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alliance for natural health INTERNATIONAL

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Response to **Communication from the Commission – TRIS/(202) 02514**
Regarding: Notification Number: 2020/9011/N (Norway)

BACKGROUND

As the Alliance for Natural Health International, an interested party representing the interests of nutritional practitioners, SME specialist food supplement manufacturers, retailers and consumers based in Europe, including in Norway and other Scandinavian countries, we duly make this submission in relation to the Draft Regulation amending the Regulation on Food Supplements in Norway.

As a non-governmental and non-commercial organisation, the Alliance for Natural Health International (ANH-Intl) has been at the forefront of risk and risk-benefit assessment of micronutrients (see additional information, p.11). In 2010, ANH-Intl published two seminal papers in the journal *Toxicology* in this area. The first[1] was a comprehensive critique of prevailing risk assessment methods being used by European authorities, which highlighted scientific problems with existing methodologies based on an exclusively risk-based toxicological approach. It also highlighted the disproportionate impact of applying a single value to all micronutrient forms based on data on the most sensitive populations exposed to the most toxic form. The second[2] emphasised the common, often unrecognised and paradoxical, overlap in micronutrient risks and benefits.

This second paper made a clear case that if risk assessment is used in isolation of any consideration of benefits, based on the most sensitive populations and the most toxic form of a given micronutrient, significant sectors of the population, in some cases a majority, could be prevented from consuming optimal intakes of vitamins and minerals.

Regulation based on risk-only assessments of the most toxic form of each nutrient would then be disproportionate, an infringement of citizen free choice as well as being a contravention of the Treaty on the Functioning of the European Union (TFEU) through its impact on trade within the single market.

In order to facilitate the development of a more proportionate, independent, science-based approach, the ANH-Intl commissioned Toegepast Natuurwetenschappelijk Onderzoek (TNO) research institute in the Netherlands to develop a risk-benefit approach for vitamins and minerals, the result of which was published in 2017 (Krul et al, 2017).[3]

The Court of Justice of the European Union (CJEU) has established that an EU Member State (or EEA country) can only impose restrictions on the dosages of food supplements, that may interfere with the functioning of the single market, if there is a "*real risk for public health* [that] *appears to be sufficiently established on the basis of the latest scientific data available at the date of the adoption of that measure*" (see *Noria Distribution SARL v France*, C-672/15; citing also judgments *Commission v Denmark*,

[1] Verkerk RH, Hickey S. A critique of prevailing approaches to nutrient risk analysis pertaining to food supplements with specific reference to the European Union. *Toxicology.* 2010; 278(1): 17-26.

[2] Verkerk RH. The paradox of overlapping micronutrient risks and benefits obligates risk/benefit analysis. *Toxicology*. 2010; 278(1): 27-38.

[3] Krul L, Kremer BHA, Luijckx NBL, Leeman WR. Quantifiable risk-benefit assessment of micronutrients: From theory to practice. *Crit Rev Food Sci Nutr.* 2017; 57(17): 3729-3746.

C-192/01; *Commission v France*, C-24/00; *Commission v Netherlands*, C-41/02; and *Commission v France*, C-333/08).

This EU case-law requires EU/EEA countries to use the latest scientific data and methods of assessing risks (and sometimes also benefits) when considering imposing statutory restrictions on vitamin and mineral dosages. Such approaches by any one country within the EU/EEA should recognise the principle of mutual recognition (Regulation (EU) 2019/515) and avoid unnecessary restrictions on individual vitamin and mineral forms in food supplements when such forms sell freely and without any evidence of any public health risk in one or more other Member States.

The present opinion is provided in the context of this scientific and legal background and is divided into two main parts. The first (pages 2-5) offers general comments, while the second (pages 5-10) concerns itself with the proposed maximum levels values for specific nutrients proposed by the Department of Public Health in Norway.

GENERAL COMMENTS

1. **Risk assessment (or risk/benefit assessment) must take into account differences between nutrient forms.** The current proposal by for a Draft Regulation in Norway proposes single values for the vitamins and minerals in question (vitamin E, vitamin B6, iron and zinc). However, it is well established that different forms of the same micronutrient, have different risk profiles, as well as different benefit and benefit/risk profiles). Well-known examples (bolded examples are especially relevant to the present submission) of differences in risk profile (greater → less) between nutrients include:

    - Vitamin A: retinol → beta-carotene
    - Vitamin B3: nicotinic acid → niacinamide → inositol hexanicotinate
    - **Vitamin B6: pyridoxine hydrochloride → pyridoxal-5'-phosphate**
    - Vitamin C: l-ascorbic acid → potassium/calcium/magnesium ascorbate
    - Vitamin D: ergocalciferol (D2) → cholecalciferol (D3)
    - **Vitamin E: alpha-tocopherol → gamma-tocopherol (the latter a major isomer in widely used 'mixed tocopherols' raw materials)**
    - Folate: pteroylmonoglutamic acid → reduced folate (e.g., calcium-l-methylfolate, (*6S*)-5-methyltetrahydrofolic acid, glucosamine salt)
    - **Iron: iron sulphate → ferrous citrate/ferrous fumarate → ferrous bisglycinate**
    - Magnesium oxide → magnesium citrate, biglycinate, etc.
    - Chromium: chromium chloride → chromium-enriched yeast
    - Selenium: sodium selenite, selenious acid → selenomethionine, selenium-enriched yeast[1]

    In order to ensure a high level of consumer protection, risk assessments that give rise to single values for micronutrients that are available in more than one form (Directive 2002/46/EC, as amended), must inevitably be based on the most intrinsically toxic form of the micronutrient. Accordingly, such risk assessments, if mandated by law, impose a disproportionate and unnecessary restriction on consumers wishing to consume higher doses of the less toxic nutrient forms.[1,2] Regulation that restricts safer forms of the same micronutrient is therefore legally disproportionate and impacts both the function of the single market while also unnecessarily limiting consumer freedom of choice.

