Public consultation on the scope of work for updating the FAO/WHO calcium, vitamin D, and zinc requirements in children aged 0–36 months

Comments received (in order of date and time received)

Survey response	
Family/last name	Uro-Chukwu
Given/first name	Henry
Organization/affiliation	Centre For Clinical / Public Health Nutrition and Nutraceutical Research and Development, College of Health Sciences, Ebonyi State University, Nigeria
Sector	Academic/research
Sector [Other]	
Country	Nigeria
Country [Other]	
Key questions and health outcomes	During late childhood, the calcium required is to be sourced from diets. In poor settings, its difficult to have diet rich in calcium from commercial sources. How can we ensure that these vast population in poor rural settings utilized calcium rich culturally accepted local food sources since most of such foods and food products have not been characterized?
Additional comments	
Key questions and health outcomes	Vitamin D is not adequate when provided from human breast milk for infants and diets for infants. Using vitamin D supplements and drops for infants have been advocated, while in toddlers use of vitamin D fortified milk and cereal are advised. In low income setting both the Vitamin D supplements / drops and fortified foods are luxuries. How will FAO/WHO encourage academic and research institutions in such settings to profile and characterize locally available vitamin D sources that can be used to enrich cereals in toddlers diets? Besides Vitamin supplements /drops, what other possibilities are considered for the infant?
Additional comments	
Key questions and health outcomes	What local dietary sources of zinc are recommended for children with diarrhea or at risk of diarrhea and in boosting children immunity?
Additional comments	
Please provide any final thoughts or comments below.	I suggest FAO/WHO should identify and partner with budding academic / research institutions such as ours based in low income settings to support in characterization and profiling of locally available and culturally acceptable food sources in addition to a knowledge translation platforms for communities in need.

Survey response	
Family/last name	Camara
Given/first name	Amadou damagbe
Organization/affiliation	UNHCR
Sector	UN organization
Sector [Other]	
Country	Congo
Country [Other]	
Key questions and health outcomes	Consumed adequate amounts of calcium and vitamin D throughout childhood, adolescence, and early adulthood can avoid Osteoporosis and osteomalacia inaduld and rickets in children are disorders characterized by porous and fragile bones, is a serious public health problem Bones increase in size and mass during periods of growth in childhood and adolescence, reaching peak bone mass around age 30. The greater the peak bone mass, When calcium intake is low or food intake is low in calcium or poorly absorbed, bone breakdown occurs as the body uses its stored calcium to maintain normal biological functions. Bone loss also occurs as part of the normal aging process, particularly in postmenopausal women due to decreased
Additional comments	High calcium intake can cause constipation and might also interfere with the absorption of iron and zinc, though this effect. High intake of calcium from supplements, but not foods, has been associated with increased risk of kidney stones
Key questions and health outcomes	Vitamin D is needed for the body to absorb and process calcium. Vitamin D deficiency can caused bone diseases, such as rickets in children and osteomalacia and osteoporosis in adults, we can get vitamin D from foods, our supply of vitamin D is produced by the body itself. Cholesterol, which is present naturally in the skin, is converted to vitamin D through the action of sunlight on the skin.
Additional comments	Symptoms of osteomalacia affect mainly the skeletal system and are similar to that observed in rickets and t characterized by the progressive loss of bone mass
Key questions and health outcomes	Zinc is an essential trace element required for maintaining intestinal cells, bone growth, and immune function. Zinc deficiency is currently opened in develop country with malnourish children. Zinc deficiency during growth periods results in growth failure in children
Additional comments	Bio-availability plays a major role in zinc absorption and phytic acid is the main known inhibitor of zinc
Please provide any final thoughts or comments below.	All these vitamins (D), and minerals (Calcium and Zinc) their use in an adequate way are necessary for the good health and the mental, physical and social and intellectual development of the child

Survey response	
Family/last name	Muhammad Ajmal Khan Baloch
Given/first name	Muhammad
Organization/affiliation	Nahar King Welfare Organization (NKWO)
Sector	UN organization
Sector [Other]	
Country	Pakistan
Country [Other]	
Key questions and health outcomes	NKWO Team already member of SUN CSA Pakistan and already working in the field as Practical issues . Whereas as per give project, NKWO will outcome achieved 95%
Additional comments	As per our survey after this Project volleyball community automatic to sustainability
Key questions and health outcomes	Calcium, Vitamin D and Zing is important for better life, whereas above three items are need to the our vulnerable community especially in this time due COVID-19
Additional comments	No
Key questions and health outcomes	Zinc is important for human and animal and all crops, I want work as per your policy and our local environment through ur support
Additional comments	Best result
Please provide any final thoughts or comments below.	As per your give Project Instruct, WHO and WFP and SUN CSA Pakistan, Government of Pakistan all line department technical support NKWO will provide you exemplary result as per of object and sustainability of this Project.

Survey response	
Family/last name	Brugård Konde
Given/first name	Åsa
Organization/affiliation	National Food Agency
Sector	Government
Sector [Other]	
Country	Sweden
Country [Other]	
Key questions and health outcomes	
Additional comments	
Key questions and health outcomes	In the key questions ethic groups are mentioned, but we would specifically like to focus on skin colour. We would like to nominate the requirement of vitamin D in children with light or dark skin living in northern Europe as a topic for a systematic litterature review. Researchers in Umeå and Malmö have found that children with light skin would need 20 µg and children with dark skin 28 µg vitamin D per day to maintain a concentration of S-25(OH)D på>50 nmol/L during the winter season. Does this mean that the recommended intake would need to be increased and would it be relevant with different RI:s for children with light versus dark skin ?
Additional comments	References: Öhlund I, Silfverdal SA, Hernell O, Lind T. J PediatrGastroenterolNutr. 2013;56(5):551-5. Serum 25-Hydroxyvitamin D Levels In Pre-School Children In Northern Sweden Are Inadequate After The Summer Season And Diminishes Further During Winter. Åkeson PK, Lind T, Hernell O, Silfverdal SA, Öhlund I. J PediatrGastroenterolNutr. 2016;62(4):643-9. Serum Vitamin D Depends Less on Latitude Than on Skin Color and Dietary Intake During Early Winter in Northern Europe. Öhlund I, Lind T, Hernell O, Silfverdal SA, Karlsland Åkeson P. Am J ClinNutr. 2017;106(1):105-112. Increased vitamin D intake differentiated according to skin color is needed to meet requirements in young Swedish children during winter: a double-blind randomized clinical trial. Åkeson PK, Åkesson K, Lind T, Hernell O, Silfverdal SA, Öhlund I. J PediatrGastroenterolNutr. 2018;67(3):388-394. Vitamin D Intervention and Bone -A RandomisedClinical Trial in Fair and Dark Skinned Children at Northern Latitudes.
Key questions and health outcomes	
Additional comments	

Please provide any final thoughts or comments below.	Thank you for the opportunity to comment on the key questions, that seem to be very well elaborated.

Survey response	
Family/last name	Igbine.
Given/first name	Lizzy
Organization/affiliation	Nigerian Women Agro Allied Farmers Association.
Sector	Non-governmental agency
Sector [Other]	
Country	Nigeria
Country [Other]	
Key questions and health outcomes	The necessities of calcium in the growth metabolism of the child should not be over emphasised.. Calcium should be an important primary composition of nutrient is a babies food.
Additional comments	Non
Key questions and health outcomes	Vitamin D enhances the growth of the child. and should be considered while formulating babies Nutritional composition of foods.
Additional comments	Lack of these Vital Vitamins causes defficiencies.
Key questions and health outcomes	
Additional comments	
Please provide any final thoughts or comments below.	

Survey response	
Family/last name	Rycken
Given/first name	Laurence
Organization/affiliation	International Dairy Federation
Sector	Private sector
Sector [Other]	
Country	Belgium
Country [Other]	
Key questions and health outcomes	Calcium: o In addressing the efficiency of calcium absorption, we encourage consideration the effects of anti-nutrients in foods as well as of the form in which the calcium is delivered, and how that correlates to its absorbability. The latter would help to distinguish potential differences between calcium-fortified foods and calcium supplements (which can have inferior absorption). Additionally, distinguish the food matrix from which the calcium is derived from, such as dairy milk/products, which have additional nutrients and structures that enhance calcium's absorption and utilization. o Consider exploring the following additional question - which dietary pattern(s) promotes the optimal level of calcium and is associated with more beneficial health outcomes (such as bone health, growth indicators, etc.)? There is a growing body of research that suggests overall dietary pattern matters more than just isolated nutrients to achieve optimal bone health in children. o Consider how overall dietary patterns impact calcium requirements, for example the effect of adequate protein on the tolerable upper limits (UL) for calcium. Lower protein diets might have lower calcium intakes, but the effect of those differences could be significant. If children need adequate amounts of protein for health, the appropriate calcium level should match that.
Additional comments	• We request further clarification on dermal losses, does this include hair and nails? • In addressing the efficiency of calcium absorption, we encourage an emphasis to consider the form in which the calcium is delivered (e.g. whole food, fortification, or supplement) and its absorbability. This helps to distinguish the similarity between calcium-fortified foods, like plant-based beverages, and calcium supplements. Additionally, distinguish the food matrix where the calcium is derived from, such as dairy milk, which has additional nutrients and structures that enhance absorption and utilization. • It would help to clarify if healthy children aged 0-9 years is for bone growth only, while healthy children and adult category will be considered for dermal losses only. • Consideration should be given to include a question about the dietary pattern which promotes the optimal level of calcium, and overall health outcomes (bone, growth indicators, etc.) including food source, combination of foods, fortification, and

