Micronutrients play a critical role in overall nutrition and health. This is highlighted by the plethora of continuous research published in high profile scientific journals focused on the benefits of vitamins and minerals. However, evidence shows that many people worldwide fail to meet recommended intake levels. The impact of low micronutrient intake is a major public health concern, resulting in vulnerability to infection and disease.

Optimal intake is therefore essential to reduce these and other risks. But what is an optimal intake? Existing data indicates that there is a need to revisit approaches to defining appropriate nutritional requirements for a variety of vitamins, such as vitamin E. Recent studies demonstrate the benefits for specific groups when they take high dose vitamins. Studies also show that vitamins taken in pharmaceutical applications support human health.

This whitepaper explains the role and importance of vitamin dietary reference intakes (DRIs) and draws on the latest clinical data to show the benefits of vitamin intake beyond currently recognized health effects and the nutritional range. Highlighting key studies, it also describes the vital function of nutrition under clinical conditions and demonstrates the significance of drug-nutrient interactions on health. In addition, a summary of the use of vitamins in pharmaceutical applications is provided.
Vitamins for pharmaceutical applications

Introduction

Emerging data suggest that intake of micronutrients in higher doses holds promise for roles beyond currently recognized health effects for selected individuals and population groups. For example, research shows that vitamin E protects essential fatty acids from lipid peroxidation and that improved vitamin E status is protective for cognitive function.1,2 Understanding the role of vitamins beyond the nutritional range and their use in the pharmaceutical industry can lead to the creation of innovative, safe and high quality products that will serve the interests of consumer health.

Recommended intakes and requirements

Figure 1: Micronutrient intake panel in Germany, US, UK and the Netherlands

Modern lifestyles may lead to suboptimal vitamin intakes, even in affluent countries. A recent study reviewed vitamin intakes in Germany, the UK, The Netherlands and the USA and compared the data with respective national recommendations. Data on adults from the most recently published national dietary intake surveys for the first three countries and on adults from the US National Health and Nutrition Examination Survey from 2003 to 2008 were used as a basis for the analysis. The proportions of the populations with intakes below recommendations were categorized as < 5, 5–25, >25–50, >50–75 and >75% below recommendations. The data generated are presented in a 'traffic light display', illustrated in figure 1, using colors from green to red to indicate degrees of sufficiency.

The data was compared with the results from the European Nutrition and Health Report 2009. The study demonstrated that, although inter-country differences exist, intakes of several...
vitamins are below recommendations in a large part of the population in each country. The most critical vitamin appears to be vitamin D.

The variation between the countries is most probably due to differences in recommendations, levels of fortification and local dietary habits. The findings demonstrate that a gap exists between vitamin intakes and requirements for a significant proportion of the population, even though diverse foods are available.

DRIs can play an important role in addressing nutritional inadequacies. Stakeholders across the healthcare, nutrition and pharmaceutical industries can use DRIs and the latest clinical evidence on the benefits of vitamins on human health to understand appropriate nutritional requirements for populations worldwide. They can then pave the way in revisiting approaches to defining appropriate dietary requirements and educating consumers on their health needs.

Nutrition under clinical conditions

Nutrition inadequacies and malnutrition are even more prevalent under clinical conditions. There is a particularly high prevalence of malnutrition and low vitamin intake in vulnerable populations, such as ill and or elderly patients, as well as patients recovering in hospitals and other care facilities. Malnutrition for such patients can lead to a higher risk of infection and a longer time spent in hospital.

**Figure 2: Nutritional status of elderly persons in different settings**

<table>
<thead>
<tr>
<th>Setting</th>
<th>Malnourished</th>
<th>At Risk</th>
<th>Wellnourished</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospital</strong></td>
<td>14%</td>
<td>86%</td>
<td>39%</td>
</tr>
<tr>
<td><strong>Nursing Home</strong></td>
<td>14%</td>
<td>33%</td>
<td>53%</td>
</tr>
<tr>
<td><strong>Community</strong></td>
<td>6%</td>
<td>32%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>Rehabilitation</strong></td>
<td>9%</td>
<td>91%</td>
<td>50%</td>
</tr>
</tbody>
</table>

DRIs are used by healthcare providers and government agencies to establish the guidelines for how much of each nutrient an individual needs. The DRIs include four types of information:

- Estimated Average Requirements (EAR)
- Recommended Dietary Allowances (RDA)
- Adequate Intakes
- Tolerable Upper Intake Level

**Did you know?**

Those affected by, or at risk of, malnutrition in Europe:

- 5% of the entire population;
- 10% in those over 65 years;
- 15% in ages 75-80 living at home;
- 35-40% of all hospital admissions; and
- up to 60% in care homes.

