The paradox of overlapping micronutrient risks and benefits obligates risk/benefit analysis

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Abstract

With risk analysis methods in the process of being deployed by European authorities for the purpose of limiting maximum dosages of vitamin and mineral supplements across the European Union (EU), scientific validation of recently emerging approaches using existing risk and benefit data is deemed essential. This review explores the function of existing European nutrient risk analysis methodologies applied to two vitamins, niacin and folate, and two minerals, selenium and fluoride. A major weakness of existing models is their exclusive focus on a single, most sensitive adverse effect on the most susceptible sub-population. Analysis of the four nutrients revealed, paradoxically, that dosages that induce risks in sensitive populations commonly overlap with those which induce benefits in the majority. This situation appears to be the norm, rather than the exception. Such overlaps are exacerbated when risk evaluations fail to consider differences between molecular forms of the same nutrient. A new conceptual risk/benefit model is proposed to replace the over-simplified two-tail risk model that has been widely accepted by regulatory authorities in Europe and the USA in recent years. This new model, which reveals pertinent zones of overlap between risks and benefits, demonstrates that statutory limitation of dosages at levels beneath existing tolerable upper levels would in many cases prevent the majority of the population from experiencing benefits from higher dosages. Accordingly, it is proposed that a critical zone of risk/benefit analysis is established for dosages in excess of the upper level to facilitate policy and risk management decision-making. Conventional risk assessment on fluoride as undertaken by European and US authorities is explored in detail, and it is shown that risk management, if applied by public authorities in a manner which is consistent with that used for other nutrients, would make public drinking water fluoridation programmes unfeasible in light of dental fluorosis risk to children. Possible explanations for the common overlap in dosages which induce both beneficial and adverse effects are given, both at a population and individual level. The review concludes by proposing that statutory restriction of vitamin and mineral food supplement dosages should be delayed in the EU until validated and more scientifically rational methodologies are developed. Where significant health benefits are known to result from habitual or short-term ingestion of dosages in excess of either upper levels or proposed statutory 'maximum levels', risk/benefit analysis should be undertaken to allow re-evaluation of risk management strategies.

1. Introduction

Safety concern over the increasing consumer use of food or dietary supplements (nutraceuticals) is acting as the main driver for the development of specific regulatory regimes (Coppens et al., 2006). Methodologies for risk analysis specific to nutrients have been in the process of development for well over a decade, and in the European Union (EU) they are being used in risk management for the purpose of limiting maximum allowable dosages of vitamin and mineral food supplements (Verkerk and Hickey, this issue). The development of these methodologies has been led by a number of organisations (Table 1).

The general process by which vitamins and mineral dosages are to be limited in food supplements within the EU is set out in the framework Directive on food supplements (Article 5, EC Directive 2002/46/EC). The Directive requires that maximum permitted levels (MPLs) be set EU-wide, “taking into account”: upper levels (ULs) as established by scientific risk assessment based on generally accepted data; intake from other dietary sources, and; recommended daily allowances (RDAs) (population reference intakes). It should be stressed that, legally, “taking into account” does not necessarily mandate a formulaic approach by which mean highest...
dietary intake levels are subtracted from ULs in order to generate MPLs.

The key deficiencies of existing risk analysis methodologies have been set out conceptually in a separate paper (Verkerk and Hickey, this issue). The present paper evaluates the function of existing risk analysis models using two vitamins (niacin and folate) and two minerals (selenium and fluoride) as specific examples, and provides possible explanations for the relationships found. In view of the effects of national and regional statutory restriction of dosages based on existing methods, alternative approaches are proposed.

2. Key challenges with recently emerged risk analysis methodologies

An ultra-precautionary approach to risk management of vitamin and mineral food supplements, particularly when also applied to risk assessment, creates unique problems in the case of nutrients. Some of the most pertinent problems, highlighted with examples, are:

- Limiting the risk of excess, may induce risk of inadequacy, e.g., limiting intake of folate by virtue of perceived risks of folic (pteroylmonoglutamic) acid may prevent consumers benefiting from the use of folate to reduce homocysteine levels (Caruso et al., 2006; Mager et al., 2009).
- Where risk is managed by regulatory prohibition, benefits will be denied among population groups and for nutrients where risks and benefits overlap (FAO/WHO, 2006), e.g., limiting vitamin D levels to <10 μg/d (=2 × EU recommended daily allowance [RDA]) would prevent individuals from consuming 25–50 μg/d. These higher levels, in the absence of significant solar exposure, have been associated with reduced risk of cancer (Autier and Gandini, 2007) and cardiovascular disease incidences (Sood and Arora, 2009).
- Using a single, most sensitive risk factor in the most susceptible population group as the basis for regulatory prohibition creates unjustified restriction for the majority of the population, e.g., in the case of nicotinic acid (niacin), significant health benefits may occur following intakes well above the 10 mg/d EU UL. Such benefits, for cholesterol management, are demonstrated graphically in Fig. 2. The EU UL (as well as the 35 mg tolerable upper level [TUL] in the USA) is based largely on two reports in the scientific literature dating back to 1938 (Sebrell and Butler, 1938; Spies et al., 1938). Some 50 years of clinical experience of high dose usage under the supervision of physicians, with the attendant medical records, has not been drawn on.
- Basing risk assessment and management decisions on the most potentially toxic molecular form of a nutrient discriminates against other, safer forms of the same nutrient, e.g., restrictions on niacin based on the perceived risks of nicotinic acid have disproportionate impact on other forms of niacin such as inositol hexanicotinate.
- Most of the data used in risk assessment are not directly relevant to healthy populations, having been derived mainly from clinical studies evaluating the therapeutic potential of high nutrient dosages in diseased subjects (Renwick and Walker, 2008).