	supplements. Regarding research on optimal bone health, it appears that overall dietary pattern matters more than just isolated nutrients. In addition to vitamin D, vitamin K2 should also be considered for optimal bone health. Vitamin K2 may increase serum osteocalcin, which is responsible for binding calcium to bone tissue (Lundberg HE. 2020. IJClinicalTrials). • When observing optimal calcium levels, does the overall dietary pattern impact calcium needs? E.g.: When consuming adequate protein in the diet- the UL for calcium may shift. Lower protein diets may have lower calcium limits, but what is the effect of those differences? If children require adequate protein intakes for health, the appropriate calcium level should match that • We feel that this is a key aspect to highlight in the research. Do fortified foods act in the body in the same way that supplements or whole foods do? The forms are often similar, however food matrices can impact on absorption and utilization of nutrients
Key questions and health outcomes	Vitamin D: Due to the increasing prevalence of childhood obesity across all age groups, assessing biometrics (weight) should also be considered, since obesity/adiposity has been associated with vit D deficiency.
Additional comments	• The assessment of biometrics (weight), obesity/adiposity should also be included in the subgroup analyses since childhood obesity is a growing issue of concern and is associated with vitamin D deficiency. • Consideration of illnesses and drug-nutrient interactions which impact on impact Vit D status should also be taken into account. • It would be useful to clarify why pregnant or lactating women are also assessed. • We have noted that this is a different approach to that taken for calcium and zinc; we therefore assume that within Vitamin D studies comparators were identified but the same was not found for calcium and zinc. • There is limited consensus (and various paediatric guidelines) on the appropriate cut offs for 25-OHD to determine vitamin D status (sufficiency vs deficiency): A range of values have been suggested by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition; American Academy of Pediatrics among others however, which value will be used for the purpose of this review?
Key questions and health outcomes	Zinc: o It is important to better understand the value and contribution of animal source foods in infants' diets, as these foods help meet recommendations for under consumed nutrients such as zinc. Are nutrients/zinc from animal sourced foods better absorbed and utilized compared to supplements and fortified foods?
Additional comments	• As previously mentioned, consideration for illnesses or drug-nutrient interactions that could impact on zinc metabolism should be taken into account. • It is important to better understand the value and contribution of animal source foods in infants' diets, as

	these foods help meet recommendations for zinc. Is zinc from animal source foods better absorbed and utilized compared to non-animal sourced foods, supplements, and fortified foods?
Please provide any final thoughts or comments below.	The International Dairy Federation, the leading source of technical and scientific expertise in dairy since 1903, welcomes the opportunity to provide comments to the Scoping materials for updating FAO/WHO nutrient requirements for children aged 0-36 months. Nutrition during the first 1000 days has far-reaching impacts on a child's ability to succeed in school and life, and greatly influences their health outcomes as they grow older, including their likelihood of having a chronic disease. Milk's unique nutrient package can be difficult to replace in a healthy dietary pattern, especially for growing and developing children. Dairy foods can play a key role in nutrition throughout life. The first 1,000 days of life (birth through age 2) are an important window for overall growth and development. Milk and dairy foods offer a unique package of nutrients essential for optimal health, and growth and development. Young children who do not meet the daily recommended servings of dairy milk, yogurt, or cheese, may have inadequate intakes of important nutrients, such as calcium, vitamin D and protein which are necessary for optimal growth and development. Establishing healthy eating patterns, especially among those most vulnerable, including infants and young children, is a key component of chronic disease prevention efforts and health promotion. Please find below some general comments as well as more detailed comments provided to the elements of the scoping materials. General comments We have noted that a range of health outcomes are being considered for vit D but not for calcium and zinc, for which minimum requirements for (bone) growth only are considered. Further consideration should be given to the benefits of nutrient intake beyond that required for normal growth & development for all nutrients in this review. We would also request further clarification for the age group breakdown for each nutrient and specific output related to each age group (e.g. 0-6 months; 6-12 months and 1-3 years). In addition, infant gender should also be considered in the assessment due to differing metabolism and therefore requirements, especially during the early years of development.

Survey response	
Family/last name	Parnarauskienė
Given/first name	Justė
Organization/affiliation	Vilnius University hospital Santaros klinikos
Sector	Academic/research
Sector [Other]	
Country	Lithuania
Country [Other]	
Key questions and health outcomes	It should be differentiated recommendation for breastfed, infant formula-fed children and after starting complementary feeding. Because they are different sources and make different absorption rate. Absorption rate dependency of calcium supplements form.
Additional comments	
Key questions and health outcomes	Good subgroup analyses
Additional comments	There are many cases of D hypovitaminosis. I think it should be remeasured lower healthy level of serum 25 (OH)D.
Key questions and health outcomes	
Additional comments	
Please provide any final thoughts or comments below.	-

Survey response	
Family/last name	Kent
Given/first name	George
Organization/affiliation	University of Hawaii (Emeritus)
Sector	Academic/research
Sector [Other]	
Country	United States of America
Country [Other]	
Key questions and health outcomes	
Additional comments	
Key questions and health outcomes	
Additional comments	
Key questions and health outcomes	
Additional comments	
Please provide any final thoughts or comments below.	The Scope and Purpose document should explain the meaning of “nutrient” because understandings of the term vary in the general public and also among professional nutritionists and dietitians. It is important to correct any suggestion that delivering the nutrients in the right quantities is all that matters.

Survey response	
Family/last name	Lee
Given/first name	Warren T K
Organization/affiliation	FAO
Sector	UN organization
Sector [Other]	
Country	Thailand
Country [Other]	
Key questions and health outcomes	Q1. The experts would need to define what the optimal level of calcium intake is that would allow healthy bone mineral accretion at this age and future bone mineral mass at skeletal maturity. Does it need to consider any functional health outcome for optimizing bone mass for the prevention of bone loss later in life? So the experts may need to consider to expand the scoping materials for study when considering dietary calcium needs for bone growth in young children. Q3. Non dietary factor such as physical activity would also need to be considered in bone growth and bone mineral accretion in young children.
Additional comments	Study Criteria - Population: Bullet #1: In order to determine the lasting effect of habitual calcium intake on bone mineral accretion from early childhood to adolescence, it would be useful to extend the age group to 16-17-y where pubertal growth spurt has completed in most children and that a majority of adult bone mass has been accumulated, One may argue that hormonal changes during peri-puberty period could mask the contribution of early Ca intake to bone mass increments at growth spurt. If one could pool data from different cohorts studies (from early childhood to adolescence) - with a bigger sample size - we may be able to discover the impact of early age exposure of calcium and other dietary intakes and life style factors on bone growth and bone mineral accumulation at adolescence. Study Criteria - Outcomes: - In measurements of Ca needs, losses & absorption, calcium and protein intake (sources and quantity) and sodium are also important in addition to Vit. D status. - It would be useful to study the vitamin D sparing effect on calcium needs in terms of optimal bone mineral accretion and bone growth. - Bone mineral density/bone mineral content status should also be part of the functional health outcomes of Ca needs
Key questions and health outcomes	Vitamin D: requirements - Key questions Q1. The experts will need to define what are the prioritized functional health outcomes of vitamin D intake. Q1: Planned subgroup analyses: * Ethnic group - Skin pigmentation evaluation is also important in addition to ethnicity Study Criteria - Populations, Bullet #1: In order to determine the lasting effect of vitamin D status on bone mineral

	accretion from early childhood to adolescence, it would be useful to extend the age group to 16-17-y where pubertal growth spurt has completed in most children and that a majority of adult bone mass has been accumulated, One may argue that hormonal changes during peri-puberty period could be the major determinant on bone mass increments at growth spurt. If one could pool data from different cohorts studies (from early childhood to adolescence) - with a bigger sample size - one may be able to discover the impact of early age exposure of Vit D and other dietary intakes and life style factors on bone growth and bone mineral accumulation at adolescence. So the experts may consider to expand the scope when considering Vit D status for bone growth in young children.
Additional comments	
Key questions and health outcomes	
Additional comments	
Please provide any final thoughts or comments below.	

Survey response	
Family/last name	Mensik
Given/first name	Petr
Organization/affiliation	EU Specialty Food Ingredients
Sector	Private sector
Sector [Other]	
Country	Belgium
Country [Other]	
Key questions and health outcomes	
Additional comments	
Key questions and health outcomes	Q 1. What is the effect/association of higher vs lower levels of vitamin D intake on health outcomes in children aged 0-36 months? - EU Specialty Food Ingredients would propose to add the following subgroup analyses: • Skin type • Mandatory food fortification • Country Q 2. What is the effect/association of higher vs lower serum 25(OH)D concentrations on health outcomes in children aged 0-36 months? - EU Specialty Food Ingredients would propose to add the following subgroup analyses: • As regards the source of vitamin D: For dietary supplements - different forms of supplements • Calcium intake • Skin type • Mandatory food fortification • Country Q 3. What is the effect/association of higher vs lower vitamin D intake on serum 25(OH)D concentrations in children aged 0-36 months? - EU Specialty Food Ingredients would propose to add the following subgroup analyses: • Ethnic group • Skin type • Mandatory food fortification • Country
Additional comments	
Key questions and health outcomes	
Additional comments	
Please provide any final thoughts or comments below.	