3 Vitamins are below recommendations in a large part of the population in each country. The most critical vitamin appears to be vitamin D.

4 The variation between the countries is most probably due to differences in recommendations, levels of fortification and local dietary habits. The findings demonstrate that a gap exists between vitamin intakes and requirements for a significant proportion of the population, even though diverse foods are available.

5 DRIs can play an important role in addressing nutritional inadequacies. Stakeholders across the healthcare, nutrition and pharmaceutical industries can use DRIs and the latest clinical evidence on the benefits of vitamins on human health to understand appropriate nutritional requirements for populations worldwide. They can then pave the way in revisiting approaches to defining appropriate dietary requirements and educating consumers on their health needs.

6 Nutrition inadequacies and malnutrition are even more prevalent under clinical conditions. There is a particularly high prevalence of malnutrition and low vitamin intake in vulnerable populations, such as ill and or elderly patients, as well as patients recovering in hospitals and other care facilities. Malnutrition for such patients can lead to a higher risk of infection and a longer time spent in hospital.
The implications for malnourished patients does not always stop there. A recent study investigated undernutrition and risk of mortality in elderly patients within one year of hospital discharge and found that being undernourished at the time of hospital discharge is an independent risk factor for 1-year mortality in elderly patients. The severity of the nutritional depletion was assessed using body mass index (BMI), weight loss indices, and arm circumferences. Even after controlling for functional status and other indicators of illness severity, the relationship between each of these nutritional indices and the outcome remained significant — the more nutritionally depleted, the greater the risk. The study found indicators of chronic nutritional depletion (e.g. low BMI and long-term weight loss) to be the best predictors of post discharge mortality.

Malnutrition can lead to increased:
- need of care;
- risk for infections;
- risk for complications (morbidity);
- need for treatments in hospitals;
- length of stay; and
- risk of dying from diseases (mortality).

20-30 Million Europeans are affected by malnutrition and the cost for Europe is €120-170 billion/year.

Factors predisposing malnutrition and micronutrient deficiency can include poor nutrient intake, caused by issues like having difficulty eating, medication, depression and dementia, as well as suboptimal nutrient utilization, such as malabsorption or nutrient loss. In the elderly particularly, malnutrition is a prevalent issue which can form a cycle that is difficult to break if left untreated:

Reduced mobility
Reduced capacity to feed oneself
Loss of muscle mass
Apathy, depression, reduced attention
Reduced appetite

Figure 3 estimates of the survivorship function as generated by the Cox regression model for specific sets of covariate values. The upper curve is for body mass index (BMI) > 20 kg/m2 with all of the other independent variables in the model set equal to their population means. The lower curve was produced in the same manner except it is for BMI < 20 kg/m2.

Did you know?

Nutritional management can be introduced as part of a medically supervised diet to meet specific dietary needs as a result of a disease or condition. This management could help support optimal patient health before, during and after medical treatment and subsequently help reduce predisposition to higher risk of infection and mortality after hospital discharge.
Examples of additional benefits provided by vitamins in higher doses

Emerging scientific findings show the benefits of vitamin intake beyond currently recognized health effects and the nutritional range for risk groups like elderly or people with certain malfunctions. The following examples highlight how a higher intake of nutrients beyond nutritional requirements may provide additional benefits in defined groups; playing a part in supporting human health during illness. The diseases listed include diabetes, cancer, multiple sclerosis (MS), cardiovascular disease (CVD), non-alcoholic fatty liver disease and Alzheimer’s disease. These are prevalent issues worldwide, affecting a significant number of people.

**Vitamin B1 and diabetic patients**

There is evidence of thiamine (vitamin B1) deficiency in diabetics. Vitamin B1 is important for maintaining a healthy nervous system and improving the cardiovascular functioning of the body. Its benefits stretch further according to a new study. A high-dose therapy with vitamin B1 in a rat model (experimentally induced diabetes in rats) prevented development of diabetic nephropathy, otherwise known as kidney disease. In humans, these preliminary results led to a double-blind, placebo-controlled pilot study. In this study, high-dose vitamin B1 therapy was shown to reverse early stage diabetic nephropathy – 300 milligrams (mg) vitamin B1 per day decreases microalbuminuria. The use of vitamin B1 in this range is safe and further large-scale long-term clinical studies are still required.