3. The risk of over-simplification

Occam's razor, a guiding principle in the development of models of complex systems, especially biological ones, suggests that the simplest model is usually the best one. To verify a model's successful function, it must be validated against known data and relationships. A familiar two-tailed conceptual model depicting a 'safe intake level' either side of the risk of inadequacy tail (left tail) and the risk of excess tail (right tail) has become generally accepted (IOM, 1998; SCF, 2000; EVM, 2003; EFSA, 2006) (see Fig. 1, Verkerk and Hickey, this issue).

Since this model considers neither the multiple adverse effects nor the benefits across a wide intake range, it is, at the very least, a gross over-simplification (Verkerk and Hickey, this issue). An alternative conceptual model (Fig. 1) is proposed here that depicts hypothetically the more complex nature of responses, as well as the multiple risk and benefit responses that are intrinsic to nutrients. The model shows how beneficial effects may arise above the UL and that risk–benefit evaluation is required across a “zone of overlap”. Such evaluation requires detailed knowledge of the nature, severity, transience and reversibility of adverse effects, as well as the nature of benefits. Such data should relate to populations as a whole, as well as specific and relevant sub-populations.

The exclusion of benefits, other than those derived from meeting minimal, ‘essential’ requirements for vitamins and minerals, is generally not justified by regulatory authorities. However, possible reasons include: simplicity of the models (principle of parsimony); beneficial effects are regarded by health authorities as being medicinal in action and therefore not relevant to food supplements, which may need to be delivered at supra-physiological doses to yield benefits, and; health authorities do not consider the benefits of supplements as significant hence their tendency to avoid general recommendations for supplements. With respect to the latter, there are limited exceptions, e.g., folic acid for women planning pregnancy to reduce the risk of neural tube defects.

While food supplements are defined as a category of food in the legal systems of both the EU and the USA, the approach taken to their respective risk analysis is very different when compared to that for conventional foods. This is despite the fact that available data reveal that conventional foods contribute to substantially higher rates of reported adverse effects than food supplements, despite supplements being used regularly by 2% to over 65% of western populations (Block et al., 2007; Skeie et al., 2009). For example, the Centers for Disease Control (CDC) found that conventional foods (in part because of the presence of pathogens within them) cause approximately 76 million illnesses, 325,000 hospitalisations and 5000 deaths in the USA each year (Mead et al., 1999). By contrast, data from the USA’s National Poison Data System...
Niacin (vitamin B3) exists in a number of molecular forms and, as with most vitamins and minerals, there are substantial variations in both the risk and benefit associated with ingestion of these different forms. Three molecular forms are commonly used in supplements, namely nicotinic acid, nicotinamide (=niacinamide) and inositol hexaniacinate. Both nicotinic acid and its amide, nicotinamide, are found in foods, such as yeast, meat, fish, milk, eggs, green vegetables, and cereal grains. Dietary tryptophan, found particularly in protein-containing foods such as red meat, poultry, eggs, and dairy products, is also partially converted to niacin (approximately at a 60:1 ratio) following ingestion (Horwitt et al., 1981). Niacin, the term generally used for all molecular forms of vitamin B3, is generally present in the animal tissues as nicotinamide, or as the coenzymes nucleotides, nicotinamide adenine dinucleotide (NAD\(^+\)) and nicotinamide adenine dinucleotide phosphate (NADP\(^+\)), the balance of which are maintained via de novo synthesis and complex redox reactions (Belenky et al., 2007).

4. Risk/benefit evaluation of micronutrient

4.1. Niacin

Chronic lack of niacin in the diet results in the deficiency disease pellagra. Clinical presentation includes a combination of multi-system alterations typically involving gastrointestinal, skin and central nervous system abnormalities, notably delusions, diarrhoea, inflamed mucous membranes, mental confusion, scaly skin sores (Brust, 2007). However, inadequate intakes of other nutrients, including other B vitamins, may also contribute to pellagra, including the amino acids tryptophan (which converts \textit{in vivo} to niacin) and leucine (Krieger and Statter, 1987; Bender, 1991). Pellagra has been most commonly associated with populations primarily subsisting on maize (corn), which is extremely low in bioavailable niacin. The addition of lime to cultivated corn (nixtamalisation) improves niacin bioavailability, although the primary sources of nicotinic acid in an omnivorous diet are through the consumption of meats (especially poultry and red meat). Fortified cereal products generally contain the recommended daily allowance (RDA) of niacin which has been determined as 18 mg/d (in Europe and the USA).