2. **Risk-benefit assessment is applicable to micronutrients because, as nutrients, they offer benefits but they may also pose potential risks to health when consumed to excess.** There is no suggestion that the Norwegian Food Safety Authority (NFSA, Mattilsynet) or the Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) have utilised a risk/benefit approach despite a clearly documented (and peer review published) view that such approaches are the most scientifically advanced and relevant in relation to micronutrients.[3,4]

   In its study on 'Delivering on EU Food Safety and Nutrition in 2050 — Future challenges and policy preparedness', the Commission recommends the "*streamlining of risk assessment approaches and inclusion of risk-benefit assessment*" as well as using risk-benefit assessment and management (pages 10-11, 60-61, 73-75).[5] The risk-benefit approach developed by the TNO specifically oriented to micronutrients[3] represents the most recent and thorough development of such an approach. This approach takes into account differences in risk-benefit profile between nutrient forms, and the authors of the study provide a worked example of the approach for two forms of iron, namely sulphate and bisglycinate. The TNO approach demonstrates an over 5-fold difference in the decision incidence for risk and benefit, for these two forms with Krul *et al* (2017)[3] proposing a decision benefit-risk incidence of 13.1 mg for iron sulphate and 69.2 mg/d for iron bisglycinate.[3]

   This kind of between-form variation in decision incidences for risk and benefit is likely to apply also to different isomers of vitamin E (e.g. dl-alpha-tocopherol versus gamma-tocopherol-rich 'mixed tocopherol' formulations), the vitamin B6 forms pyridoxine and pyridoxal, and other micronutrients.

3. **Target groups must be specified and levels adjusted accordingly.** Given considerable differences in risk-benefit profile, tolerance, susceptibility and need between different population groups, it is imperative that the target groups (e.g. age groups, gender, pregnant, lactating, etc.) are clearly specified. It appears that the Norwegian authority is considering applying different levels for children and adolescents, as compared with adults, but it also needs to consider other groups such as pregnant and lactating women. It does not follow that such groups require less of a micronutrient, as evidenced by scientific consensus for folate.

4. **Advisory statements are appropriate risk management measures.** While it is of paramount importance that the population as a whole is protected from substances that might otherwise cause harm, statutory restriction by way of limiting daily doses on product labels is only one way of achieving this. The major disadvantage of this approach stems from its origins from traditional risk assessment for micronutrients, as developed originally by the Institute of Medicine (IOM) in the USA, being based on a toxicological model.[6] This approach ignores benefits from

[4] Renwick AG, Flynn A, Fletcher RJ, Müller DJ, Tuijtelaars S, Verhagen H. Risk-benefit analysis of micronutrients. *Food Chem Toxicol.* 2004; 42(12): 1903-22.

[5] European Commission, Joint Research Centre. *Delivering on EU Food Safety and Nutrition in 2050 - Future challenges and policy preparedness*. 2016. 96 pp. https://ec.europa.eu/jrc/en/publication/eur-scientific-and-technical-research-reports/delivering-eu-food-safety-and-nutrition-2050-future-challenges-and-policy-preparedness.

[6] See explanation given in Introduction section of Reference 1.

consumption by population groups other than the most sensitive ones in amounts that are in excess of those determined to be safe even to the most sensitive population groups. A more proportionate approach, as used with many other food groups that have clear risks and benefits, such as allergens (e.g. dairy, gluten, etc), is to recommend or mandate the use of advisory statements (warnings) on labels that protect the most sensitive group(s) from over-exposure. Such an approach (voluntary, not mandatory), has been used by the UK Department of Health (DoH) for over a decade and appears to have been helpful in avoiding unnecessary adverse events linked to vitamin and mineral over-exposure (see Appendix 1).[7] Extensive information is also provided by Health Canada (Appendix 2).

5. **Impacts of excessive restriction on micronutrient-deficient populations.** There is an absence of adequate or reliable risk (and benefit) data that define the dose/response relationship of the micronutrients in question, and key forms of each. If a precautionary approach is used that only considers risk of excess, and not risk of inadequacy, certain populations may suffer disproportionately. There is, for example, evidence of prevalent micronutrient deficiencies in Western European countries.[8,9] Zinc deficiency among certain populations is especially commonplace.[10] Given the current pandemic, such deficiencies which may be associated with more severe Covid-19 disease[11] should be addressed as a priority. With regard to this specific example, it would be against the public interest and the need to achieve a high level of citizen protection to place restrictions on intakes that might interfere with the public's efforts to build immunocompetence by supplementing with zinc.