Survey response	
Family/last name	BHATTACHARJEE
Given/first name	LALITA IYER
Organization/affiliation	FOOD AND AGRICULTURE ORGANIZATION
Sector	UN organization
Sector [Other]	
Country	Bangladesh
Country [Other]	
Key questions and health outcomes	Question on calcium requirement for children between 24 to 36 months of age Given the number of milk and milk products, calcium-rich processed food available in the market, foods being supplemented or fortified with calcium, vitamins A and D (which are labelled) and through habitual diets taken at home, is it not necessary to define the maximum quantity of the nutrient to be taken (requirement) without the risk of an excessive intake?
Additional comments	(1) FAO in Bangladesh is currently engaged in technically supporting (the Institute f Nutrition and Food Science, Dhaka University) the estimation of the nutrient density of a food or diets across the life span and to this end we are evaluating quality and the proportion of a selected nutrient in relation to the energy content. Can/will nutrient density be also used as a basis to define the requirements of children? (2) Bangladesh is also in the process of updating its Dietary Guidelines and we (FAO and WHO there) are technically supporting the process. The average requirement for energy has been stipulated as 2430 kcal/d as per the Desirable Dietary Pattern (DDP) proposed based on research. To this end, about 55% of total energy from cereals is proposed in the DDP which amounts to 400 g cereal/day. This seems a bit high though it is much lower that what an average Bangladeshi habitually consumes. Apart from this, energy is derived from other foods proposed in the DDP. The question is, based on global updates and for healthier diets, are we going to propose lower CHO calories in the near future?
Key questions and health outcomes	The RDI for vitamin D for children above 1 year is 600 IU or more/day. Exposure to sunlight can also ensure enough vitamin D though many children do not get adequate amounts in developing countries of Asia. Vitamin D insufficiency in both underweight and normal children below 2 years of age has been reported in Bangladesh. How much of daily exposure to sunlight is being prescribed, at what time of the day and are these different across skin colours?
Additional comments	
Key questions and health outcomes	

Additional comments	
Please provide any final thoughts or comments below.	I would like to attend this consultation.

Survey response	
Family/last name	Ntagungira
Given/first name	Jean de Dieu
Organization/affiliation	Pentagon Technology Co Ltd
Sector	Private sector
Sector [Other]	
Country	Rwanda
Country [Other]	
Key questions and health outcomes	The Health service delivery is central to achieving the objective of mainstreaming nutrition in As such, the proposed commitments place health service delivery at the front and center. The subsequent five pillars of the health system play supportive roles in the health service delivery platform. Through indirect and direct mechanisms, the commitments in these pillars of the health system combine and interact to improve health service delivery more
Additional comments	non
Key questions and health outcomes	The Health service delivery is central to achieving the objective of mainstreaming nutrition in . As such, the proposed commitments place health service delivery at the front and center. The subsequent five pillars of the health system play supportive roles in the health service delivery platform. Through indirect and direct mechanisms, the commitments in these pillars of the health system combine and interact to improve health service delivery more
Additional comments	approaches are briefly outlined below: the clinical approach, nutrient balance, functional indicators of nutritional sufficiency (biochemical, physiological, molecular), and optimal nutrient intake. A detailed analysis of the relative merits of these approaches is beyond the scope of this chapter, but additional information on each can be found in subsequent chapters of this report. When no information is available the default approach to define a recommended intake based on the range of observed intakes of “healthy” populations is used.
Key questions and health outcomes	
Additional comments	
Please provide any final thoughts or comments below.	if we examine the iron intake of a population we may find that vegetarians may be well below the recommended intake while those who consume meat may be getting sufficient iron. To achieve adequacy in this case we need to increase iron intake in the former but not the latter group

Survey response	
Family/last name	ONOJA
Given/first name	IFEOMA UZOAMAKA
Organization/affiliation	UNIVERSITY OF NIGERIA TEACHING HOSPITAL UNTH, ITUKU/OZALLA EN
Sector	Government
Sector [Other]	
Country	Nigeria
Country [Other]	
Key questions and health outcomes	1 What are the modalities set for educating the women that attend antenatal clinics on the importance of calcium and other micro nutrients to both her and her child? HEALTH OUTCOME: There would be better feeding / dietary knowledge.
Additional comments	i quite agree with the out come and the priority.
Key questions and health outcomes	The questions are very important and the prioirity of the set out come are in order
Additional comments	My opinion on UV light or sun as a source of Vitamin D is that the way the society is structured now children 0-36 months rarely go outside to play and receive vitamin D from early morning sunshine. (insecurity)
Key questions and health outcomes	i strongly agree with raised questions and priority of health outcomes outlined.
Additional comments	
Please provide any final thoughts or comments below.	At the grass root level let the government ensure that health out post are equipped with human capital and facilities that would ensure women of child bearing age who attend both ante/ post natal clinics to be properly educated on adequacy of their diets.

Survey response	
Family/last name	WETZLER
Given/first name	Sandrine
Organization/affiliation	Anses
Sector	Government
Sector [Other]	
Country	France
Country [Other]	
Key questions and health outcomes	
Additional comments	
Key questions and health outcomes	- Taking into account the mother's diet in the case of breastfeeding - Taking into account the adiposity of the infant (storage and mobilization of vitamin D reserves)
Additional comments	
Key questions and health outcomes	
Additional comments	
Please provide any final thoughts or comments below.	

Survey response	
Family/last name	Swift
Given/first name	Sibyl
Organization/ affiliation	Natural Products Assocation
Sector	Non-governmental agency
Sector [Other]	
Country	United States of America
Country [Other]	
Key questions and health outcomes	
Additional comments	RE: “Public consultation on the scope of work for updating the FAO/WHO calcium, vitamin D, and zinc requirements in children aged 0-36 months” (July 7, 2020) Dear Dr. Abdollahi: The Natural Products Association (NPA) is submitting this letter as general comment to the “Public Consultation on the Scope of Work for Updating the FAO/WHO calcium, vitamin D, and zinc requirements in children aged 0-36 months”. The NPA was founded in 1936 to promote and protect the unique values and shared interests of retailers and suppliers of natural nutritional foods and natural products, including conventional foods, medical foods, dietary supplements, and foods for special dietary use. The NPA is a non-profit 501(c)(6) association whose mission is to advocate for the rights of consumers to have access to products that will maintain and improve their health, and for the rights of retailers and suppliers to sell these products. We are the oldest and largest trade association in the natural products industry representing over 1,100 members accounting for almost 10,000 retail, manufacturing, wholesale, and distribution locations of natural products, including foods, dietary supplements, homeopathic products, and health/beauty aids. As an observer in the CODEX Alimentarius, NPA has an interest to submit comments on this topic on behalf of our members. Thank you for the opportunity to comment. Background Deficiencies in vitamins and minerals, particularly in micronutrients is a global public health issue. Many of these nutrients have a direct influence on the growth and development of pediatric populations, while other directly impact immunocompetence which is particularly critical in developing nations. It is not always possible to consume the required micronutrients and vitamins that are required for optimal health. In both developing countries and industrialized nations healthy, nutrient-rich diets are not available to everyone. The World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) previously published (2004) vitamin and mineral requirements that covered all ages. In light of the fact that new information has

	been published on nutrition requirements for children, FAO and WHO have sought to update nutrient requirements for vitamin D, zinc, and calcium intake for children, beginning with ages 0-36 months. Calcium is an essential mineral commonly found in dairy, green leafy vegetables, tofu, and nuts. In certain populations whose requirements are higher, it is difficult to consume sufficient quantities through the diet alone, and therefore, requires supplementation to ensure its adequate intake. Furthermore, some foods that are commonly found in the diet prevent its absorption (e.g., spinach, which contains vitamin K and binds to calcium before it can be absorbed). Many developing countries do not have access to a calcium-rich diet, which only exemplifies why calcium supplementation recommendations are critical for achieving adequate intake of calcium globally. Calcium functions to support nerve function and muscle contractility, heart functioning, and intracellular signaling . This mineral serves a critical role in the deposition of new bone and its subsequent mineralization. Diets that do not provide adequate amounts of calcium contribute to an increase in bone resorption and a significant reduction in bone mineral density . Peak bone mass in adulthood is largely determined by calcium intake during childhood. Deficient intake of calcium-rich foods during childhood can negatively impact adult bone mineral density . Calcium intakes are historically low in many developed countries, which predisposes those populations to an increased risk for developing osteoporosis and osteopenia ; both of these bone metabolism diseases are associated with increased fracture risk. Calcium supplementation in children that was initiated to increase the total calcium intake resulted in significantly increased bone mineral density (BMD) and weight in subjects aged 12 to 18 months. Similar measures increased bone mineral content (BMC) in subjects that were 12 months of age . In fact, supplementation with calcium for one to two years in these populations has been associated with a significantly higher accretion of bone mineral, by approximately 1-5%12. Others have studied the effects of calcium supplementation in children whose diets did not contain sufficient sources of calcium and found that supplementation led to a 1-3% (significant for bone) higher deposition of bone mineral content11. This data is critical for determining best practices for calcium supplementation recommendations in countries that are considered developing or low-income and have a higher incidence calcium deficiency in their general population10 Calcium works in conjunction with vitamin D to stimulate bone formation. This process will only fully function with adequate vitamin D status is combined with similarly appropriate levels of dietary calcium. The end result is a positive calcium balance that contributes to bone deposition. If either calcium or vitamin D are not present in sufficient quantities, diseases like osteoporosis are still likely to occur . Osteoporosis is a condition with low bone volume but normal mineralization that predisposes those afflicted to a greater risk for the incidence of hip fracture which is associated with a higher mortality rate in the elderly. The incidence of osteoporosis is fairly high, even in industrialized nations and can be addressed with proper nutrition during childhood when peak bone mass is achieved. As previously mentioned, peak bone mass occurs when bone mineral is deposited in childhood, but adequate levels of calcium must be present to achieve a positive calcium balance to perform this