However, in addition to the use of niacin to eliminate risk of pellagra, there are numerous other benefits of niacin. Such benefits are generally experienced only when intakes are considerably higher than the RDA. As with the risk of pellagra, the absence of the benefits may also be regarded as risks of inadequacy. Established benefits of niacin intake include the following:

- Blood lipid management (control of hyperlipidemia) (Schechtman and Hiatt, 1996).
- Improved choroidal circulation for eye health (Metelitsina et al., 2004).
- Improved blood glucose control (Goldberg and Jacobson, 2008).
- Management of anxiety (Thompson and Proctor, 1953; Akhundov et al., 1993).

Given that ULs for niacin have been set at 10 and 35 mg/d by the Scientific Committee on Food (SCF)/European Food Safety Authority (EFSA) (EU) and the Institute of Medicine (IOM) (USA) respectively, it is noteworthy that most of the benefits, such as blood lipid management, occur substantially above these dosages. Fig. 2 shows the intake–response relationship in terms of both the low-density lipoprotein cholesterol (LDL) lowering and the high-density lipoprotein (HDL) raising effects of niacin as established from high-quality niacin monotherapy trials. It should be stressed,
However, that adverse effects, notably flushing, tend to reduce compliance at dosages in excess of 1 g daily, and especially 2 g daily. Niacin’s mechanism of action in blood lipid management is thought to be associated with its direct and noncompetitive inhibition of hepatocyte diacylglycerol acyltransferase-2, a key enzyme for triglyceride synthesis. This inhibition results in accelerated intracellular hepatic apo B degradation and the decreased secretion of VLDL and LDL particles (Kamanna and Kashyap, 2008).

4.1.3. Conclusion

Significant benefits of niacin occur at intake levels above the UL. Therefore, dosages giving rise to both risk and benefit overlap. Risk–benefit evaluation of niacin use above 10 mg/d is required to allow the safe and beneficial use of niacin acid at daily levels that exceed the UL. Labelling may be used to help inform consumers of the flushing effect, and these should indicate that flushing is transient and can be diminished through regular use. Different risk management strategies are required for different forms of niacin given clear differences in the propensity to induce flushing between different forms of the nutrient.

4.2. Folate

Folate (also known as vitamin B9) is a generic term for a group of water-soluble compounds composed of a pteridine ring and glutamic acid. Folate is essential for DNA synthesis, repair and methylation, as well as a variety of metabolic processes (Massaro and Rogers, 2002). Dietary folates appear to have significant cancer protective effects (Kristal and Lippman, 2009) and are widely distributed in green-leaved vegetables (Massaro and Rogers, 2002). They are a mixture of polyglutamylated folates which are digested (and deconjugated) to monoglutamyl folates by the action of folytpoly-gamma-glutamate carboxypeptidase (FGCP), also known as pteroylpolyglutamate hydrolase (PPH), an enzyme that is anchored to the intestinal brush border membrane and is expressed by the glutamate carboxypeptidase I (GGPII) gene (Devlin et al., 2000).

The synthetic form, commonly known as folic acid (pteroylmonoglutamic acid), is widely used in supplements and fortified foods. Folic acid requires chemical reduction to one of several polyglutamic forms, which are the bioactive forms. Conversion rates by the enzyme dihydrofolate reductase in the liver vary 5-fold (Bailey and Ayling, 2009), so use of polyglutamic forms such as 5-methyltetrahydrofolate (5-MTHF) (including its calcium salt) and 5-formyltetrahydrofolate (5-FTHF) (folinic acid), have become increasingly relevant for supplementation.

Bioavailability of dietary folates has been shown to be typically between 50% and 100% of that of folic acid (Brouwer et al., 1999; Gregory, 2001; Hannon-Fletcher et al., 2004; Winkels et al., 2007).

4.2.1. Risk of inadequate intake or benefits

Increased risk of neural tube defects in infants born to folate-deficient mothers is well established, although supplementation with folic acid will not necessarily ensure 100% elimination of such congenital abnormalities (Heseke et al., 2008). Evaluation of folate status in Germany suggests most Europeans are unlikely to meet the reference intake levels (RDAs) and are therefore folate deficient (Gonzalez-Gross et al., 2002). Inadequate intakes may contribute to increased risk of cardiovascular disease (McNulty et al., 2008) and cancer (Fairfield and Fletcher, 2002), as well as other health risks, including neural tube defects in babies born to folate-deficient mothers (Fletcher and Fairfield, 2002).

Additionally, a range of polymorphisms in various genes (e.g., 5,10-methylene tetrahydrofolate reductase [MTHFR], C677T), which reduce rates of deconjugation of polyglutamate folates, appear to be widely distributed in the population (affecting some
10–30%). These individuals require higher levels of folate intake, particularly in the polyglutamate form, to normalise the metabolic disorder induced by the polymorphism (Prinz-Langenohl et al., 2009).

Adequate consumption of dietary folates, such as 5-MTHF, is considered to lower the risk of cardiovascular disease, in particular by improving endothelial function in atherosclerosis (Buccianti et al., 2002; Baragetti et al., 2007). The mechanism of action is likely to be associated with 5-MTHF’s role in maintaining endothelial function and vascular superoxide production by preventing peroxynitrite-mediated oxidation of tetrahdrobiopterin (BH4), which acts as a cofactor for nitric oxide synthase (eNOS), elevated levels of which are associated with atherosclerosis in humans (Antoniades et al., 2006). Ronco et al. (2007) showed that 5-MTHF, but not folic acid, stimulated the production of endothelin-1 in LDL-treated human endothelial cells, suggesting that this mechanism may be involved in folate’s role in the reduction of cardiovascular disease risk.