6. **Nutrient intake and status are not necessarily proportional.** It is often assumed by regulators that the greater the intake of a given micronutrient, the higher the circulating levels of that same nutrient. This is not the case, particularly where the form consumed in a supplement is not the bioactive form (e.g. high doses of pyridoxine hydrochloride may induce vitamin B6 [pyridoxal] deficiency).[12] The dose-response distribution for many nutrients is also often skewed, meaning that it

[7] Food supplements. Label advisory statements and suggested reformulations. Department of Health, UK, 2011. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/204323/Advisory_Statements_DH_FINAL.pdf. Provided in full in Appendix 2.

[8] Ames BN. Low micronutrient intake may accelerate the degenerative diseases of aging through allocation of scarce micronutrients by triage. *Proc Natl Acad Sci U S A.* 2006 Nov 21; 103(47): 17589–17594.

[9] Troesch, B., Hoeft, B., McBurney, M., Eggersdorfer, M., & Weber, P. Dietary surveys indicate vitamin intakes below recommendations are common in representative Western countries. *Brit J Nutr*. 2012; 108(4): 692-698.

[10] Jung A, Spira D, Steinhagen-Thiessen E, Demuth I, Norman K. Zinc Deficiency Is associated With Depressive Symptoms-Results From the Berlin Aging Study II. *J Gerontol A Biol Sci Med Sci.* 2017; 72(8): 1149-1154.

[11] Singh S. Covariation of Zinc Deficiency with COVID- 19 Infections and Mortality in European Countries: Is Zinc Deficiency a Risk Factor for COVID-19? *J Sci Res* 2020; 64(2): 153-157.

[12] Vrolijk MF, Opperhuizen A, Jansen EHJM, Hageman GJ, Bast A, Haenen GRMM. The vitamin B6 paradox: Supplementation with high concentrations of pyridoxine leads to decreased vitamin B6 function. *Toxicol In Vitro.* 2017; 44: 206-212.

is difficult to establish central values, while there may be many more people than expected in a normal distribution of values facing risk of inadequacy or excess than considered with the widely used standard deviation cut-off method.

7. **Nutrient and micronutrient interactions.** Micronutrients interact not only with each other, but also with food matrices causing variations in absorption and bioavailability.[13] Most studies considered by health authorities in the establishment of tolerable upper levels or maximum supplementation levels involve isolated nutrient intakes. For example, the negative effects of iron supplementation on indices of zinc and copper status and of zinc supplementation on iron and copper status have been reported.[14] It is inappropriate to limit supplemental intakes via statutory measures when the scientific studies on which the measures are based do not apply to the real world conditions under which supplementation occurs.

SPECIFIC COMMENTS

The focus of these comments is on micronutrients for which maximum levels have been proposed by the Norwegian authority, namely vitamin E, vitamin B6, iron and zinc.

Vitamin E

There is extensive and long-standing evidence from epidemiological and retrospective studies that higher intakes of vitamin E in the diet are associated with reduced all-cause mortality, especially that caused by heart disease.[15,16,17,18]

Supplementation studies have typically been unable to demonstrate benefit as evidenced by meta-analysis of previous studies.[19]

While methodological concerns with meta-analyses on vitamin studies, including in

[13] Mocchegiani E, Costarelli L, Giacconi R, et al. Micronutrient–gene interactions related to inflammatory/immune response and antioxidant activity in ageing and inflammation. A systematic review, *Mech Ageing Dev* 2014; 136–137: 29-49.

[14] Sandström, B. Micronutrient interactions: Effects on absorption and bioavailability. *Brit J Nutr* 2001; 85(S2): S181-S185.

[15] Kushi LH, Folsom AR, Prineas RJ, et al. Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. *N Engl J Med*. 1996; 334(18): 1156-62.

[16] Yochum LA, Folsom AR, Kushi LH. Intake of antioxidant vitamins and risk of death from stroke in postmenopausal women. *Am J Clin Nutr.* 2000; 72(2): 476-83.

[17] Stampfer MJ, Hennekens CH, Manson JE, et al. Vitamin E consumption and the risk of coronary disease in women. *N Engl J Med. 1*993; 328(20): 1444-9.

[18] Keaney JF, Jr., Simon DI, Freedman JE. Vitamin E and vascular homeostasis: implications for atherosclerosis. *FASEB J.* 1999; 13(9): 965-75.

[19] Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med.* 2005; 142(1): 37-46.

relation to vitamin E,[20] limit the applicability of such analyses and therefore their use in establishing maximum levels, there are known variations in bioavailability and interactions between different vitamin E isomers and isomer profiles that need to be taken into account.

For example, bioavailability of the natural, single stereoisomeric form (*RRR*, formerly *d*) of alpha-tocopherol has been found to be twice that of the synthetic form (all-*rac*, formerly *dl*) of alpha-tocopherol.[21]

Even more relevant is that high doses of the alpha-tocopherol isomer (whether natural or synthetic) suppress the circulating levels of the gamma-tocopherol isomer, the latter being more prevalent in food sources, certain supplements, as well as being more important as a scavenger of reactive nitrogen species and detoxifying nitrogen dioxide.[22]

It is thus scientifically irrational as well as legally disproportionate to apply a maximum level determined on the basis of clinical studies of alpha-tocopherol to gamma-tocopherol.