	function17. The calcium requirements are greater during growth and harder to achieve in many developing countries. We strongly recommend that the committee utilize studies that explore the benefits of calcium supplementation to achieve the appropriate calcium intake in ages 0-36 months. Furthermore, we recommend that more bone outcomes are included, particularly those that would allow for recommendations of calcium intake that would promote the achievement of peak bone mass. (9) Cormick G, Belizan JM (2019). Calcium intake and health. Nutrients, 11: 1606. doi: 10.3390/nu11071606. (10) Reid IR, Bolland MJ (2020). Calcium and/or Vitamin D supplementation for the prevention of fragility fractures: who needs it? Nutrients, 12: 1011. doi: 10.3390/nu12041011. (11) Zhu K, Prince RL (2012). Calcium and bone. Clinical Biochemistry, 45: 936-942. doi: 10.1016/j.clinbiochem.2012.05.006. (12) Cashman KD (2002). Calcium intake, calcium bioavailability and bone health. British Journal of Nutrition, 87(suppl 2): S169-S177. doi: 10.1079/BJN/2002534. (13) Chung M, Ruan M, Cara KC, Yao Q, Penkert LP, Chen J (2020). Vitamin D and calcium in children 0-36 months: a scoping review of health outcomes. Journal of the American College of Nutrition. doi: 10.1080/07315724.2020.1774822. (14) Morris HA, O'Loughlin PD, Anderson PH (2010). Experimental evidence for the effects of calcium and vitamin D on bone: a review. Nutrients, 2: 1026-1035. doi: 10.3390/nu2091026. (17) Bouillon R, MArcocci C, Carmeliet G, Bikle D, White JH, Dawson-Hughes B, Lips P, Munns CV, Lazaretti-Castro M, Giustina A, Bilezikian J (2019). Skeletal and extraskeletal actions of vitamin D: current evidence and outstanding questions. Endocrine Reviews, 40(4): 1109-1151. doi.org/10.1210/er.2018-00126.
Key questions and health outcomes	
Additional comments	Vitamin D is a fat-soluble vitamin that plays a significant role in calcium and phosphorus homeostasis and bone metabolism . Vitamin D is produced when UVB radiation is introduced to the skin or from the limited foods that contain vitamins D2 or D39 such as egg yolks, fatty fishes, or cheese. The active form of vitamin D (1,25(OH)2D) functions to preserve the homeostasis of serum levels of calcium and phosphorus which are essential for bone mineralization . Vitamin D as 1,25(OH)2D3, works in conjunction with calcium to increase absorption of serum calcium and increases mineralization of bone. When calcium is not available in sufficient quantities, bone resorption increases, and bone mineral is removed as mineralization is stopped9. Data from randomized clinical trials supports a link in vitamin D and calcium supplementation on improved bone mineral density (BMD) such as decreased risk for hip and nonvertebral fractures . Children that experience vitamin D deficiency for extended periods of time are at an increased risk for developing rickets . In children, recommendations for vitamin D supplementation are typically 400 UI/day for the first year and then 600 UI/day for children over one year of age . Vitamin D also plays a critical role in maintaining normal functioning in the immune system. Vitamin D receptors have been identified in monocytes, macrophages, and the thymus . Low levels of vitamin D are linked to increased inflammatory cytokines (TNF-alpha and IL6),

	while supplementation with vitamin D not only down-regulates the production of inflammatory cytokines but also upregulates inhibitory cytokines . Deficiencies in vitamin D are attributed to an increased severity of infections, but more importantly, an increased incidence of resultant morbidity and/or mortality . In a systematic review, Jayawardena et al. suggested that supplementation with vitamin D may be an effective preventive measure against viral infections in populations that are deficient in vitamin D . There is also data to support supplementation of vitamin D having a positive impact on the incidence of acute respiratory tract infections in populations that are deficient19 and reduction of the risk for developing such an infection. Specifically, a systematic review of randomized, double-blind trials of vitamin D supplementation determined that there is an approximately 12% reduction in the likelihood that subjects developed acute respiratory tract infections . There are limited natural food sources of vitamin D, outside of oily fish, egg yolks, and meat. These categories of food are often lacking in diets in developing countries, or by choice in industrialized nations (e.g., vegan or vegetarian diets). Therefore, it is not surprising that data supports the existence of a global deficiency of vitamin D . Many industrialized nations, such as the United Kingdom, already recommend supplementation of vitamin D for certain populations, including young children18. Most countries should consider issuing recommendations for vitamin D supplementation due to deficiencies in its levels in the general population worldwide and the low availability in food. This particularly critical in populations aged 0-36 months where they may not be exposed to sunlight in a manner sufficient to address their vitamin D requirements and therefore we recommend that that the committee continue to review studies that utilized supplementation for this population. Furthermore, based on our comments today, we ask the committee to include an outcome measure related to incidence of acute respiratory illness. (17) Bouillon R, MArcocci C, Carmeliet G, Bikle D, White JH, Dawson-Hughes B, Lips P, Munns CV, Lazaretti-Castro M, Giustina A, Bilezikian J (2019). Skeletal and extraskeletal actions of vitamin D: current evidence and outstanding questions. Endocrine Reviews, 40(4): 1109-1151. doi.org/10.1210/er.2018-00126. (18) Mendes MM, Charlton K, Thakur S, Ribeiro H, Lanham-New SA (2018). Future perspectives in addressing the global issue of vitamin D deficiency. Proceedings of the Nutrition Society, Conference on “Targeted approaches to tackling current nutritional issues” Symposium 3: Global strategies to improve micronutrient status; current opinion and implications for nutrition policy. doi: 10.1017/S0029665119001538. (19) Panfili FM, Roversi M, D’Argenio P, Rossi P, Cappa M, Fintini D (2020). Possible role of vitamin D in COVID-19 infection in pediatric populations. Journal of Endocrinological Investigation. doi: 10.1007/s40618-020-01327-0. (20) Wintergerst ES, Maggini S, Hornig D (2007). Contribution of selected vitamins and trace elements to immune function. Annals of Nutrition and Metabolism, 51(4): 301-323. Doi: 10.1159/000107673. (21) Weir EK, Thenappan T, Bhargava M, Chen Y (2020). Does vitamin D deficiency increase the severity of COVID-19?. Clinical Medicine, 20(4): e107-108. doi: 10.7861/clinmed.2020.0301. (22) Maggini S, Pierre A, Calder PC (2018). Immune function and micronutrient requirements change over the life course.

	Nutrients, 10:1531. doi:10.3390/nu10101531. (23) Jayawardena R, Sooriyaarachchi P, Chourdakis M, Jeewandara C, and Ranasinghe P (2020). Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 14(367-382). https://doi.org/10.1016/j.dsx.2020.04.015.
Key questions and health outcomes	
Additional comments	Zinc is considered an essential trace mineral; it is critical to maintaining the homeostasis and functioning of both innate and acquired immune function. It must be consumed through the diet or supplementation, but only in small quantities as a trace mineral. Zinc plays a critical role in children's growth and development. The importance of adequate intake is demonstrated when children whose levels are not sufficient experience significantly stunted growth, which is resolved when supplementation with zinc is initiated. Zinc deficiency can compromise immune function and increase the risk of infection, affecting an estimated 30% of the global population, predominantly but not entirely in developing countries . Several studies have supported this role for zinc deficiency being associated with immunosuppression, specifically in pediatric populations . This is particularly critical today, when the world is battling a global pandemic without vaccines or medications that have been demonstrated to be effective at this time. Zinc deficiency has been linked to an increased likelihood for contracting viral infections and duration of illness. At a cellular level, zinc deficiency has been associated with increased oxidative stress, increased DNA damage, disruptions to DNA repair mechanisms, impaired macrophage function, and inhibited neutrophil function A study in children aged one month to five years old demonstrated clinical signs of improvement (shorter length of illness, improved respiratory rate, and increased oxygen saturation) when zinc supplementation was incorporated into the children's treatment program compared to the controls (non-supplemented group) . WHO's report expounded upon the benefits of zinc supplementation in children. A review by Jayawardena et al. summarized the benefits of supplementation with vitamins and trace minerals on immunity in viral respiratory disorders . The results of their systematic review indicate that supplementation with zinc may be effective in the prevention and reduction of symptoms related to viral infections. Another meta-analysis examined RCTs that provided zinc supplementation to determine if they had an effect on respiratory tract infections in children under five years of age concluded that supplementation reduced the frequency and severity of respiratory illnesses . A randomized control trial of zinc supplementation in children found that zinc supplementation reduced the incidence of acute respiratory illnesses . Supplementation with zinc has been shown to significantly improve infant and children's ability to fight off infection in developing countries and increases the likelihood that they will survive such an infection8. For the reasons that we have described above, we ask that the committee consider studies that utilized supplementation of zinc for the age range covered by this consultation. We also ask that the committee consider adding respiratory illnesses and duration of illness to the list of potential outcomes in