4.2.2. Risk of excess intake

For over half a century, the greatest perceived risk of excess folic acid intake has been the masking of neurological symptoms of undiagnosed pernicious anaemia in the elderly (Wilkinson and Israels, 1949). However, given that pernicious anaemia is itself caused by malabsorption of cobalamin (vitamin B12), this problem is offset where high dose supplemental vitamin B12 is delivered as an adjunct.

Since this time, studies have arisen that suggest that high intakes of monoglutamatic folic acid may contribute to increased risk of certain cancers. Retrospective analysis of two Norwegian studies, the Norwegian Vitamin Trial and the Western Norway B Vitamin Intervention Trial, designed to investigate the effects of lowering homocysteine by supplementation with the B vitamins folic acid, vitamin B12 and B6, unexpectedly gave rise to an increased incidence of cancer (especially of the lung) and all-cause mortality (Ebbing et al., 2009). The studies included 6387 patients with ischemic heart disease, with mean age of about 62 years. The increased cancer risk was associated specifically with supplementation of 800 μg/d folic acid with vitamin B12. Of particular interest is that this level is beneath the UL (or GL) of 1000 μg/d for folic acid generated independently by EFSA, EVM and the IOM.

While methodological issues limit the conclusiveness of these findings, their potential significance from a public health perspective is such that further study is of paramount importance. In terms of possible mechanisms, there is some evidence that folic acid might accelerate the growth of very early, and as yet undetected cancer forms (neoplasms) (Hubner and Houlston, 2009). There is also some evidence that high levels of unmetabolised folic acid within the serum may affect the function of natural killer cells (Troen et al., 2006).

These studies may, in due course, trigger the lowering of the UL of folic acid. However, given the fact that such risks have not been associated with intakes of polyglutamate forms of folate, these levels should not be applied to such food-form folates.

4.2.3. Conclusion

Using conventional nutrient risk analysis (Coppens et al., 2006; Verkerk and Hickey, this issue), the Norwegian studies may suggest a revision of the UL from 1000 μg/d to a value beneath 100 μg/d (assuming lowest observable adverse effect level [LOAEL] = 800 μg/d and an uncertainty factor of 10). Although mean dietary intakes of folate are around 300 μg/d in Europe (de Bree et al., 1997), subtraction of these levels from ULs to determine a MPL is not relevant because the same risks associated with folic acid do not apply to food-derived folates. Optimum folate intakes may be in the order of 5 times greater than this, a level of approximately 1500 μg/d having been estimated following UK government ‘healthy eating’ guidelines (Verkerk and Hickey, this issue). Trials evaluating the benefits of food-form folates such as 5-MTHF have been undertaken at dosages up to 15 mg/d (Cagnacci et al., 2009).

As with the above example (niacin), in the case of folates there is a clear case of overlap between adverse and beneficial effects. The level considered appropriate among women of child-bearing age to reduce the risk of neural tube defects (400 μg/d) is likely to be greater than a revised UL which takes into account the latest scientific findings from retrospective studies of cancer risk among populations with high cardiovascular disease risk (Ebbing et al., 2009). Additionally, homocysteine normalization requires even greater intake levels, approximately 650 μg/d (de Bree et al., 1997).

Furthermore, it is apparent that unless discrete ULs and MPLs are set for folic acid and the polyglutamate forms respectively, the general public will be prevented from accessing adequate levels of polyglutamate folate.

4.3. Selenium

Selenium is an essential trace element consumed in sub-milligram amounts, primarily in organically bound forms, in the diet. Gross deficiency leads to a range of diseases or disorders, the most well-known being the cardiomyopathy, Keshan disease (Tinggi et al., 2009). The element is required for the function of a number of key selenium-dependent enzymes (selenoproteins) necessary for a wide range of metabolic processes, including thyroid hormone regulation, immune function and reproduction (Kryukov et al., 2003). It acts as a cofactor for the reduction of key antioxidant enzymes, including certain selenium-dependent glutathione peroxidases (Margis et al., 2008).

4.3.1. Risk of inadequate intake or benefits

Determinations of dietary adequacy (e.g., the EU RDA, USA dietary reference intake) have centred on establishing the necessary intakes to maximise synthesis of plasma glutathione peroxidase (GSHPx) activity. While such levels protect against Keshan’s disease and other symptoms of gross selenium deficiency, they do not equate necessarily to the levels required for other benefits, such as optimal immune function or reduction of cardiovascular and cancer risk (Thomson, 2004; Rayman, 2005).

Low selenium status has been found to interfere with thyroid hormone regulation. In a study of an elderly, selenium-deficient group, supplementation (50 μg/d) restored thyroid hormone status given selenium’s role in facilitating conversion of thyroxine (T4) to the active form 3,3,5-triiodothyronine (T3) through the action of a selenium-dependent deiodinase enzyme (Olivieri et al., 1996). Among a range of metabolic processes affected by selenium deficiency, inadequate selenium intake adversely affects male fertility (Schneider et al., 2009). However, no additional benefit of supplementation (even up to 300 μg/d) was found in an elderly population with mild hypothyroidism where selenium status was adequate prior to the start of supplementation (Rayman et al., 2008).