Proposal for vitamin E – vitamin E includes 8 characterised isomers, alpha-, beta-, gamma- and delta-tocopherol and alpha-, beta-, gamma- and delta-tocotrienol. EU Directive 2002/46/EC ("Food Supplements Directive", FSD) presently authorises 7 different isomers or isomer mixtures in food supplements, five being tocopherol/tocopheryl isomers, one being a mixed tocopherol mixture (50-70% gamma-tocopherol), the other being a tocotrienol-tocopherol 8-isomer mixture (with minimum values for each isomer). Presently the VKM proposal refers to intakes (mg/day) of vitamin E with unspecified isomers. Clarification is needed if this applies only to alpha-tocopherol equivalents (α-TE), which would then require the use of the same units stipulated in the FSD on product labels, namely mg α-TE. There is no scientific justification to mandate levels of vitamin E isomers less than 300 mg/d if they include isomers other than *RRR* or all-*rac* isomers of alpha-tocopherol which competes with gamma-tocopherol intake in the diet and supplements.

Vitamin B6

Vitamin B6 is the generic name for 3 distinct compounds (vitamers) pyridoxine, an alcohol; pyridoxal, an aldehyde; and pyridoxamine, which contains an amino group. Additionally, each of these vitamers have 5'-phosphate esters, with pyridoxal 5'-phosphate (P5P) and pyridoxamine 5'-phosphate (PMP) being the bioactive coenzyme forms of vitamin B6.[23] Pyridoxine (most often as the hydrochloride form) has been most widely studied as a supplement, largely because it is cheaper and more stable than the bioactive P5P form. In

[20] Berry D, Wathen JK, Newell M. Bayesian model averaging in meta-analysis: vitamin E supplementation and mortality. *Clinical Trials.* 2009;6(1):28-41

[21] Burton GW, Traber MG, Acuff RV, et al. Human plasma and tissue alpha-tocopherol concentrations in response to supplementation with deuterated natural and synthetic vitamin E. *Am J Clin Nutr.* 1998; 67(4): 669–684.

[22] Gutierrez AD, de Serna DG, Robinson I, Schade DS. The response of gamma vitamin E to varying dosages of alpha vitamin E plus vitamin C. *Metabolism.* 2009; 58(4): 469-78.

[23] McCormick D. Vitamin B6. In: Bowman B, Russell R, eds. *Present Knowledge in Nutrition*. 9th ed. Washington, DC: International Life Sciences Institute; 2006.

the USA, the FDA ruled that pyridoxamine should be regulated as a drug given it was a component of a drug developed by Biostratum Inc. for prevention of the progression of diabetic nephropathy.[24] It has yet to be added to Annex II of the Directive 2002/46/EC in the EU, however, given recognition of its clear nutritional status as a form of vitamin B6, it is permitted as an ingredient in natural health products in Canada, under Health Canada's Natural Health Products Regulations.

The former US Institute of Medicine (IoM) (now the HMD of NASEM) set an Upper Level of 100 mg/d, the UK Expert Group on Vitamins and Minerals (EVM) established a level of 10 mg/d using the flawed trial of Dalton & Dalton (1987)[25] on post-menopausal women which showed peripheral neuropathy, incorrectly attributed to B6 (this same effect results from B6 deficiency). Renwick (2006)[26] provides a forceful criticism of Dalton & Dalton (1987). Most significantly, Vrolijk *et al* (2017)[7] demonstrated that pyridoxine alone, not pyridoxal or pyridoxamine, had the potential to induce neuropathy at high doses, this being related to the competitive inhibition of the bioactive pyridoxal coenzyme form in neuronal receptor sites. This mechanism explains why high dose pyridoxine may give rise to the same neuropathic effects as vitamin B6 deficiency.

EFSA (2006),[27] while indicating its awareness of the flawed nature of the Dalton & Dalton (1987) study, still used the study in its own risk assessment. However, by using a smaller uncertainty factor than the UK EVM, determined a TUL of 25 mg/d. The US IOM (now HMD/NASEM), the ASEAN Alliance of Health Supplement Associations (AAHSA) (2012), [28]the Council for Responsible Nutrition (CRN) and the International Alliance of Dietary Food Supplements Associations (IADSA) (2014) all determined Upper Levels of 100 mg/d for vitamin B6 by avoiding consideration of the flawed Dalton & Dalton (1987) study. However, neither IOM, AAHSA nor CRN/IADSA made a distinction between the pyridoxine and pyridoxal forms (e.g. P5P), probably due to insufficient comparable data at that time on the two vitamers (e.g. Vrolijk et al [2017])[7].

Based on the requirement of Member States to undertake risk assessment using the latest available scientific data (see judgment *Noria Distribution SARL v France*, C-672/15), there is no legal basis to establish by statute an unnecessarily low maximum level for vitamin B6 (any form) using old, flawed data, notably Dalton & Dalton (1987). Equally, it is legally disproportionate to use scientific data for pyridoxine supplementation, and apply this to supplementation with the bioactive, coenzyme form, P5P.