	light of some of the work that we have highlighted in our comments. (1) Wu D, Lewis ED, Pae M, Meydani SN (2019). Nutritional modulation of immune function: analysis of evidence, mechanisms, and clinical relevance. Frontiers in Immunology, 9(3160). doi: 10.3389/fimmu.2018.03160. (2) Caulfield, L. E., Zavaleta, N., Shankar, A. H., & Merialdi, M. (1998). Potential contribution of maternal zinc supplementation during pregnancy to maternal and child survival. The American Journal of Clinical Nutrition, 68(2), 499S–508S. doi:10.1093/ajcn/68.2.499s (3) Acevedo-Murillo JA, Garcia-Leon ML, Firo-Reyes V, Santiago-Cordova JL, Gonzalez-Rodriguez AP, Wong-Chew RM (2019). Zinc supplementation promotes a Th1 response and improves clinical symptoms in fewer hours in children with pneumonia younger than five years old. A randomized controlled clinical trial. Frontiers in Pediatrics, 7(431). doi.org/10.3389/fped.2019.00431 (4) https://apps.who.int/iris/bitstream/handle/10665/42716/9241546123.pdf;jsessionid=1972B2AD667A4AB0CA7ECD30DA630E5D?sequence=1 (5) Jayawardena R, Sooriyaarachchi P, Chourdakis M, Jeewandara C, and Ranasinghe P (2020). Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 14(367-382). https://doi.org/10.1016/j.dsx.2020.04.015. (6) Aggarwal R, Sentz, Miller MA (2007). Role of zinc administration in prevention of childhood diarrhea and respiratory illnesses: a meta-analysis. Pediatrics, 119(6):1120-1130. https://doi.org/10.1542/peds.2006-3481.
Please provide any final thoughts or comments below.	Importance of Dietary Supplements The World Health Organization estimated that traditional cases of seasonal influenza resulted in three to five million hospitalizations and almost 650,000 deaths annually . The outbreak of the coronavirus, COVID-19, is no exception with its significant impact on the respiratory system. There is mounting data in support of a beneficial role for supplementation with specific vitamins and minerals in reducing the duration of respiratory infections, in both children and adults. Zinc plays a critical role in growth and maintenance of a healthy immune system. Children that are zinc deficient are more prone to respiratory illnesses than those that are not and supplementation with zinc reduced the incidence of acute respiratory illness . Zinc and vitamin D are essential for antibody production, but their intake is often inadequate when consumed through the diet alone . As previously discussed, sources of vitamin D are often found to be deficient in both developing countries and industrialized nations, including in the United States where almost 10% of the population was at risk for deficiency13. Inadequate intake of micronutrients can negatively impact the body's ability to fight off and recover from illness, which is especially critical considering the global health crisis from COVID-19. Ideally, individuals, including pediatric populations would consume an optimal intake of these critical nutrients through their diet, however this has yet to be achieved. Therefore, it is essential that dietary supplements are considered in the studies supporting and recommendations resulting from the FAO/WHO public consultation. Conclusion We support the current review of the recommended levels of vitamin D, zinc and calcium by FAO/WHO. We appreciate your consideration of our comments, particularly those pertaining to the importance of appropriate supplementation of micronutrients and vitamins that can support the

	body’s natural defenses against infection in susceptible populations, such as children aged 0-36 months. Thanks for your consideration of this matter.

Survey response	
Family/last name	ter Borg
Given/first name	Sovianne
Organization/affiliation	National Institute for Public Health and the Environment (RIVM)
Sector	Government
Sector [Other]	
Country	Netherlands
Country [Other]	
Key questions and health outcomes	Why is dose-response no suggested method for calcium?
Additional comments	For vitamin D, studies are excluded if the effect cannot be separated from those of calcium. Will you do the same for studies on calcium for which the effect of vitamin D cannot be separated? As mentioned in vitamin D, is there interest in the relation with COVID-19 infections, severity and symptoms?
Key questions and health outcomes	
Additional comments	For vitamin D, in case of insufficient data for children 0-36 mo, it was decided to expand the literature search to adults up to 60 years of age. We however are concerned that data of older adults, even up to 60 years, may not be suitable, as characteristics such skin properties (vit d conversion) differ. Although we realize that the focus is on vitamin d intake, oral vitamin D dose-response curves may be limited (?) and vitamin D injection may provide additional insight. We therefore suggest not to exclude these studies beforehand. Dose-response data is very nice to use. In your proposal, you only suggest this method for the minimum requirements, so adverse effects associated with 'low' intakes. Why not also try to use this method for the other side of the distribution: adverse effects related to 'high' intakes. In fact, the dose-response will be somehow U-shaped.
Key questions and health outcomes	Why are dose-response curves not included for zinc? Interaction zinc and copper, this is only mentioned regarding the UL, but it may also be important for the DRI at the other side of the distribution (requirement)
Additional comments	As mentioned in vitamin D, is there interest in the relation with COVID-19 infections, severity and symptoms?
Please provide any final thoughts or comments below.	We noticed some very interesting research questions and we are very curious to see the results. Kind regards, S. ter Borg and J. Verkaik-Kloosterman

Survey response	
Family/last name	Bahmanpour
Given/first name	Salmeh
Organization/affiliation	Nutrition Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
Sector	Academic/research
Sector [Other]	
Country	Iran (Islamic Republic of)
Country [Other]	
Key questions and health outcomes	what is the difference between physiological- and clinical- dose of calcium in children age 0-36 months? Which recommendation is more reliable and Evidence-Based for calcium requirement in children age 0-36 months; RDA(Recommended Dietary Allowance ,RNI(Reference nutrient intake), AI(Adequate Intake), Codex, or EUD(EU Directive)? Does disease-specific formulations meet the needs for calcium during conditions like celiac disease or enteral nutrition? what are health benefits and adverse effects of Plant-based sources of calcium in children age 0-36 months?
Additional comments	The EAR and RDA of calcium was 500 mg/day and 700 mg/day, respectively, for children 1 to 36 monthsof age. The calcium need for bone growth in children 0-36 month is 210-500 mg per day is beneficial to achieving long-term increases in bone mineralization. Calcium is excreted in the urine and feces, although up to about 182 mg (average, 60 mg) may be lost daily from the skin, especially with extreme sweating . Of the calcium that is filtered, most is reabsorbed by the kidneys such that urinary calcium losses range from about 100 to 240 mg (2.5–6 mmol) per day, with an average of about 170 mg. Fecal losses of calcium from endogenous sources (the sloughing of mucosal cells and calcium that is not reabsorbed from digestive juices—saliva, gastric juice, pancreatic juice, and bile) range from about 45 to 100 mg (1.12–2.5 mmol) per day. Overall, calcium absorption in averages about 25% to 30%. Calcium absorption from calcium supplements (providing 250 mg of calcium) varies from about 27% to 39%, depending upon the specific calcium salt used in the supplement, the amount of calcium ingested, and whether it is consumed under fasting conditions or with food; ingestion with food generally enhances absorption. Absorption also tends to be higher when calcium is consumed in amounts less than 500 mg About 4% to 10% (or ~8 mg) of dietary calcium is absorbed by the colon each day.
Key questions and health outcomes	what is the effect of vitamin D intake on serum 25(OH) D concentration?
Additional comments	The recommendations, which assume minimal sun exposure, suggest an intake of 600 IU (15 μg) of vitamin D for children (age

	1 year and older), adolescents, and adults including women who are pregnant or lactating. By which achieving the target level of≥20ng/mL for 25(OH)D. An intake of at least 1000 IU of vitamin D is essential to maintain levels of 25(OH)D >30ng/mL.
Key questions and health outcomes	what factors affect zinc absorption from meals and whole diet? what are the routes for endogenous losses and amount of zinc loss?
Additional comments	Several factors influence the efficiency of zinc absorption and contribute to its relatively wide range of absorption (12 to 60%). - the absorption of zinc increases as its physiologic status decreases, - zinc availability from soy and wheat may be improved by the addition of casein, cysteine, or histidine, to which zinc binds preferentially (a beneficial chelation) - phytate present in grains and legumes can bind zinc and decrease its absorption. - Zinc absorption is also decreased by substances such as oxalic acid and polyphenols, such as the tannins. - High dietary fiber intake may also decrease zinc absorption - an iron-to-zinc intake ratio of 2:1 or higher substantially reduces zinc absorption in humans. - less available as zinc sulfate and zinc carbonate - more bioavailable as amino acid chelates (e.g., zinc alanine, zinc glycine) and as zinc gluconate. - Zinc absorption appears to be somewhat positively influenced by the presence of meat. - Ligands or chelators including organic acids (like citric acid and picolinic acid) may enhance the absorption of zinc. - high fiber content of the diet and low meat intake. - Folate (a B vitamin) supplements may negatively impact zinc absorption. Overall, about 20% to 30% of zinc is absorbed from diet. However, fractional zinc absorption varies from approximately 10% to 80%; at higher intakes (such as 20 mg or more) absorption diminishes, whereas at lower intakes absorption increases. In contrast to intestinal zinc losses, renal and skin (dermal) losses of zinc, as well as zinc losses in semen and menses, are relatively constant and small. Most zinc filtered by the kidneys is reabsorbed by the tubules. About 0.3 to 0.7 mg of zinc/ day is typically excreted in the urine. The zinc appearing in the urine is believed to be derived from the small percentage of plasma zinc that is complexed with histidine and cysteine. Zinc losses of ~0.4 to 0.6 mg/day occur with exfoliation of skin and with sweating. Other minor routes of zinc loss include (for men) semen (0.1 mg/day) and (for women) menses (0.1 mg/day). Hair contains ~0.1 to 0.2 mg zinc/g of hair
Please provide any final thoughts or comments below.	