**Vitamin B2 and CVD patients**

A recent study investigated 197 premature CVD patients, prescreened for the MTHFR 677C-->T polymorphism, from an original cohort of 404 to select those with the TT genotype (n = 60) and a similar number with heterozygous (CT; n = 85) or wild-type (CC; n = 75) genotypes. Of these, 181 completed an intervention in which participants were randomized within each genotype group to receive 1.6 mg per day vitamin B2 (riboflavin) or placebo for 16 weeks. Among patients taking one or more antihypertensive drugs at recruitment (82%), the results show that target blood pressure (<140/90 mmHg) had been achieved in only 37% patients with the TT genotype compared with 59% with the CT and 64% with the CC genotype (P < 0.001).

Vitamin B2 intervention reduced mean blood pressure specifically in those with the TT genotype (from 144/87 to 131/80 mmHg; P < 0.05 systolic; P < 0.05 diastolic), with no response observed in the other genotype groups. The systolic blood pressure response to vitamin B2 intervention in patients with MTHFR 677 TT genotype therefore demonstrates that genetically susceptible individuals may benefit the most from vitamin B2 supplementation. The study demonstrates that it would take about 10 kilos of weight loss to achieve the blood pressure lowering that was reported by vitamin B2.10,11 The findings of the study may have important implications for the prevention and treatment of hypertension, especially as the TT genotype has a high prevalence in many countries.12

**Did you know?**

Elevated blood pressure is a leading risk for death worldwide. Optimizing vitamin B2 status offers a promising low-cost targeted strategy for managing elevated blood pressure in genetically at-risk groups.
### Biotin (Vitamin B7) and MS patients

A recent Phase III clinical trial on vitamin B7 and patients suffering from progressive multiple sclerosis (MS) produced positive results. The study found evidence of the efficacy and safety of a highly-concentrated pharmaceutical-grade vitamin B7 administered at a dose of 300 mg per day in the treatment of primary and secondary progressive MS, a major area of unmet medical need.

The vitamin B7 studied will require a chronic administration of a very high dose to treat patients with progressive MS, corresponding to 10,000 times the recommended daily intake, which requires a pharmaceutical grade extra-pure source of vitamin B7.13

### Vitamin C and cancer

Despite the FDA not having approved the use of IV high-dose vitamin C as a treatment for cancer, studies show that administration of high-dose IV vitamin C improved quality of life for cancer patients.14, 15 Improvements in physical, mental and emotional functions, symptoms of fatigue, nausea, vomiting, pain and appetite loss were documented.16 In addition, a meta-analysis on vitamin C and breast cancer indicates that post-diagnosis use of vitamin C supplementation may be associated with a reduced risk of mortality.17

New research demonstrates that cancer cells are much less efficient in removing hydrogen peroxide than normal cells, and more disposed to damage and death from a high amount of hydrogen peroxide. This explains why the high levels of vitamin C do not affect normal tissue, but can be damaging to tumor tissue.18

### Vitamin C and the common cold

The common cold is a viral infectious disease of the upper respiratory tract. Colds can lead to the upper respiratory system becoming less resistant to secondary bacterial infection, resulting in issues such as middle ear infection, pneumonia, bronchitis, sinus infection or strep throat.19

The body’s immune system can fight the infection after producing antibodies, but there are currently no medicines that will cure the common cold. However, there may be a way to reduce the risk of contracting the common cold. A recent Cochrane meta-analysis shows that vitamin C reduces the incidence, duration and severity of the common cold when ≥ 200 mg/d is taken daily.20

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**Figure 6: Vitamin C may reduce the incidence, duration and severity of a common cold**

**Incidence of colds**

- **Total colds**
  - > 200mg Vitamin C
  - General population: ~3% less
  - Severe stress: ~50% less

**Duration of common cold**

- Without Vitamin C supplement
  - 1–2g Vitamin C
  - Children > 200mg: ~1 day less = 8%
  - Adults > 200mg: ~1 day less = 14%
  - Children 1–2g Vitamin C: ~1 day less = 18%

**Severity of the colds**

- 0.1% less days indoors of off work or school (7 trials) (p=0.00035)
- 0.14% less on symptom severity score (9 trials) (p=0.0018)
- Total: 0.12% (p=0.00001)
Vitamins for pharmaceutical applications

