other factors.

Another issue is that some phytochemical effects will be receptor mediated. Receptor mediated functions like those of phytoestrogens (eg isoflavones) may be agonist or antagonist and act on a hierarchy of estrogen receptors in different tissues. Therefore one class of phytochemicals may have several types of dose-response relationships and tolerable upper intake levels (TUL). Again, a variety of food sources of phytochemicals is likely to be the safest strategy for intake.

The potential interaction between endogenous and exogenous estrogens, which may be phytoestrogens or xenoestrogens (plasticiser, pesticides such as plychlorinated biphenyls), is an example of how the adverse effects of exogenous estrogens may be minimised in a complex food and contaminant environment.

Approaches to optimising phytochemical intake

Until recently, nutritionists have focused primarily on the nutrient elements in foods and counselled that we consume a 'balanced diet'. With the interest in dietary fibre and new insights into many of the phytochemical components found in foods, this perspective is becoming outdated. The growing array of phytochemicals opens up opportunities for more healthful food choices and for the development of functional foods to serve particular physiological or pathological needs. With opportunities for the cultural broadening of the human diet, with more food items, interest in functional foods, food restoration and fortification, the public will require a greater level of nutritional literacy and logic.

A 'Food & Phytochemical approach' could be used to assess food intake in terms of the proportions and variety of food required to minimise risk of food-related disorders. Since it is not known exactly which food constituents are responsible for protection against chronic diseases, this approach places more emphasis on food, thus encompassing nutrients and phytochemicals.

A food guide which encompasses this approach is not currently available. Until more unequivocal evidence is obtained, a modification can be made using the Healthy Eating Pyramid (formerly called Healthy Diet Pyramid) of the Australian Nutrition Foundation (ANF) by increasing the variety of fruit and vegetables. Other guidelines which have an advantage over the ANF pyramid would also be worth considering and include the Asian Diet Pyramid and the Mediterranean Diet Pyramid which recommend the consumption of legumes, nuts, tea and fish on a daily basis (26). For humans, eating a wide variety of foods appears to maximise the potential benefits of biodiversity, particularly of plant foods, whilst diluting out any potentially toxic constituents. Foods from these various sources can be scored and the total score used as an indicator of the adequacy of the diet (27). The phytochemical adequacy of the diet can be assessed to some extent by the food variety score (11, 27).

It is particularly interesting to consider how non-nutrient (by the present definition), food components with hormone-like actions may appear in the human diet, and the implications this might have for food choice. Animal foods may contain certain phytochemicals including those with hormonal-like properties from the food consumed by the animal. Additionally, digestion of animal proteins may provide peptides which have hormone-like actions, such as morphiceptin, which is a peptide with opioid activity derived from milk proteins. The peptides of one animal when eaten by another animal may produce hormone-like actions in that animal. Thus composite hormone-like activities may be exerted by food, as the compounds go up the food chain, ultimately ending in humans.

Food selection for phytochemical intake will need to take account of a number of potential sources of such compounds as the industry that surrounds them seeks commercial advantage through their promotion:

- food
- food pattern
- elite clone and standardised cultivars of food
- food ingredients
- formula food
- "nutraceuticals"
- pharmaceuticals

The problem is that the well meaning identification and promotion of phytochemicals from food and non food sources may lead to unintended and unfavourable health consequences.

Conclusion

The advent of phytochemical science in human nutrition and health has created an altogether new paradigm. It questions some of our long standing concepts about essentiality of nutrients, of ESADDIs, of the food and environmental context in which food components are eaten, and of optimal exposure during different life stages.

The stage is set for a new more integral way of describing, monitoring and recommending food component intakes. Fortunately, at the time when food science and biomedical science are in a new conjunction, information technology should help us model food component intake in accordance with these new concepts (28). An IPPI is one step along this path.