Dietary selenium has been shown, but not unequivocally, to have a protective function against certain cancers (notably prostate and colon) at levels that exceed the RDA (55 μg/d in EU) (Rayman, 2005). There are increasing indications from animal models that specific intakes of selenium which minimise DNA damage through reduction of oxidative stress upregulate apoptosis in cancer prone cells (e.g., prostatic epithelial cells) so reducing cancer incidence. Waters et al. (2005) supported this hypothesis with a study using prostate cancer prone beagle dogs, showing a non-linear dose–response relationship for selenium, in which both highest and lowest doses did not reduce prostate cancer incidence. This dose–response was found to correlate with that derived for...
humans. The authors hypothesised that a ‘U’ shaped curve (as conceptualised by inverted curve B1 in Fig. 1) describes the relationship between optimal selenium intake and prostate cancer prevention. Although the Selenium and Vitamin E Cancer Prevention Trial (SELECT) (200 mg/d) has yielded negative results (Lippman et al., 2009), given the weight of opposing evidence, methodological and dosage considerations in the SELECT trial may have precluded success (El-Bayoumy, 2009; Schrauzer, 2009).

4.3.2. Risk of excess intake

Selenium is consumed supplementally in both its inorganic (e.g., selenite, selenate) and organic forms (e.g., selenomethionine, selenocysteine). It is clearly both acutely and chronically toxic at higher levels of intake (> 1 mg, chronic intake). Characteristic symptoms of selenosis have been widely reported in highly localised areas (notably in China) where selenium levels in agricultural soils are unusually high (Yang et al., 1983; Tan et al., 2002).

Brazil nuts, one of the foods with the highest known contents of selenium (mainly as selenomethionine), may typically contain 30–140 μg Se per nut (based on a mean weight 4 g/nut) (Chang et al., 1995), although levels equivalent to 500 μg/nut have been found (Chunhieng et al., 2004). There is no evidence in the literature of selenium-mediated adverse reactions to brazil nuts, possibly because habitual high dose consumption is rare, or because selenium in such forms is less toxic. Consumption of 2 brazil nuts a day, delivering around 100 μg Se, was found to elevate glutathione peroxides in plasma an equivalent amount compared with 100 μg selenomethionine taken supplementally (Thomson et al., 2008) so lesser bioavailability is unlikely to be responsible for the apparent safety of brazil nuts.

The EFSA used a Chinese study from an affected area (Yang et al., 1989) on which to base its no observable adverse effect level (NOAEL). The study found symptoms of toxicity (selenosis) in those habitually consuming in excess of 910 μg/d. Based on a 3-fold uncertainty factor (UF), an UL of 300 μg/d was derived (for total intake from food and supplements).

4.3.3. Conclusion

Based on an UL of 300 μg/d and dietary intakes in Europe varying from 30–110 μg/d (EFSA, 2006), conventional risk management would typically determine a MPL of around 100 μg/d (=UL – highest mean intake). The German risk assessment agency, Bundesinstitut für Risikobewertung (BfR), has been more conservative and proposed a MPL of 25–30 μg/d (Domke et al., 2005), which is intended to ensure the EU RDA (55 μg/d) was established on population reference values from several Member States and, in particular, data from the USA (SCF, 2003).

Most of the US data used to establish the ‘adequate intake’ (AI) (3 and 4 mg/d for adult females and males respectively) and the Tolerable Upper Level (TUL) (10 mg/d for adults) (IOM, 1997) was based on extensive research conducted in the USA during the 1930–40s by dentists and researchers are widely regarded as the pioneers of dental fluoridation.

4.4. Fluoride

Fluoride, the iconic form of the gas fluorine, is an extremely reactive halogen, widely distributed in the environment and present in various chemical forms, some being highly bioavailable, others not. Primary sources of human exposure are food, beverages (especially tea), drinking water (especially if fluoridated artificially), dental products and pesticides (NRC, 2006). Fluoride has a particularly strong affinity to calcium, hence its propensity for both adverse and beneficial roles in bone and tooth health (IOM, 1997).

Artificial fluorides, such as hydrofluorosilicic acid, are added to municipal drinking water (mostly at around 1 mg/L) in the USA, Ireland and parts of the UK for the purpose of lowering dental caries rates among children (McDonagh et al., 2002; Clarkson et al., 2003; Parnell et al., 2009). A large body of research on fluorides relate to investigations of their effect on rates of dental caries in children when taken systemically or topically (IOM, 1997; NRC, 2006) where it acts through a number of mechanisms, including affecting re-/de-mineralisation of the enamel hydroxyapatite crystal (Featherstone, 2004) and interfering with the metabolism of key acidogenic streptococci associated with dental caries (Loesche, 1986).