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[24] FDA Response to Biostratum, Inc. (Kathleen M Sanzo, Esq) - Petition Partial Approved and Denial (2009): https://www.regulations.gov/document?D=FDA-2005-P-0259-0004

[25] Dalton K, Dalton MJ. Characteristics of pyridoxine overdose neuropathy syndrome. *Acta Neurol Scand.* 1987 Jul; 76(1): 8-11.

[26] Renwick AG. Toxicology of micronutrients: adverse effects and uncertainty. *J Nutr.* 2006 Feb; 136(2): 493S-501S.

[27] EFSA. *Tolerable Upper Levels for Vitamins and Minerals*. European Food Safety Authority, Parma. 2006.

[28] ASEAN Alliance for Health Supplement Associations (AAHSA) Joint Working Group. ASEAN Maximum Levels of Vitamins & Minerals in Health Supplements. 2012. https://asean.org/storage/2017/09/ASEAN-General-Principles-for-Max-Levels-Vitamins-Minerals-HS-V4.0-wi....pdf

Proposal for vitamin B6 – a 100 mg/d limit would be an appropriate and scientifically rational limit for pyridoxine (hydrochloride and 5'-phosphate forms) as per IOM (1998), AAHSA/ASEAN (2012) and CRN/IADSA (2014). Equally, in the order of twice this limit (i.e. 200 mg/d) should apply to the pyridoxal-5'-phosphate form, P5P. For additional precaution, any product containing dosages >25mg B6 should have advisory text that advised that the product is intended "*for short term use only*". There are no pyridoxamine forms currently permitted in the EU (Annex II, Directive 2002/46/EC, as amended).

Zinc

The role of zinc as a critical element in the functioning of the immune system of mammals including humans has been known since the mid-1970s.[29,30] However, more recently, research has demonstrated that zinc's key mechanism of action in the immune system is by stimulating serum thymulin (a thymus specific hormone involved in T cell function)[31] and modulation of T helper cell functions (correction of Th1/Th2 imbalance in zinc deficiency).[32]

Additionally, in zinc deficient subjects, lytic activity of natural killer cells and the percentage of precursors of cytolytic T cells is decreased.[33]

It is well known that even mild zinc deficiency may result in compromised immune function.[34,35] Furthermore, although the precise mechanism of zinc's action is not fully understood, there is good evidence that zinc, *in vitro*, can potentiate 10-fold the anti-viral action of the human cytokine interferon-alpha.[36]

The adverse effects of a zinc deficiency include, but are not limited to, an increased severity

[29] Moynahan EJ. Letter: Zinc deficiency and cellular immune deficiency in acrodermatitis enteropathica in man and zinc deficiency with thymic hypoplasia in fresian calves: a possible genetic link. *Lancet*, 1975; 2(7937): 710.

[30] Moynahan EJ. Acrodermatitis enteropathica in two siblings treated with zinc sulphate supplements alone. *Proceedings of the Royal Society of Medicine*, 1975; 68(5): 276.

[31] Prasad AS, Meftah S, Abdallah J, Kaplan J, Brewer GJ, Bach JF, Dardenne M. Serum thymulin in human zinc deficiency. *Journal of Clinical Investigation*, 1988; 82(4): 1202-10.

[32] Shankar AH, Prasad AS. Zinc and immune function: the biological basis of altered resistance to infection. *American Journal of Clinical Nutrition,* 1998; 68(suppl): 447S–63S.

[33] Beck FW, Prasad AS, Kaplan J, Fitzgerald JT, Brewer GJ. Changes in cytokine production and T cell subpopulations in experimentally induced zinc-deficient humans. *American Journal of Physiology,* 1997; 272(6 Pt 1): E1002-7.

[34] Ibs KH, Rink L. Zinc-altered immune function. *Journal of Nutrition*, 2003; 133 (5 Suppl 1): 1452S-6S.

[35] Sprietsma JE. Modern diets and diseases: NO-zinc balance. Under Th1, zinc and nitrogen monoxide (NO) collectively protect against viruses, AIDS, autoimmunity, diabetes, allergies, asthma, infectious diseases, atherosclerosis and cancer. *Medical Hypotheses*, 1999; 53(1): 6-16. Review.

[36] Berg K, Bolt G, Andersen H, Owen TC. Zinc potentiates the antiviral action of human IFN-alpha tenfold. *Journal of Interferon Cytokine Research*, 2001; 21(7): 471-4.

and duration of viral and other infections,[37] poor immune system modulation,[38] as well as an increased propensity of lung epithelia and airways to become inflamed.[39] Correction of a zinc deficiency rapidly restores normal immune system function and modulation.[40,41,42 ,43]

Zinc deficiencies are widespread across the globe,[44] and may result from a combination of factors including low zinc status in foods caused by mineral depletion of agricultural soils,[45,46] dietary changes leading to reduced consumption of red meats,[47] and increased consumption of cereals high in phytates which reduce zinc absorption from the gastrointestinal tract.[48]

The UK's National Diet and Nutrition Survey (NDNS) has shown consistent intakes of food that are below the lower reference nutrient intake (LRNI) which equates to significant deficiency, e.g. 27% of girls in the age group 11 to 18-years old.[49] These deficiencies suggest

[37] Beck FW, Prasad AS, Kaplan J, Fitzgerald JT, Brewer GJ. Changes in cytokine production and T cell subpopulations in experimentally induced zinc-deficient humans. *American Journal of Physiology,* 1997; 272 (6 Pt 1): E1002-7.