Survey response	
Family/last name	Leemhuis
Given/first name	Christel
Organization/affiliation	Australian Government Department of Health
Sector	Government
Sector [Other]	
Country	Australia
Country [Other]	
Key questions and health outcomes	Comments on Key Questions • Australia supports the comprehensive key questions set out in the document for deriving requirements and upper levels for calcium. • It is wise to anticipate that data and evidence may not be sufficiently available to directly determine nutrient requirements for calcium in the population group of interest i.e. 0–36 months. The scoping materials refer to expanding the age range to 9 years or beyond with the possible need to use extrapolation methods to derive requirements for 0–36 months. • Australia notes that several extrapolation methods are used by authoritative bodies around the world to derive nutrient requirements for this age group. This includes extrapolating data for only some components in factorial computations when these data are not directly available for the age group. Australia considers it important to determine the appropriate type and equation for extrapolation methods before decisions are made to use this methodology. • Reference is made in the scoping materials to ongoing work to obtain global representative data on the composition and volume of breast milk (to what age range would this apply?). • Australia observes that nutrient requirements established for infants 0–
Additional comments	Methodology for arriving at revised Nutrient Reference Values • The Australian Government supports the proposed approach of FAO/WHO for deriving nutrient requirements for children aged 0-36 months. The approach also aligns with the process adopted in Australia to update the 2006 Australia and New Zealand Nutrient Reference Values. • Australia has commenced a priority driven review of the 2006 Australia and New Zealand Nutrient Reference Values (NRVs). The NRVs detail the recommended amounts of macronutrients and micronutrients required for difference ages and sexes to maintain nutritional adequacy, avoid toxicity and chronic disease. • The first phase of the review includes selected sodium and iodine NRVs. Phase 2 will investigate adequate intake (AI) across all nutrients for infants aged 0-12 months and selected fluoride NRVs. The AI for infants will be based on the composition of breastmilk from healthy mothers, using average daily intake volume and updated reference weights. • Governance structures have been developed to ensure this work delivers reliable and practical advice for the populations of interest. • The NHMRC has established nutrient specific expert working groups to provide advice and guidance

	to the NHMRC on the review of the evidence and develop the nutrient specific NRVs. The expert working groups are overseen by a government Steering Group and a Steering Group Advisory Committee. • To support the review of the NRVs, a pilot methodological framework was developed and can be accessed at https://www.nrv.gov.au/. The framework aims to ensure broad stakeholder support and confidence in the recommendations of subsequent nutrient reviews through inclusion of methodologies and approaches that support the objectives of consistency, transparency and efficiency. • The Framework is designed for application across a range of nutrients, providing high-level guidance that can be applied to all nutrients under review. • Evidence will be evaluated through the GRADE process (Grading of Recommendations, Assessment, Development and Evaluation). GRADE is an internationally recognised approach to rate the quality of evidence and the strength of recommendations and is considered the standard in guideline development. As per GRADE processes, risk of bias will be assessed by appropriate methods. NHMRC and its expert working groups are currently considering risk of bias tools such as Cochrane Risk of Bias 2.0. • Phase 1 of this work is expected to be completed at the end of 2022 and Phase 2 in 2023.Multidisciplinary and multi-institution research is often the key to scientific advancement.
Key questions and health outcomes	Comments on Key Questions • Australia supports the comprehensive key questions set out in the document for deriving requirements and upper levels for vitamin D. • It is wise to anticipate that data and evidence may not be sufficiently available to directly determine nutrient requirements for vitamin D in the population group of interest i.e. 0–36 months. The scoping materials refer to expanding the age range to 9 years or beyond with the possible need to use extrapolation methods to derive requirements for 0–36 months. • Australia notes that several extrapolation methods are used by authoritative bodies around the world to derive nutrient requirements for this age group. This includes extrapolating data for only some components in factorial computations when these data are not directly available for the age group. Australia considers it important to determine the appropriate type and equation for extrapolation methods before decisions are made to use this methodology. • Reference is made in the scoping materials to ongoing work to obtain global representative data on the composition and volume of breast milk (to what age range would this apply?). • Australia observes that nutrient requirements established for infants 0–
Additional comments	Methodology for arriving at revised Nutrient Reference Values • The Australian Government supports the proposed approach of FAO/WHO for deriving nutrient requirements for children aged 0-36 months. The approach also aligns with the process adopted in Australia to update the 2006 Australia and New Zealand Nutrient Reference Values. • Australia has commenced a priority driven review of the 2006 Australia and New Zealand Nutrient Reference Values (NRVs). The NRVs detail the

	recommended amounts of macronutrients and micronutrients required for difference ages and sexes to maintain nutritional adequacy, avoid toxicity and chronic disease. • The first phase of the review includes selected sodium and iodine NRVs. Phase 2 will investigate adequate intake (AI) across all nutrients for infants aged 0-12 months and selected fluoride NRVs. The AI for infants will be based on the composition of breastmilk from healthy mothers, using average daily intake volume and updated reference weights. • Governance structures have been developed to ensure this work delivers reliable and practical advice for the populations of interest. • The NHMRC has established nutrient specific expert working groups to provide advice and guidance to the NHMRC on the review of the evidence and develop the nutrient specific NRVs. The expert working groups are overseen by a government Steering Group and a Steering Group Advisory Committee. • To support the review of the NRVs, a pilot methodological framework was developed and can be accessed at https://www.nrv.gov.au/. The framework aims to ensure broad stakeholder support and confidence in the recommendations of subsequent nutrient reviews through inclusion of methodologies and approaches that support the objectives of consistency, transparency and efficiency. • The Framework is designed for application across a range of nutrients, providing high-level guidance that can be applied to all nutrients under review. • Evidence will be evaluated through the GRADE process (Grading of Recommendations, Assessment, Development and Evaluation). GRADE is an internationally recognised approach to rate the quality of evidence and the strength of recommendations and is considered the standard in guideline development. As per GRADE processes, risk of bias will be assessed by appropriate methods. NHMRC and its expert working groups are currently considering risk of bias tools such as Cochrane Risk of Bias 2.0. • Phase 1 of this work is expected to be completed at the end of 2022 and Phase 2 in 2023.Multidisciplinary and multi-institution research is often the key to scientific advancement.
Key questions and health outcomes	Comments on Key Questions • Australia supports the comprehensive key questions set out in the document for deriving requirements and upper levels for zinc. • It is wise to anticipate that data and evidence may not be sufficiently available to directly determine nutrient requirements for zinc in the population group of interest i.e. 0–36 months. The scoping materials refer to expanding the age range to 9 years or beyond with the possible need to use extrapolation methods to derive requirements for 0–36 months. • Australia notes that several extrapolation methods are used by authoritative bodies around the world to derive nutrient requirements for this age group. This includes extrapolating data for only some components in factorial computations when these data are not directly available for the age group. Australia considers it important to determine the appropriate type and equation for extrapolation methods before decisions are made to use this

	methodology. • Reference is made in the scoping materials to ongoing work to obtain global representative data on the composition and volume of breast milk (to what age range would this apply?). • Australia observes that nutrient requirements established for infants 0–
Additional comments	Methodology for arriving at revised Nutrient Reference Values • The Australian Government supports the proposed approach of FAO/WHO for deriving nutrient requirements for children aged 0-36 months. The approach also aligns with the process adopted in Australia to update the 2006 Australia and New Zealand Nutrient Reference Values. • Australia has commenced a priority driven review of the 2006 Australia and New Zealand Nutrient Reference Values (NRVs). The NRVs detail the recommended amounts of macronutrients and micronutrients required for difference ages and sexes to maintain nutritional adequacy, avoid toxicity and chronic disease. • The first phase of the review includes selected sodium and iodine NRVs. Phase 2 will investigate adequate intake (AI) across all nutrients for infants aged 0-12 months and selected fluoride NRVs. The AI for infants will be based on the composition of breastmilk from healthy mothers, using average daily intake volume and updated reference weights. • Governance structures have been developed to ensure this work delivers reliable and practical advice for the populations of interest. • The NHMRC has established nutrient specific expert working groups to provide advice and guidance to the NHMRC on the review of the evidence and develop the nutrient specific NRVs. The expert working groups are overseen by a government Steering Group and a Steering Group Advisory Committee. • To support the review of the NRVs, a pilot methodological framework was developed and can be accessed at https://www.nrv.gov.au/. The framework aims to ensure broad stakeholder support and confidence in the recommendations of subsequent nutrient reviews through inclusion of methodologies and approaches that support the objectives of consistency, transparency and efficiency. • The Framework is designed for application across a range of nutrients, providing high-level guidance that can be applied to all nutrients under review. • Evidence will be evaluated through the GRADE process (Grading of Recommendations, Assessment, Development and Evaluation). GRADE is an internationally recognised approach to rate the quality of evidence and the strength of recommendations and is considered the standard in guideline development. As per GRADE processes, risk of bias will be assessed by appropriate methods. NHMRC and its expert working groups are currently considering risk of bias tools such as Cochrane Risk of Bias 2.0. • Phase 1 of this work is expected to be completed at the end of 2022 and Phase 2 in 2023.Multidisciplinary and multi-institution research is often the key to scientific advancement.
Please provide any final thoughts or comments below.	The Australian Government Department of Health welcomes the opportunity to provide comment on the Scoping materials for updating FAO/WHO nutrient requirements for children aged 0-36 months. In

	consultation with the National Health and Medical Research Council (NHMRC) and Food Standards Australia New Zealand (FSANZ), the Department of Health has also submitted information on the approach currently being undertaken in Australia to updating the 2006 Australia and New Zealand Nutrient Reference Values. Opportunities for further collaboration • The Australian Government supports collaborative approaches to health and medical research. In recognition of the similar approaches and work currently in progress by both FAO/WHO and the NHMRC, opportunities for future collaboration would be welcomed. • Further information on the review of Nutrient Reference Values for Australia and New Zealand can be accessed at https://www1.health.gov.au/internet/main/publishing.nsf/content/nutrient-ref-values.