4.4.1. Risk of inadequate intake or benefits

The primary benefit associated with supplemental fluorides are linked to their potential to reduce the risk of dental caries (Dean, 1947; IOM, 1997; EFSA, 2006). The EU RDA (3.5 mg/d) was established by the European Commission in 2003 based on population reference values from several Member States and, in particular, data from the USA (SCF, 2003). Most of the US data used to establish the ‘adequate intake’ (AI) (3 and 4 mg/d for adult females and males respectively) and the Tolerable Upper Level (TUL) (10 mg/d for adults) (IOM, 1997) was based on extensive research conducted in the USA during the 1930–40s by a group of dentists, including Drs H. Trendley Dean, Francis Arnold and Frank McClure (Dean, 1938, 1947; Dean et al., 1942; IOM, 1997).

These dentists and researchers are widely regarded as the pioneers of drinking water fluoridation.

The AI of 0.05 mg/kg bw (=1 mg/d for a 20 kg child) was determined as the level shown to “reduce the occurrence of dental caries maximally in a population without causing unwanted side effects including moderate dental fluorosis” (IOM, 1997). The best-fit intake–response curves in Fig. 3 are reproduced from the IOM 2003 (1997), which in turn derived its data from Dean (1938) and Dean et al. (1942). These data continue to be widely used by regulatory authorities despite the fact that, during those early studies, fluoride in drinking water was the only significant source of fluoride. Today, by contrast, intakes in drinking water are confounded by other sources including a broad range of food and beverages, toothpaste and other oral hygiene products, infant formulae and fluoride supplements (Levy, 1994).

The intake–response curve, as drawn by IOM (Fig. 2), suggests a significant dose response at doses in excess of 1 mg/L, although it also shows a dental fluorosis threshold which is remarkably close to the 1 mg/L/optimal concentration proposed by Dean et al. (1942). In...
terms of the margin between benefit and risk, Dean (1947) found endemic, albeit mainly mild, dental fluorosis in areas where fluoride was present at around 2 mg/L. A plot of the original data points (Fig. 4) reveals an apparently near-flat or marginal (beneficial) dose–response at dosages above 1 mg/L, suggesting the IOM (1997) best-fit curve plot may be misleading.

Of relevance to the food supplement usage of fluoride is the nature of the beneficial effect: Given that dental caries is a preventable infectious disease, strongly associated with poor diets and excess sugar consumption (Zero, 2004), is it nutritional or medicinal in nature? Disease prevention or treatment, in European law (Directive 2001/83/EC as amended) and the laws of most other regions or countries, is regarded as a medicinal claim, not a nutritional one. It is therefore ironic that in the EU, calcium fluoride, potassium fluoride, sodium fluoride and sodium monofluorophosphate are allowed as sources of fluoride in food supplements (Regulation (EC) No. 1170/2009).

4.4.2. Risk of excess intake
There is general agreement that the most sensitive adverse health effect of fluoride exposure is dental fluorosis (EFSA, 2006). There is debate as to what is an acceptable threshold of dental fluorosis, and a number of subjective indices have been used to quantify the severity of the condition. Most important are the Dean index of dental fluorosis (DFI) and the Thylstrup-Fejerskov index (TFI), the latter being considered generally more accurate (Rozier, 1994).

There is increasing evidence that exposures in excess of 0.05 mg F/kg bw induce dental fluorosis in children (see below). The condition may also impact on the quality of life of children and have negative psychosocial consequences (Alkhathib et al., 2004; Edwards et al., 2005; Macpherson et al., 2007).

Genetic predisposition to dental fluorosis plays an important role in the severity of dental fluorosis, in addition to intake levels, and the timing and duration of exposure in relation to tooth eruption and enamel formation (amelogenesis) (Vieira et al., 2005; Wurtz et al., 2008).

Some 50 years after the pioneering work of Dean and colleagues, Heller et al. (1997), analysed dose–response data from the 1986–87 National Survey of Oral Health of US Schoolchildren conducted by the National Institute of Dental Research (NIDR). The researchers found that a concentration of 0.7 mg/L represented the optimal trade-off between benefits of fluoride in reducing dental caries and risk of fluorosis. This level is significantly lower than that found by Dean et al. (1942) and may reflect the additional sources of fluoride exposure associated with contemporary lifestyles. The authors also found little additional benefit in dental caries reduction was achieved at water concentrations of 0.7–1.2 mg/L. Dental fluorosis rates were found to be 22%, 30% and 41% in areas with 0.3–0.7, 0.7–1.2 and <1.2 mg/L fluoride concentration respectively. These figures equate with those found in an Irish North-South survey, in which 35% of children in fluoridated area (target concentration: 1 mg/L) were found to have ‘mild’ or ‘very mild’ dental fluorosis (Whelton et al., 2002). A systematic review carried out using data from 9 countries (Australia, Canada, Finland, Ireland, Italy, New Zealand, Sweden, Britain, and the USA) by York University (UK) concluded that dental fluorosis would likely occur in 48% (95% CI: 40–57%) of the population exposed to municipal water fluoridated at the level of 1 mg/L (McDonagh et al., 2000).

A recent longitudinal study (Warren et al., 2009) in Iowa, USA has cast further doubt over the long-standing ‘optimal’ level of fluoridation which has been estimated, based on the limited work of Dean (1938) and others, as between 0.05 and 0.07 mg F/kg bw (on which the 1 mg/L target for water fluoridation level has been determined). The authors warned against using ‘optimal’ or target levels for fluoridation because of variations in exposure and susceptibility. They also found overlap between dental caries and dental fluorosis groups and determined that thresholds for children both free of fluorosis and with low dental caries rates was at or below 0.05 mg F/kg bw. Levy (1994), in evaluating exposures from drinking water, food, beverages, toothpaste and fluoride supplements found that up to 20% of the child population might exceed the mean amount for each category, by up to several times. This resulted in total exposures well above the 0.05 mg F/kg bw level.