[38] Rink L, Gabriel P. Extracellular and immunological actions of zinc. *Biometals*, 2001; 14(3-4): 367-83.

[39] Truong-Tran AQ, Carter J, Ruffin R, Zalewski PD. New insights into the role of zinc in the respiratory epithelium. *Immunology and Cell Biology*, 2001; 79(2): 170-7.

[40] Ruel MT, Rivera JA, Santizo MC, Lonnerdal B, Brown KH. Impact of zinc supplementation on morbidity from diarrhea and respiratory infections among rural Guatemalan children. *Pediatrics*. 1997; 99(6): 808-13.

[41] Sazawal S, Black R, Jalla S, Mazumdar S, Sinha A, Bhan MK. Zinc supplementation reduces the incidence of acute lower respiratory infections in infants and preschool children: a double blind controlled trials. *Pediatrics* 1998; 102: 1–5.

[42] Prasad AS, Fitzgerald JT, Bao B, Beck FW, Chandrasekar PH. Duration of symptoms and plasma cytokine levels in patients with the common cold treated with zinc acetate. A randomized, double-blind, placebo-controlled trial. *Annals of Internal Medicine*, 2000; 133(4): 245-52.

[43] Mocchegiani E, Muzzioli M. Therapeutic application of zinc in human immunodeficiency virus against opportunistic infections. *Journal of Nutrition*, 2000; 130 (5S Suppl): 1424S-31S.

[44] Prasad AS. Zinc deficiency in humans: a neglected problem. *Journal of the American College of Nutrition*, 1998; 17(6): 542-3. Editorial.

[45] Welch RM (2001). In: *Perspectives on the Micronutrient Nutrition of Crops* (Eds Singh K, Mori S, Welch RM). Scientific Publishers, Jodhpur, India. 294 pp.

[46] Thomas D. A study on the mineral depletion of the foods available to us as a nation over the period 1940 to 1991. *Nutrition and Health*, 2003; 17(2): 85-115.

[47] Richardson NJ. UK consumer perceptions of meat. *Proceedings of the Nutrition Society*, 1994; 53; 281-287.

[48] Lonnerdal B. Dietary factors influencing zinc absorption. *Journal of Nutrition*, 2000; 130 (5S Suppl): 1378S-83S.

[49] NDNS: results from years 7 and 8 (combined). Results of the National Diet and Nutrition Survey (NDNS) rolling programme for 2014 to 2015 and 2015 to 2016: *https://www.gov.uk/government/statistics/ndns-results-from-years-7-and-8-combined*.

that the majority of the population is not consuming adequate levels for optimal immune system function,[50,51] which is of critical significance given the current pandemic.

Compromised immune function caused by widespread mild zinc deficiency in the UK and other industrialised countries, as well as more severe zinc deficiency in developing countries,[52] may have a considerable influence on mortality and morbidity associated with an avian influenza pandemic.

Proposal for zinc — the emerging nutritional science on zinc in terms of its essentiality for immunocompetence suggests a wide variation in individual need. However the level of 40 mg/d for adults, as proposed by VKM is appropriate, although there should be no deduction applied form this upper level, given that some population groups (e.g. vegans or vegetarians who do not consume animal sources of zinc and also have high phytate intakes) will have both low intakes and poor absorption. There is also a need to take into account the need for elevated levels owing to interactions with other micronutrients, e.g. copper.

Iron

Any discussion on maximum levels of iron cannot be made without considering form, given extensive data demonstrating adverse effects such as constipation and nausea caused by certain salts (e.g. sulphate) that are not caused by similar doses of amino acid chelated forms (e.g. bisglycinate).[53] There are considerable differences in requirement between different populations groups of adults, even with the same age groups (e.g. men versus women, and between breastfeeding, lactating and pregnant women).[3]

Proposal for iron — while the levels proposed 50 mg tolerable upper level for adults by VKM appears reasonable, it is not scientifically rational if applied to all forms of iron. It applies absolutely to iron bisglycinate (so-called 'gentle' iron), but may induce adverse effects in the most sensitive individuals, especially if used long-term. A risk management approach is recommended for high dose, non-chelated iron supplements, that includes the requirement for use of an advisory statement to the effect "[doses > 20 mg] may induce nausea or gastrointestinal upset in sensitive individuals. Reduce daily dosage if such adverse effects are noted."

[50] Prasad AS. Zinc in Human Health: Effect of Zinc on Immune Cells. *Mol Med.* 2008 May-Jun; 14(5-6): 353–357.

[51] Prasad AS. Zinc is an Antioxidant and Anti-Inflammatory Agent: Its Role in Human Health. *Front Nutr.* 2014; 1:14.

[52] Prasad AS. Effects of zinc deficiency on Th1 and Th2 cytokine shifts. *Journal of Infectious Diseases,* 2000; 182 Suppl 1: S62-8.

[53] Melamed, N., Ben-Haroush, A., Kaplan, B. *et al.* Iron supplementation in pregnancy—does the preparation matter? *Arch Gynecol Obstet* (2007); 276: 601–604.