Survey response	
Family/last name	ACAKPO
Given/first name	Alfred
Organization/affiliation	Secretariat Permanent du Conseil de l'Alimentation et de la Nutrition (SP/CAN)
Sector	Government
Sector [Other]	
Country	Benin
Country [Other]	
Key questions and health outcomes	Q4: What nutrients (micronutrients/macronutrients) decrease the efficiency of absorption of calcium ?
Additional comments	Populations: Obese will be included / studied particularly as the efficiency of absorption in that group depend on gastritis/ulcer. Also many obeses suffered from hypocalcemia
Key questions and health outcomes	
Additional comments	
Key questions and health outcomes	
Additional comments	
Please provide any final thoughts or comments below.	

Survey response	
Family/last name	LADINO
Given/first name	LILIANA
Organization/affiliation	Universidad El Bosque
Sector	Academic/research
Sector [Other]	
Country	Colombia
Country [Other]	
Key questions and health outcomes	
Additional comments	
Key questions and health outcomes	Vitamin D2 is equivalent to Vitamin D3?
Additional comments	As the current scientific evidence has been shown only vitamin D3 (cholecalciferol) should be considered a source of vitamin D. Vitamin D2 (ergocalciferol) should not be consider or the dosage should be different between D3 and D2. Many human studies have shown that vitamin D3 is more effective with respect to supporting serum vitamin D levels than vitamin D2.
Key questions and health outcomes	
Additional comments	
Please provide any final thoughts or comments below.	The requirements in children aged 0-36 months should be based on current scientific evidence: Am J Clin Nutr. 1998 Oct;68(4):854-8. J Clin Endocrinol Metab. 2004 Nov;89(11):5387-91. J Clin Endocrinol Metab. 2011 Apr;96(4):981-8. doi: 10.1210/jc.2010-0015. Epub 2011 Feb 2. Am J Clin Nutr. 2006 Oct;84(4):694-7. Proc Nutr Soc. 2017 Aug;76(3):392-399. doi: 10.1017/S0029665117000349. Epub 2017 Mar 28. Endocr Pract. 2018 Oct 5. doi: 10.4158/EP-2018-0415. [Epub ahead of print] J Clin Endocrinol Metab. 2016 Aug;101(8):3070-8. doi: 10.1210/jc.2016-1871. Epub 2016 May 18. Endocrinology. 2016 Sep;157(9):3384-7. doi: 10.1210/en.2016-1528. J Clin Endocrinol Metab. 2016 Aug;101(8):3070-8. doi: 10.1210/jc.2016-1871. Epub 2016 May 18.

Survey response	
Family/last name	Office of Global Affiars
Given/first name	Multilateral Affairs
Organization/affiliation	HHS
Sector	Government
Sector [Other]	
Country	United States of America
Country [Other]	
Key questions and health outcomes	Calcium requirements, question 1, consider adding “teeth” when speaking of bone growth and consider vitamin D status and or intake, when posing this question. We would also like further explanation as to why bone strength and growth are being considered as the sole impact of hypocalcemia. Calcium requirements, question 3, How are the effects of health conditions, such as EED, on efficiency of absorption of calcium being considered?. There are different types of calcium sources with distinct bioavailability rates, e.g., carbonate vs citrate. Furthermore, the effects of excess intake of calcium in other minerals is not mentioned, and should be part of the discussion. When reviewing the study criteria, if healthy children 0 – 9 years are included as potential populations included, then life stage of this age range should be considered when interpreting results for 0 – 36 month olds. Also, should the health outcomes in the study criteria include health outcomes mentioned in the key questions? Consider adding fractures and bone mineral density to the list of adverse effects identified in the upper calcium limits outcomes. What is the metabolic justification of extrapolating results from pre-pubertal children, considering that the metabolism of infants and young children may be different?
Additional comments	Overall, regarding the sources of calcium, include supplemental calcium so that all sources are captured regarding the intake. Lastly, for all systematic reviews, list any language restrictions on literature searches.
Key questions and health outcomes	In reference to the anticipated approach, vitamin D is mostly synthesized through exposure of the skin to sun light. In a dose-response approach, both requirements and excess might depend on geographic location, outdoor activities, and race. Such factors should be taken into account, and can be very difficult to have global values to accurately depict such differences. How are exposure to sun and race going to be weighed for the RNI recommendations of the 0-36 months old children? A few thoughts for all questions covered in this section, please clarify that WHO will be looking at race/ethnicity and not just ethnicity, as it is not clear if WHO is using the words interchangeably or not. Also, consider adding a sub-group analysis by skin color/darker high risk and a sub-group analysis by air quality.

	Secondly, should a key question in the vitamin D section relate to the status of a physiological effect, as with Calcium and bone growth? Physiological measures of vitamin D status are indicated in outcomes, but it is not explicit in the key questions among those proposed for vitamin D analysis. Lastly, the population for the requirements questions includes healthy pregnant or lactating women and their offspring. Will maternal intake (including supplements) and status be taken into account? For example, when analyzing results by breastfeeding status, would vitamin D supplement dosage in the lactation mother, or human milk composition be taken into consideration? Vitamin D requirements, question 1, provide more elaboration on the health outcomes that will be measured and to also consider adding infection status (ex. vitamin D negative acute phase reactant) to the planned subgroup analyses. Vitamin D requirements, question 2 and 3, consider including calcium intake and ethnic groups in the planned subgroup analyses for key questions. Vitamin D requirements, question 3, the effect or association of vitamin D intake on serum (OH) D concentrations is specified in the previous question. In the population study criteria, there is a comment on question 3, the reasoning for excluding premature infants in the assessment is understood, yet with increasing efforts and improvements in premature infant survival, will this become an increasing limitation to the guidance over time? In an ideal situation, supplemental guidance would be provided for this population. When it comes to the intervention study criteria, “valid biomarker measurement of vitamin D intake, i.e. 25(OH)D” should be revised to say vitamin D status, and vitamin D can be endogenously synthesized. “Analytical method for determining circulating 25(OH)D (including by calibration to NIST standard, etc. where appropriate)” should also analyze by participation in external quality assurance program. As far as the outcomes in the study criteria, will biomarkers be considered when evaluating the evidence on other health outcomes? The effect of inflammation on biomarkers of vitamin D status should be added to the list of additional background reviews to be conducted.
Additional comments	Overall, it is important to consider studies with children who are not affected by acute illness. When discussing sun/UV-B exposure, specify if mothers are heavily covered by clothing. Whether infant and children under 3 years are or are not heavily covered should be considered when analyzing the data.. It seems as though the evidence reviewed from the included studies might include participants from different regions with potentially variable vitamin D status. Will there be a sub-group analysis based on the baseline status of the participants (or mothers, if they are included in the studies)?
Key questions and health outcomes	Zinc requirements, questions 1-3, make a distinction between routine physiologic losses and pathological losses (populations with high frequency of diarrhea, etc.). In regards to questions 1 and 2, question 2

	could be more specific and it is unclear how this question is related to the sub-question 2a. Perhaps question 2 is meant to be a sub-question for question 1, with question 2a as a main question? Zinc requirements, question 5, there is reference to the factors that affect zinc absorption from meals and whole diets. Will nutrient-nutrient interaction be considered in this context? (Note: Under Zinc: upper limits, absorption/status of other minerals in the context of higher vs. lower levels of zinc intake is considered, but not sure if Q5 would consider the vice-versa (i.e. effect of other nutrients on zinc absorption)). Secondly, it is not clear if iron intake/status would be taken into consideration on just key question 5a or others as well. On should consider incorporating this concept into other key questions when possible. The effect of inflammation on zinc metabolism and biomarkers of intake or status should be added to the list of additional background reviews to be conducted.
Additional comments	Lastly, the section on Vitamin D noted subgroup analyses, are there important subgroup analyses that should be noted for zinc. For example, it may be beneficial to look at subgroups by age within the 0-36 month range, or at least to look at the 0-6 month range distinctly?
Please provide any final thoughts or comments below.	Note recent work relevant to developing the recommendations, such as; The National Academies of Sciences Report: "Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease Endpoints", National Academies Press (US) 2017 August 3. "DRI Dietary Reference Intakes Calcium and Vitamin D", National Academies Press (US) 2010, "USDA Scientific Report of the 2020 Dietary Guidelines Advisory Committee"; "Feeding Infants and Children from Birth to 24 Months: Summarizing Existing Guidance (2020)" The National Academies Press July 2020. The United States also notes that existing data on composition of Human Milk is not robust and would caution basing updated NRV recommendations based on current data sets. While these recommendations are being updated as new composition data is developed, that data is not yet ready for work on Vitamin D, Calcium and Zinc. Note that the work to update United States Dietary Guidelines 2020 referenced above, for the first time is to focus recommendations for birth to 24 months and has found in some cases human milk is not sufficient to meet requirements after 6 months of age. The Interagency Committee on Human Research is the federally recognized body where U.S. Dietary Requirement/DRI studies are organized. More international cooperation on co-supporting Dietary Requirement/DRI studies would be valuable. For example, the. The U.S. government and Health Canada have in the past pooled resources to accomplish these studies. United States and Canadian researchers have developed a new kind of DRI/Dietary value called a "CDDR" (Chronic Disease Risk Reduction Intake), which is the range of nutrient values that could either increase or decrease future chronic disease risk. This would clearly be

	important in children, given the DOHAD (Developmental Origins of Health and Disease) hypothesis. Have the authors of this document considered whether there is sufficient evidence to identify a CDDR for any of these nutrients in this age group? A CDDR is different from a UL, which is discussed. ULs are normally based on acute adverse events, whereas CDDRs look out farther over time, often involve a chronic disease biomarker, and may be either adverse or beneficial. Consider adding questions, since this is an important developmental period, about positive and negative chronic disease DRIs for these nutrients, due to the fact that adverse events for UL are usually acute. The references below show how CDDRs were applied to the nutrient sodium and the methods and guiding principles for their use from NASEM: • https://www.nationalacademies.org/news/2017/08/new-report-recommends-methods-and-guiding-principles-for-developing-dietary-reference-intakes-based-on-chronic-disease • https://www.nationalacademies.org/news/2019/03/sodium-and-potassium-dietary-reference-intake-values-updated-in-new-report