✓ Vitamin E and a range of health issues

CVD
New research indicates that genotype matters also when it comes to vitamin E; sub-populations with specific genetic makeup may profit from this vitamin. A recent study into vitamin E and CVD showed that vitamin E supplementation at a dose of 400 mg reduces and normalizes the risk for cardiovascular events in diabetics with haptoglobin genotype 2-2 (Hp 2-2). The Hp gene exists in two variants, the Hp1 and the Hp2 variant. In Western societies, 36% have Hp 2-2. Diabetic individuals with Hp 2-2 have a marked increased oxidative stress. Increased risk for cardiovascular events has been linked to Hp 2-2 genotype in diabetics.

Non-alcoholic fatty liver disease
Meanwhile, vitamin E has also been shown to reduce the risk of non-alcoholic fatty liver disease, which is a prevalent and increasing issue worldwide, due to rising obesity levels. Data shows that supplementation with vitamin E at a dose of 400 mg was superior to a placebo for the treatment of nonalcoholic steatohepatitis in adults without diabetes.22

Cognitive health
Vitamin E (at a dose of 2000 IU) has also been proven to delay pathologies in Alzheimer’s disease – an age-dependent and progressive neurological disease and the fourth-leading cause of death in industrialized societies.

Figure 8: Alzheimer’s disease and vitamin E study: survival time without pathological "event".23

Burns
In a study to test whether burn injury reduces body stores of vitamin E, α-tocopherol concentrations were measured in adipose tissue samples. After receiving a burn injury, pediatric patients were assessed. Surgically obtained samples were taken at various intervals and stored at −80°C in a biorepository. α- and γ-Tocopherols, cholesterol, and triglycerides were measured in the same tissue.

The results found that the burn injury experienced by the pediatric patients changed their metabolism so that vitamin E status decreased during the month after injury. Further studies are needed to evaluate the mechanism and consequences of the observed vitamin E depletion. In addition, research on vitamin E supplementation in a higher dose in burn patients should be undertaken to determine whether it could help restore the depleted stocks of vitamin E in the body.24

Figure 7: Results from ICARE study (Milman 2008)21
How should vitamins be used in pharmaceutical applications?

So far, it is clear from emerging scientific research that vitamins can go beyond currently recognized health effects and the nutritional range, supporting human health in higher doses. Such clinical data and a clear understanding of drug-nutrient interactions must be used to define how vitamins should be used within the pharmaceutical industry. Grading of Recommendations Assessment, Development and Evaluation (GRADE) is a method for assessing the quality of the evidence found for specific vitamins for use in pharmaceutical applications. This can be used as a reference, for example, by pharmaceutical and healthcare professionals. In addition, certificates of suitability (CEPs) and US Drug Master Files (DMFs) for essential micronutrients are a necessary measure to ensure that new products are developed to be safe and of high quality for high dose applications and specific claims. Pharma-grade vitamins, carotenoids and lipids can be used as Active Pharmaceutical Ingredients (APIs) to support the development of customized solutions to suit specific applications.

The pyramid (Figure 9) shows the distinction between general food and nutrition, specialist nutrition or dietary supplementation and pharmaceuticals or prescribed medical treatments.

Did you know?

- Lipid-lowering therapy with statins can significantly reduce the incidence of cardiovascular disease and the risk of coronary events. However, aggressive lowering of lipids by statins comes with the risk of decreasing EPA and DHA levels simultaneously. EPA and DHA can be considered as an alternative way to help reduce plasma triglyceride levels and to beneficially influence the levels of other blood lipids as well. Clinical trials have shown that EPA and DHA as supplementation is also effective when added in combination with other lipid-lowering drugs like statins.

- Nonsteroidal anti-inflammatory drugs (NSAIDs), such as Aspirin, Ibuprofen and Naproxen, can cause peptic ulcer, diminish renal function and impair Vitamin B6 metabolism. However, they may have additive or synergistic effects with certain micro- or macronutrients, for example, to reduce pain. If an adequate dose of EPA and DHA (which have anti-inflammatory properties) is provided, NSAIDs might be taken at a lower dose to have a clinical benefit and reduce potential side effects of the drug.
Food-drug interactions are defined as alterations of pharmacokinetics or pharmacodynamics of a drug or nutritional element or a compromise in nutritional status as a result of the addition of a drug. Pharmacokinetic is the word used to describe when the absorption, distribution, metabolism, or elimination (ADME) is altered. Meanwhile, pharmacodynamic refers to a situation where the pharmacological effects of two products are additive or oppositional. Examples of where drug-nutrient interactions occur include statins, contraceptives, proton pump inhibitors, and cases where vitamins have a synergistic effect with drugs. Drug-nutrient interactions can lead to a raising or lowering of bioavailability of a nutrient induced by drug intake. For example, according to a study, drug-nutrient interactions can result in reduced absorption of certain oral antibiotics. This can lead to suboptimal antibiotic concentrations at the site of infection, increasing the risk of treatment failure.