CONCLUSIONS

It is essential, as proposed by the European Commisison's 2016 report[5] and demonstrated by Krul et al (2017),[3] that a risk/benefit approach is utilised for micronutrients, given the risk of imposing risks of inadequacy on some populations in order to prevent risks of excess intake on others.

This approach does not appear to have been taken in developing upper levels of intake by the VKW. Moreoever, the simple deduction of mean food and supplemental intakes form tolerable upper levels is flawed scientifically.[1,2]

It is critical that a scientifically rational approach that takes into account the different risk/benefit profiles of different micronutrients is employed. The need to avoid unnecessary and disproportionate restrictions on intakes has been brought into sharp focus by the role of micronutrient deficiencies (most notable vitamin D[54] and zinc[11]) during the current pandemic.

We strongly urge the European Commission to take heed of our recommendations (see boxed section for each micronutrient above) for each of the four micronutrients that are subject to Draft Regulation in Norway.

ABOUT THE ALLIANCE FOR NATURAL HEALTH INTERNATIONAL

Alliance for Natural Health International is an independent, internationally-active, UK-headquartered, non-profit organisation established in 2002 that promotes natural, sustainable and bio-compatible approaches to healthcare—using the tools of 'good science' and 'good law'.

Its core activities include research and education and it has been at the forefront of research on scientific methodologies of risk/benefit assessment affecting food supplements. As an alliance, ANH-Intl collaborates with scientists, lawyers, medical doctors, health practitioners, politicians, consumers and companies to help shape scientific and legal frameworks that broaden the support for, and adoption of, natural and sustainable healthcare.

Find out more at: www.anhinternational.org.

[54] Rhodes, JM, Subramanian, S, Laird, E, Griffin, G, Kenny, RA (Institute of Translational Medicine, University of Liverpool, Liverpool, UK; Trinity College Dublin, Dublin, Ireland; St George's, University of London, London, UK; Mercers Institute for Ageing, St James Hospital, Dublin 8, Ireland). Perspective: Vitamin D deficiency and COVID-19 severity – plausibly linked by latitude, ethnicity, impacts on cytokines, ACE2 and thrombosis. *J Intern Med*, 2020: https://doi.org/10.1111/joim.13149.

APPENDIX 1: LIST OF UK ADVISORY STATEMENTS
Label advisory statements and re-formulations agreed with the FSA and industry, May 2004.

Nutrient	**Threshold to trigger statement** (recommended daily amount)	**Label advisory statement/reformulation**
Vitamin C	> 1000 mg	'[This amount of Vitamin C]* may cause mild stomach upset in sensitive individuals.'
Iron	> 20 mg	'[This amount of Iron]* may cause mild stomach upset in sensitive individuals'
Calcium	> 1500 mg	'[This amount of Calcium]* may cause mild stomach upset in sensitive individuals.'
Magnesium	> 400 mg	'[This amount of Magnesium]* may cause mild stomach upset in sensitive individuals.'
Nickel	All nickel-containing products See footnote [1]	'[Nickel]* may cause a skin rash in sensitive individuals.'
Beta-carotene	1) >7 mg 2) See footnote[2]	1) Encourage reformulation to < 7 mg/day. 2) Label statement: '[Beta-carotene]* should not be taken by heavy smokers.'
Nicotinic acid	> 20 mg	1) Encourage reformulation to nicotinamide. 2) If nicotinic acid is used, label statement: '[This amount of Nicotinic acid]* may cause skin flushes in sensitive individuals'.
Zinc	> 25 mg	Label statement: 'Long term intake [of this amount of zinc]* may lead to anaemia.'
Manganese	See footnote[3]	Label statement: 'Long term intake [of this amount of manganese]* may lead to muscle pain and fatigue.'
Phosphorus	> 250 mg	Label statement: '[This amount of Phosphorus]* may cause mild stomach upsets in sensitive individuals.'[4]
Vitamin B6	> 10 mg > 100 mg	Label statement: 'Long term intakes [of this amount of vitamin B6]* may lead to mild tingling and numbness.' Encourage reformulation to lower daily amount.

Label advisory statement agreed with Department of Health and Ministry of Agriculture, Fisheries and Food (MAFF) in 1991

Vitamin A > 800µg[5] of preformed vitamin A (as retinol, not beta-carotene)

Label statement: This product contains vitamin A. Do not take if you are pregnant or likely to become pregnant except on the advice of a doctor or antenatal clinic.

Notes on the table:

* For single nutrient products, the words in square brackets may be deleted.

[1] Nickel is not included on the lists of vitamins and minerals that are permitted for use in food supplements under the EU Food Supplements Directive; the substance is included here for information only.

[2] Government officials considered that the labels of all food supplements containing beta-carotene should carry the advisory statement '[Beta-carotene]* should not be taken by heavy smokers.' Industry considered that this should only be on products recommending a daily amount > 7mg. This footnote is for information only; it will not appear on labels.

[3] Government officials considered that the labels of all food supplements recommending a daily amount greater than 0.5mg manganese should carry this advisory statement. Industry considered that this statement could only be justified on products recommending a daily amount greater than 4mg. This footnote is for information here; it will not appear on labels.