Survey response	
Family/last name	Inez Schoenmakers, PhD and Professor William D Fraser, BSc MB ChB MD FRCPath Eur Clin Chem
Given/first name	
Organization/affiliation	University of East Anglia
Sector	Academic/research
Sector [Other]	
Country	The United Kingdom of Great Britain and Northern Ireland
Country [Other]	
Key questions and health outcomes	
Additional comments	
Key questions and health outcomes	
Additional comments	We thank the WHO/FAO for the opportunity to contribute to the review of the working group for the update of FAO/WHO requirements and upper levels of calcium, vitamin D and zinc. Our expertise lies in clinical and basic research of the role of calcium and vitamin D in human health, particularly in relation to skeletal health. We have considered the following documentation: - Scoping materials for updating FAO/WHO nutrient requirements for children aged 0-36 months

	- The associated paper Vitamin D and Calcium in Children 0-36 Months: A Scoping Review of Health Outcomes. By Chung M, Ruan M, Cara KC, Yao Q, Penkert LP, Chen J. AJCN 2020 We would like to suggest to the working group to consider the following points as part of the review process. Point are given by section of the document 'Scoping materials for updating FAO/WHO nutrient requirements for children aged 0-36 months'. Study inclusion criteria Throughout the document, the population included in the review is defined as 'generally healthy' (with some exceptions). Unclear is whether this includes or excludes data pertaining to children with common ailments that affect infants and small children and which may influence bio availability of nutrients and requirements. For the nutrients under consideration the most relevant are: - Intestinal parasites and intestinal bacterial overgrowth - Diarrheal diseases - Infectious diseases common in early childhood - Factors affecting iron status and iron-deficiency anemia - Cath-up growth Calcium/Q2 & Vitamin D Q1 & 2: In the section on calcium, the aim appears to be to assess factors determining the balance & retention of calcium. However in other sections (Vitamin D Q1 & 2) only absorption is listed as an outcome. Since vitamin D has wider regulatory functions in calcium and bone metabolism beyond calcium absorption alone, outcomes should also include studies evaluating calcium balance and retention. Calcium/Q3: bio-availability of calcium differs between breast milk and formula and needs to be considered Calcium/outcomes: All outcomes included are related and limited to calcium balance. No skeletal and other health outcomes are considered. Was this omitted because few new studies were published since the last WHO/FAO and IOM/NAM updates on calcium requirements? To note: (1) in non-Western populations, nutritional rickets and osteomalacia is also found in children with low calcium intakes (i.e. not only in children with vitamin D deficiency). This needs to be to be considered as an outcome. (2) Both very low calcium intakes and vitamin D deficiency is associated with an increased risk of hypocalcemia and secondary hyperparathyroidism. The complications of hypocalcemia (seizures,

	tetany and when chronic, cardiomyopathy) are often misdiagnosed. Diagnosis of hypocalcemia is depends on the access to and provisions through health care systems in place and is often undiagnosed in low resource settings. Therefore, it seems appropriate to include both (biochemically diagnosed) hypocalcemia and its symptoms in this review. (3) The link between plasma PTH concentrations (both low and high) and health outcomes in small children is poorly defined, but needs to be considered in the evaluation of calcium and vitamin D requirements, where possible. Calcium/upper limits: - evaluation will be conducted on a number of outcomes but it is however not considered that the symptoms of hypercalcemia can be nonspecific and therefore hypercalcemia is often not, or misdiagnosed. It would be more appropriate to also consider the symptoms of hypercalcemia, being poly-uria, confusion, depression, nausea, vomiting and constipation. - Soft tissue calcification, not only nephrocalcinosis, should be considered. Calcium/background: A review biomarkers of calcium status is included. It is unclear what biomarkers will be considered. Plasma calcium, urinary calcium excretion? Although these biomarkers may be informative in pathological conditions, in generally healthy children these same markers are not very informative of calcium 'status'. Plasma calcium concentrations can therefore not be generally used and urinary calcium is also a poor markers of calcium balance, particularly in young children. Assessment of dietary calcium intake remains the most reliable marker for calcium supply and fraction absorption for bio-availability. Vitamin D/Q1 Planned subgroup analyses: - The frequency of the intake of vitamin D needs to be considered since this influences it's PK profile. - The document does not seems to consider the 'vitamin D equivalent' as a factor, i.e. considering both the intake of vitamin D and 25(OH)D through foods. Dietary 25(OH)D, present in low quantities in food derived from animal sources (particularly meat) has a higher dose-response relationship and this is considered in the vitamin D equivalent. - Breast milk as a source of vitamin D and 25(OH)D is not considered. Although the body of scientific evidence is limited and concentrations are reported to be low unless the mother has a very high vitamin D intake, for many children this is may be the only

	thus important (albeit small) source of vitamin D supply. Compared to other sources, the bioavailability is however high. - Although variations affecting cutaneous synthesis of vitamin D are considered, it remains unclear whether the WHO/FAO will attempt to estimate its contribution to total vitamin D supply and status and/or will base their recommendations on the modeling and assumption of 'minimal cutaneous contributions' (aligned with other public health authorities, e.g. IOM/NAM, SACN) - Factors influencing Sun/UV-B exposure are listed as latitude, time of year assessed. Please add: dress style/skin coverage (clothing and sunscreen) and sun seeking/avoiding habits. - Body composition and body size should be considered in the vitamin D -25OHD relationship and should be considered as a factor/confounder of the relationship of 25(OH)D and health outcomes Vitamin D/Q1 and Q2 - The association between vitamin D status and health outcomes is strongly influenced by other macro and micro nutrients and these need to be considered. Most importantly, these are protein and energy intakes and calcium intake and bioavailability, but also phosphate, magnesium, zinc. Vitamin D/Q3 - Factors listed above in section Vitamin D/Q1 should be considered - Previous exposures should be considered, i.e. vitamin D supply and/or status at baseline of an interventional study since this influences the dose-response - Considering that a large proportion of infants does not receive vitamin D supplementation as recommended, the influence of maternal vitamin D status should be considered as part of this review. Maternal vitamin D status largely determines vitamin D status of the infant in the first weeks/months if the infant does not receive supplementation or is formula-fed. The infant is then predominantly reliant on the stores built up in utero. Cord blood concentration provides a proxy of vitamin D status of the infant. Vitamin D/interventions/exposures - See query re 'minimal cutaneous contributions' - Plasma 25(OH)D is an integrated marker of vitamin D produced in the skin and oral intake and strictly speaking also of the balance between supply and 25(OH)D utilization

	Vitamin D/Outcomes: the following outcomes should be considered to be included: Osteomalacia (seen in children with rickets, but it is a different pathology) and possibly bone pain as a symptom of osteomalacia Calcium absorption and retention Tooth development Hypocalcemia and associated symptoms (see under Calcium/outcomes) PTH Vitamin D/study designs For skeletal outcomes, the evidence base on which recommendations for calcium and vitamin D and target plasma 25(OH)D concentrations were based, were deemed to be 'fair' (IOM/NAM, SACN) . This evidence was partly based on evidence from designs other than RCTs. In view of the etiology of skeletal abnormalities and the fact that these often have non-reversible health consequences, it is accepted that placebo controlled RCT for these health outcomes may not be feasible or ethically acceptable. The exclusion of all types of listed studies designs therefore appears to be overly conservative. Vitamin D/upper limits - This review should consider both the adverse effects of acute and chronic intakes, where possible - Factors needed to be considered include body size and composition and genetic factors - It may be worth mentioning that cutaneous exposure generally does not lead to toxic concentrations of 25(OH)D. Vitamin D/upper limits: outcomes pls also consider to include: - Plasma 25(OH)D over 200 nmol/L - Hypercalcemia and the symptoms of hypercalcemia, being poly-uria, confusion, depression, nausea, vomiting and constipation. - Soft tissue calcification, not only nephrocalcinosis should be considered
Key questions and health outcomes	
Additional comments	
Please provide any final thoughts or comments below.	The requirements in children aged 0-36 months should be based on current scientific evidence: Am J Clin Nutr. 1998 Oct;68(4):854-8. J Clin Endocrinol Metab. 2004 Nov;89(11):5387-91. J Clin Endocrinol Metab. 2011 Apr;96(4):981-8. doi: 10.1210/jc.2010-0015. Epub 2011 Feb 2. Am J Clin Nutr. 2006 Oct;84(4):694-7. Proc Nutr Soc. 2017 Aug;76(3):392-399. doi: 10.1017/S0029665117000349. Epub 2017 Mar 28. Endocr Pract.

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