Nutrients can lead to an induction or inhibition of enzymes in the gut, which may cause a change in oral bioavailability of drugs or vice versa. Grapefruit juice acts as a selective intestinal CYP3A4 inhibitor, and can be used as an example. The exposure of some drugs can be increased by more than fivefold when taken with grapefruit juice and increase the risk of adverse effects. The use of certain drugs may affect gastrointestinal (GI) tract function and result in a loss of bodily electrolytes and fluid. Therefore, limiting drug prescriptions to essential medications for as short a period as possible and periodic re-evaluations of the treatment chosen are needed to minimize adverse drug-nutrient interactions.28

The same study indicates that some people are more at risk of nutritional compromise. For example, elderly patients are particularly at risk because more than 30% of all the prescription drugs are taken by this population. Failure to identify and properly manage drug-nutrient interactions can lead to serious consequences. Other patients at increased risk include those with cancer, AIDS and organ transplant recipients.

Successful organ transplantation has become the norm, now that improved immunosuppressive agents have been introduced. The emphasis of immunosuppressive therapy has moved from preventing rejection to balancing acceptable rates of rejection with moderation in adverse effects of the immunosuppressive agents. According to scientific research, among the many possible adverse effects of immunosuppressive therapy is the potential for these agents to affect the nutrition status of the transplant recipient. As many patients undergoing transplantation are catabolic and vulnerable to malnutrition, it is particularly important for carers of these patients to be familiar with the nutrition implications of immunosuppressive drugs.29

Comprehensive clinical data on the effects of combining pharmaceuticals with supplements can help companies understand how to develop safe, individualized treatment strategies for patients.30

Key take-away messages
- Stakeholders across the healthcare, nutrition and pharmaceutical industries should use DRIs and the latest clinical evidence on the benefits of vitamins, EPA and DHA on human health to understand appropriate nutritional requirements for populations worldwide
- Emerging research suggests that micronutrient intake in higher doses can play a role beyond essentiality for selected individuals and population groups
- Clinical data on the effects of combining pharmaceuticals with supplements can support development of safe individualized treatment strategies for patients
- More investigation into the effects of micronutrient supplementation on health when used in combination with pharmaceuticals is needed

Conclusion

Vitamins are essential micronutrients that the body needs. The health of populations worldwide can benefit from optimal intake. The review of recent clinical data heralds an exciting new phase for the role of vitamins in pharmaceutical applications. The knowledge that vitamins can play an important role in patient health beyond their traditional part in essentiality, can open up new opportunities in the pharmaceutical and healthcare industries. More investigation into the effects of micronutrient supplementation on health when used in combination with pharmaceuticals is needed, as well as a clear understanding on drug-nutrient interactions, to ensure optimal and safe patient treatment.
Vitamins for pharmaceutical applications

DSM is currently the only company in the world to hold both US DMFs and CEP certificates for all 13 essential vitamins. DSM offers its pharmaceutical customers worldwide unparalleled sustainability of supply and speed to market, accelerating the registration process to get products to market faster. With extensive experience in pharma-grade vitamins, carotenoids and lipids Active Pharmaceutical Ingredients (APIs), DSM provides customers with entirely customized support throughout every stage of a project. DSM’s full regulatory, scientific and quality expertise and GMP-qualified production sites ensure that projects are both safe and compliant. In addition to its strong IP portfolio, including carotenoids and DHA and EPA, DSM’s 400-strong R&D team provide expertise in clinical trials. DSM also has a global network of regulatory specialists, equipped to cater support in response to customers’ local regulations.

For DSM, quality is a way of life. Quality for Life™ symbolizes quality, reliability and traceability. This means that our customers are getting the best ingredients, knowing the source on which they depend. Quality for Life™ means sustainability. It is our commitment to our environment, consumers, our business partners, our people and the regulatory framework that governs our operations.

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