References

1. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary Reference Intakes: calcium, phosphorus, magnesium, vitamin D and fluoride. Washington DC: National Academy Press, 1997.
2. World Cancer Research Fund/American Institute for Cancer Research. Food, nutrition and the prevention of cancer: a global perspective. American Institute for Cancer Research. Washington DC, 1997:216-51.
3. Anonymous. Position of the American Dietetic Association: Health implications of dietary fiber. J Am Diet Assoc 1997; 97:1157-9.
4. Wahlqvist ML, Dalais FS. Phytoestrogens: emerging multifacted plant compounds. Med J Aust 1997;67:119.
5. Wilcox G, Wahlqvist ML, Burger HG, Medley G. Oestrogenic effects of plant foods in postmenopausal women. BMJ 1990;301:905-6.
6. Dalais FS, Rice GE, Bell RJ, et al. Dietary soy supplementation increases vaginal cytology maturation index and bone mineral content in postmenopausal women. Proceedings of the Second International Symposium on the Role of Soy in Preventing and Treating Chronic Disease. Brussels 1996, September 15-18.
7. Brzezinski A, Adlercreutz H, Shaoul R, et al. Short-term effects of phytoestrogen-rich diet on postmenopausal women. Menopause 1997;4:89-94.
8. Murkies AL, Lombard C, Strauss BJG, Wilcox G, Burger HG, Morton MS. Dietary flour supplementation decreases post-menopausal hot flushes: Effect of soy and wheat. Maturitas 1995;21:189-95.
9. Eden JA, Knight DC, Mackey R. Hormonal effects of isoflavones. Proceedings of the Second International Symposium on the Role of Soy in Preventing and Treating Chronic Disease. Brussels 1996, September 15-18.
10. Dalais FS, Rice GE, Wahlqvist ML, et al. Effects of dietary phytoestrogens in postmenopausal women. Climacteric 1998 *(in press)*.
11. Wahlqvist ML, Wattanapenpaiboon N, Kannar D, Fabien FD, Kouris-Blazos A. Phytochemical Deficiency Disorders: Inadequate intake of protective foods. Current Therapeutics July 1998:53-60.
12. Hertog MG. Flavonoid intake and long-term risk of coronary heart disease and cancer in the Seven Countries Study. Arch Intern Med 1995;155:381-6.
13. Sainani GS, Desai DB, Gorke NH, Natu SM, Pise DV, Sainani PG. Effect of dietary garlic and onion on serum lipids profile in Jain community. Indian J Med Res 1979;69:776-80.
14. Keys A, Menotti A, Karvonen MJ, et al. The diet and 15 year death rate in the seven countries study. Am J Epidemiol 1986;124:903-15.
15. Keys A. Wine, garlic and CHD in Seven Countries. Lancet 1980;i:145-6.
16. Warshafsky S, Kamer RS, Sivak SL. Effect of garlic on total serum cholesterol. A meta-analysis. Ann Intern Med 1993;119:599-605.
17. Silagy C, Neil A. Garlic as a lipid lowering agent - a meta-analysis. J Roy Coll Physicians London 1994a;28:39-45.

18. De Santos OS, Grunwald J. Effect of garlic powder tablets on blood lipids and blood pressure - a six month placebo controlled, double blind study. Br J Clin Res 1993;4:37-44.
19. Lehmann B. Lowering of blood lipid values with standardised garlic powder drug - long range, multicentre study [abstract]. Cardiology in Practice 1991;18.
20. Ernst E. Cardiovascular effects of garlic (*Allium sativum*): a review. Pharmatherapeutica 1987;5:83-9.
21. Issacsohn JL, Moser M, Stein EA, et al. Garlic powder and plasma lipids and lipoproteins - a multicenter, randomized, placebo-controlled trial. Arch Intern Med 1998;158:1189 -94.
22 Berthold HK, Sudhop T, Vonbergmann K. Effect of a garlic oil preparation on serum lipoproteins and cholesterol metabolism – a randomized controlled trial. JAMA 1998;279:1900-2.
23. Wei ZH, Lau BHS. Garlic inhibits free radical generation and augments antioxidant enzyme in vascular endothelial cells. Nutr Res 1998; 18:61-70.
24. Koch HP & Lawson LD. Garlic - the science and therapeutic application of *Allium sativum L.* and related species. Maryland, USA: Williams & Wilkins, 1996.
25. Loblay RH, Swain AR. Adverse food reactions. In: Wahlqvist ML, King RWF, McNeil JJ eds. Food and health. Issues and directions. London: John Libby, 1987:39-42.
26. Willett WC, Sacks F, Trichopoulou A, et al. Mediterranean diet pyramid: a cultural model for healthy eating. Am J Clin Nutr 1995;61 (suppl):1402S-6S.
27. Savige GS, Hsu-Hage B, Wahlqvist ML. Food variety as nutritional therapy. Current Therapeutics 1997;57-67.
28. Trichopoulou A, Kouris-Blazos A, Wahlqvist ML, et al. Diet and overall survival in elderly people. BMJ 1995;311:1457-60.