Additional risks of increased fluoride exposure are known, the most significant being the development of skeletal fluorosis. It is now recognised that fluoride impacts specific parts of the skeletal system of relevance to the food supplement usage of fluoride is the...
The paradox of overlapping micronutrient risks and benefits obligates risk/benefit analysis. This is clearly not the case for nutrients or foods. The notion of excluding beneficial effects in favor of benefit allows the continued sale of such common items as wheat, dairy, and peanuts. The benefit of such common items as wheat, dairy, and peanuts is not necessarily of high quality and relevance (Renwick and Walker, 2008), so complicating decision-making.

5.2. The ‘zone of overlap’

A distinct overlap between risks and benefits in 3 out of 4 micronutrient examples considered here was found. Only in the case of selenium is such an overlap not obviously apparent, although it is clear, at least, that the margin between benefit and risk is very narrow. The examples discussed here are not anomalous.

Infants are particularly susceptible. While the EU has set an UL of 1.5 mg/d for infants aged 1–3 years, consumption of fluoridated water (1 mg F/L) in food and infant formula would bring a child very close to this level, given the IOM’s own stipulation of an adequate intake for water of 1.3 L for this age group (IOM, 2005). Concomitant use of fluoridated toothpaste in water fluoridated areas (as shown by Levy, 1994) would likely cause many children to exceed the 1.5 mg/d UL.

4.4.3. Conclusion

The principle of using the most sensitive adverse effect as the basis for setting ULs in risk assessment appears to have been sidelined given regulatory authorities’ insistence that mild dental fluorosis is of cosmetic significance only. Even where moderate fluorosis is used as the key adverse health effect, the selection of an uncertainty factor (UF) of 1 by the IOM in the establishment of the US Tolerable Upper Level is, at least, inconsistent with the approach used for most other nutrients. An UF of 1 is incongruent with the uncertainties and variations in methods of data collection, in the amount, timing and duration of exposure, as well as genetic susceptibility. Available evidence points to an overlap between risk and benefit for a significant proportion, if not a majority, of the child population if European or US ULs or TULs for fluoride are ingested habitually over a lifetime, especially if this includes infant exposures in excess of 0.1 mg F/kg bw at critical times during tooth eruption and enamel formation. In terms of the SCF and EFSA’s risk assessments of micronutrients (EFSA, 2006), it is apparent that fluoride is the only nutrient subjected to risk assessment for which perceived health benefits (reduced risk of dental caries) have been taken into account. This approach is inconsistent given the clear medicinal usage of fluoride for treatment or prevention of dental caries. It is also problematic, given the common overlap of dosages yielding beneficial and adverse effects, the difficulties inherent in managing exposures from multiple sources and the varying susceptibility of population groups.

5. Discussion

5.1. General

The evaluation of both risk and benefit is an inevitable necessity in regulatory decisions affecting diet. A weighing of the evidence in favor of benefit allows the continued sale of such common items as wheat, dairy, and peanuts. The notion of excluding benefit would only be rational scientifically if no benefit could be attributed to the nutrient or food. This is clearly not the case for micronutrients, which significant proportions of the population consume at sub-optimal levels (Fairfield and Fletcher, 2002; Ames, 2006).

The absence of a mature methodology for risk/benefit analysis of nutrients is no reason to not use elements of data relating to both risk and benefit in creating regulatory frameworks for nutrients. Such ad hoc methodologies are already commonplace in the field of chemically contaminated foods, such as fish. Most evaluations suggest that the health benefits of fish consumption outweigh the risks from contaminants on the basis that risk management guidelines are publicised that aim to ensure excessive (but not risk-free) intakes of contaminants are avoided (Smith and Sahyoun, 2005; Mozaffarian and Rimm, 2006). Intake–response data for nutrients, however, for both risk and benefit are generally limited, and are not necessarily of high quality and relevance (Renwick and Walker, 2008), so complicating decision-making.
(e.g., iron sulphate and iron bisglycinate) [Verkerk and Hickey, this issue]. However, it is also clear (e.g., for nicotinic acid and folic acid) that in some, if not many, cases, overlap occurs even for the same molecular form.

Such an apparently paradoxical situation is not unusual in biology, and is well exemplified by the concept of ecological trade-offs (DeHaan et al., 2005; Jessup and Bohannan, 2008). Metabolic trade-offs are also commonplace. An emerging field in evolutionary biology is the study of nutrient sensing and management, processes that involve close functioning and molecular integration between the immune and metabolic systems (Hotamisligil and Erbay, 2008). Given the intimate co-evolution of human beings with particular foods, many of which contain toxic principles, it is no surprise that adverse effects may be detected in some of the most genetically susceptible individuals, while disrupted homeostatic mechanisms in others, might be corrected with higher nutrient exposure (Ames, 2006). Additionally, the rapid change in western diets, dietary simplification, increased exposure to toxins and harmful forms of non-ionizing radiation are likely to suggest the need for supranutritional levels of micronutrient intake (Ames, 2006; O’Keefe et al., 2008). Several studies have shown that consumption of food supplements is generally associated with other healthy behaviours, such as consuming healthy diets and exercising regularly (McNaughton et al., 2005; Reinert et al., 2007).