[4] Government officials wanted a second sentence 'Long term intake [of this amount of phosphorus] may weaken bones' to be included in the advisory statement for phosphorus. Industry did not agree that inclusion of the second sentence was warranted. Officials asked the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) to look in detail at the effects of phosphate intake on parathyroid hormone and bone metabolism including new data on phosphate regulation. The wording of the advisory statement will be reconsidered following receipt of COT advice. This footnote is for information here; it will not appear on labels.

The COT reviewed the issue and took into account the publication of new data. The outcome of this review can be found at the link below entitled ‘COT statement on phosphate and the calcium parathyroid hormone axis’. In the light of the COT advice, there is insufficient data to proceed with an advisory statement on bone. Since the long-term effects of phosphate are unknown, the issue is currently unresolved and will be kept under review.
http://www.food.gov.uk/science/ouradvisors/cot/cotstatements/cotstatementsyrs/cotstatements2 005/cotstatements2005phoscpha.

[5] Department of Health advice is to avoid any supplements containing vitamin A during pregnancy.

Notes
a) No vitamins are completely stable and they deteriorate at different rates. Amounts of vitamins are added to food supplements during manufacture to compensate for losses during shelf life. For very unstable nutrients, such as vitamin C, the threshold values above refer to the declared amount and manufacturers will strive to use only the necessary quantities in the products to ensure 100 per cent of the declared value at the end of shelf-life.
b) All sources of nutrients in a product should be taken into account when declaring the quantities of nutrients and in deciding if the trigger level for an advisory statement has been exceeded.
c) These advisory statements are based on current evidence and are subject to change in the light of new evidence and advice.

APPENDIX 2

Risk information provided by Health Canada in its Multivitamin/Mineral Supplements Monograph

Source: http://webprod.hc-sc.gc.ca/nhpid-bdipsn/atReq.do?atid=multi_vitmin_suppl&lang=eng

7.0 Risk information

7.1 Cautions and warnings

Table 13. Cautions and warnings for specific medicinal ingredients and associated daily doses

Medicinal ingredient	Daily dose	Caution(s) and warning(s)
Beta-carotene	> 6,000 µg	Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you are a tobacco smoker (Touvier et al. 2005; Omenn et al. 1996; ATBC 1994).
Chromium sourced from chromium picolinate	≥ 200 µg	Consult a health care practitioner/health care provider/health care professional/doctor/physician if you have a kidney disorder and/or diabetes (Wani et al. 2006; Cupp et al. 2003; Bunner and McGinnis 1998; Cerulli et al. 1998; McCarty et al. 1997; Wasser et al. 1997).
Iron	Where the package contains more than the equivalent of 250 mg of elemental iron	Keep out of reach of children. There is enough iron in this package to seriously harm a child. (Note: this must be preceded by a prominently displayed symbol that is octagonal in shape, conspicuous in colour and on a background of a contrasting colour) [As per Section 97 of the *Natural Health Products Regulations*, citing Sections C.01.029 and C.01.031 of the *Food and Drug Regulations* (JC 2011, 2008)].
Manganese	> 5 mg	Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you have a liver disorder (IOM 2006; IOM 2001; Krieger et al. 1995).
PABA	All doses	Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you are pregnant or breastfeeding or if you are taking sulfonamides (Maren 1976).
Selenium	≥ 70 µg	Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you have a history of non-melanoma skin cancer (Duffield-Lillico et al. 2003).
Vanadium	All doses	Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you are pregnant or breastfeeding (IOM 2006; IOM 2001).

Table 13. Cautions and warnings for specific medicinal ingredients and associated daily doses		
Medicinal ingredient	**Daily dose**	**Caution(s) and warning(s)**
Vitamin E	≥ 180 mg AT	Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you have cancer (Meyer et al. 2008; Bairati et al. 2006; Bairati et al. 2005).
	≥ 268 mg AT	Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you have cardiovascular disease or diabetes (Ward et al. 2007; Winterbone et al. 2007; Lonn et al. 2005).
	≥ 360 mg AT	Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you are taking blood thinners (CPS 2012; IOM 2006; Booth et al. 2004; Corrigan and Marcus 1974).
Vitamin $K_1$and/or K_2	All doses	Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you are taking blood thinners (ASHP 2005; Franco et al. 2004; IOM 2001; Hansten et al. 1997).

7.2 Contraindications

Table 14. Contraindications for specific medicinal ingredients and associated daily doses		
Medicinal ingredient	**Daily dose**	**Contraindication(s)**
Chromium sourced from chromium picolinate	All doses	Do not use this product if you are pregnant or breastfeeding (EFSA 2009k; IOM 2001).
Potassium	≥ 100 mg	Do not use this product with other potassium-containing supplements or with potassium-containing salt-substitutes (Sweetman 2015).
Zinc sourced from zinc picolinate	All doses	Do not use this product if you are pregnant or breastfeeding (EFSA 2009k; IOM 2001).

7.3 Known adverse reactions

Table 15. Known adverse reactions for specific medicinal ingredients and associated daily doses		
Medicinal ingredient	**Daily dose**	**Known adverse reaction(s)**
Table 14 Footnotes		
Table 14 Footnote 1 **Zinc:** Statement required if the product does not meet the minimum copper requirements outlined in Appendix VII, Table 24.		