5.3. The need for risk/benefit analysis of micronutrients

Given the large variations between risk and benefit between different forms of vitamins and minerals, risk/benefit analysis responsive to these differences has been proposed (Verkerk and Hickey, this issue). However, such analysis would be unnecessary for specific molecular forms of nutrients, irrespective of the hazard of related nutrients, for which there was no evidence of risk at intended use levels. This would apply, for example, to natural (mixed) carotenoids and polyglutamate folates, where hazard has been associated with related synthetic forms, beta-carotene and folic acid respectively.

Other nutrients and their respective forms should be subject to some form of risk/benefit analysis in order that scientifically based judgments, both quantitative and qualitative (see Fig. 1), can be made to inform regulation. Given that such analyses take time, prioritisation according to relative risk, as proposed by the FAO/WHO (2006), should be adopted.

Another important consideration is the shape and gradient of the adverse effect dose–response curve, as well as its proximity to the beneficial effect curve. Fig. 1 demonstrates that the risk of exceeding the UL is greater where the dose response is steep (e.g., for selenium), while it is less where it is shallow (e.g., polyglutamate folate).

5.4. Population vs individual effects

An important principle that complicates conventional risk assessment is that ULs are generally determined to protect the most susceptible population group from a given adverse health effect, i.e., those individuals represented by the ‘left side’ of the Gaussian distribution of response. In the EU, this approach is a requisite of Directive 2002/46/EC on food supplements. Where statutory limitation of dosage is applied to protect the most susceptible individuals from the most hazardous form of a nutrient, the Gaussian distribution associated with a given health benefit will mean that significant segments of the population will be denied benefit. These relationships are shown conceptually in Fig. 5.

5.5. Fluoride: an exceptional case

The determination of ULs for fluoride by both the SCF/EFSA and the IOM represents a clear and unjustified exception to the rule, with risk being determined on the basis of mean responses (to moderate dental fluorosis). Additionally, contrary to the case for other nutrients, the perceived benefit (reduction in the rate of dental caries among children) appears to have been considered in establishing the UL. This has allowed the AI (or RDA) to be given a value known to induce the beneficial medicinal effect whilst also being below the UL. Owing to the likely Gaussian distributions of both the beneficial and adverse effects, it can be predicted (as borne out by a variety of studies, e.g., McDonagh et al., 2000; Whelton et al., 2002; Warren et al., 2009), that more susceptible individuals in the population will be affected more severely than the average individual. Typically, more than 30% of children suffer dental fluorosis in areas where the public water supply is fluoridated at the target level of 1 mg F/L (Whelton et al., 2002). Mousny et al. (2008) found that genetic susceptibility to fluoride may even increase predisposition by those already suffering dental fluorosis to the more serious skeletal fluorosis.

A more conventional approach to the risk assessment of fluoride (as described by Coppens et al., 2006) would have resulted in an AI or MPL (determined by subtracting highest mean intakes/exposures from an UL) well beneath the current levels of 2–4 mg/d and probably beneath the level at which a population wide reduction in dental caries would be experienced. Such a reappraisal of fluoride risk would also act as barrier to water fluoridation programmes that have been in operation in the USA for some 60 years, and in Ireland for over 35.

5.6. Conclusion

The conceptual model (Fig. 1) which takes into account both risks and benefits is considered a more realistic model than the conventional two-tailed risk model (see Fig. 1, Verkerk and Hickey, this issue) which excludes any consideration of beneficial effects. New methods are required to better evaluate benefits and risks for specific molecular forms of nutrients. Quality of life adjusted life years (QALYs) or disability adjusted life years (DALYs) may in theory be used to evaluate risk/benefit (EFSA, 2007), but relevant data...
for such analyses are generally very sparse or absent. Renwick et al. (2004) proposed a model for risk/benefit analysis of micronutrients that adapts many of the principles used in risk assessment, to benefit assessment. The model has clear limitations and has yet to be validated, but has potential, in the absence of more sophisticated models, to help inform risk managers, particularly in situations where risks and benefits overlap.

In the longer term, genomic or epigenetic approaches may become invaluable in understanding humans' complex genetic, molecular, biochemical and metabolic interactions with nutrients in the face of greatly varying environments. Given the widespread distribution of susceptibility genes, it may become possible to better predict responses by individuals to different nutrients and exposures, as well improving ways in which epigenetic gene regulation can be modulated beneficially with nutrients (Choi and Friso, 2009).

It is premature to use conventional nutrient risk assessment and management methods to limit micronutrient food supplements nationally and regionally by way of legislation in the manner being contemplated by European authorities. Proportionate, case-by-case risk/benefit analysis by competent and experienced experts, coupled with graded risk management approaches (Verkerk and Hickey, this issue), is likely, in the short term, to provide a much more scientifically rational decision-making platform. In the words of Thomas Jefferson, the third President of the USA, “delay is preferable to error.”

Q3

Uncited references


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