Appendix B

Consultation dates: 20.04.17 (9am) to 05.05.17 (5pm)

Do you agree the guidance should be placed on the public health static list?			
Stakeholder Organisation / PHAC member	**Agree/Disagree (delete as appropriate)**	**Comments**	**NICE response**
Queen Mary University of London	Disagree	The scope of the guideline has been outdated by the 2016 SACN report on Vitamin D and Health. Prior to this report, a reference nutrient intake (RNI) of 10 micrograms (400 IU) vitamin D per day was set only for groups considered to be 'at risk' of vitamin D deficiency – hence the original scope of PH56. The 2016 SACN report extended this RNI to include everyone in the general UK population aged 4 years and above. Thus, the question of how to increase supplement use in at-risk groups has been superceded by a new imperative, namely to achieve an intake of 10 micrograms (400 IU) vitamin D per day in the general population aged 4 years or more (plus a 'safe intake' of 8.5-10 micrograms [340-400 IU] in younger children). Theoretically one could put this guideline on the static list, and then launch a new guideline with the revised, broader scope – but it would seem more efficient to extend the scope of the current guideline, since the existing committee members are well placed to consider the issues.	Thank you for your comment. Extending the scope of the guideline to include the whole population would be beyond the remit of the Department of Health referral, which refers to developing guidance to help safely implement existing evidence-based recommendations on the prevention of vitamin D deficiency in at-risk groups including infants and children aged under 5, pregnant and breastfeeding women, older people, people with dark skin and those who have limited exposure to the sun. The recently published SACN report on Vitamin D and Health still suggests that the following groups are at increased risk: "those with minimal exposure as a result of not spending time outdoors (e.g. frail or institutionalised people) or habitually wearing clothing that covers most of the skin while outdoors and those from minority ethnic groups with dark skin". However, some of the studies used to form the recommendations considered at risk groups to also contain children aged 18m-3y, those aged 65y and over and women of child bearing age representing pregnant and breastfeeding women. Although a separate RNI is not required for these groups, they are still in need of supplementation and therefore they will remain the focus of this guidance.

			To address these issues we will alter the guideline's title to state that the guideline is for "increasing supplement use in specific population groups" and we will make amendments to the guideline's introductory sections and glossary to ensure readers are aware of SACN's advice on RNI for the whole population.
Newcastle University	Disagree	I don't think you should mothball this guidance yet. The VITAL study (NCT01169259) is running until the end of December 2017 and I would anticipate that at some stage during late 2018 they will publish the results which are likely to affect public health policy with relation to vitamin D profoundly, one way or another. Both SACN and NICE should plan to review guidance in the aftermath of this study being published.	Thank you for your comment. Please note that the guidelines on the static list are reviewed every 5 years to determine whether they should remain on the static list. Stakeholders may also notify NICE of relevant new guidance which may transfer a guideline back to the active surveillance list at any time point. Thank you for drawing our attention to the VITAL study, however this would not be relevant to the guideline's current scope as the association between vitamin D status and health outcomes is a measure that is excluded from the guideline's remit.
Royal College of Midwives	Agree		Thank you for your comment.
National Pharmacy Association	Agree	There is no requirement to update the guidance because no evidence has been found that impacts the current guidance. There are no major studies (ongoing or to be carried out) that have been identified that will impact the current guidance.	Thank you for your comments. We will amend the guideline as stated in the surveillance report to refer to the SACN 2016 report, change in age group and reference nutrient intake.

		No new evidence/intelligence have been identified for most of the recommendations in the guidelines. I agree that the age of children in the overview section of the guidance should be amended to be in line with the SACN 2016 report, i.e. amend from children under five years to children under four years of age. The guidelines refer to SACN 2007 report which should be amended to the SACN 2016 report. Under “Recommendation 1 Increase access to vitamin D supplements “section in the guidelines, “infants and children aged under 5” should be amended to “infants and children aged under 4y” as stated in the SACN 2016 report. There are recommendations under “Recommendation 2 Clarify existing guidance” section in the guidelines, for PHE and the Department of Health to consider any risks to infants from taking a supplement if they are consuming >500ml of infant formula daily, and which supplement would be beneficial. The SACN 2016 report states in section 1.10 that “SACN's remit does not include providing advice on strategies for implementation of its recommendations; i.e., the committee’s role is risk assessment and not risk management”. The Reference nutrient Intake should be amended in the guidelines to “10”.	The SACN report states that there is insufficient data to specify a safe upper limit for single doses of vitamin D in children. The proposed safe intake range is not additional to, but includes, vitamin D intakes obtained from infant formula. The RNI/Safe intake for vitamin D refers to intakes for all dietary sources: natural food sources; fortified foods (including infant formula milk); and supplements. However there is no information to warrant us removing Recommendation 2 stating that PHE and the Department of Health should consider any risks to infants from taking a supplement containing the RNI when they are consuming more than 500ml of infant formula per day. Therefore this recommendation will remain within the guideline.
Public Health England	Agree	We agree that the guideline should be placed on the static list, after it has been refreshed, to reflect the 2016 Scientific Advisory Committee on Nutrition (SACN) report on Vitamin D and Health.	Thank you for your comment

Health Food Manufacturer's Association	Agree		Thank you for your comment
Royal College of Physicians	Agree	The RCP is grateful for the opportunity to respond to the above consultation. We have liaised with our Nutrition Committee and would like to make the following comments. We welcome the NICE initiative in the light of the Scientific Advisory Committee on Nutrition (SACN) advice to DH in 2007. It is important note however that SACN has produced another report in 2016 which has been summarised by the British Nutrition Foundation as follows: • Serum 25(OH)D concentration is an indicator of exposure to vitamin D (i.e., from the diet and skin synthesis). In order to protect musculoskeletal health, it is recommended that the serum 25(OH)D concentration of individuals in the UK should not fall below 25 nmol/L at any time of the year. This level is considered to be a population protective level. • In the UK, population groups at increased risk of having a serum 25(OH)D concentration below 25 nmol/L are those with minimal sunshine exposure as a result of not spending substantial time outdoors (e.g., frail and institutionalised people) or due to the habitual wearing of clothing that covers most of the skin while outdoors. • It is not possible to make a recommendation regarding the amount of sunlight exposure that would be required during the summer to maintain serum 25(OH)D concentration at or above 25 nmol/L in 97.5% of the population during winter because of the number of factors that affect endogenous (skin) vitamin D production. • A Reference Nutrient Intake (RNI) for vitamin D of 10 µg/d is therefore proposed for the UK population aged 4	Thank you for your comment. We will amend information in the guideline on the RNI, as stated in the surveillance report. Extending the scope of the guideline to include the whole population would be beyond the remit of the Department of Health referral, which refers to developing guidance to help safely implement existing evidence-based recommendations on the prevention of vitamin D deficiency and goes on to say that it will focus on at-risk groups including infants and children aged under 5, pregnant and breastfeeding women, older people, people with dark skin and those who have limited exposure to the sun. The recently published SACN report on Vitamin D and Health still suggests that the following groups are at increased risk: "those with minimal exposure as a result of not spending time outdoors (e.g. frail or institutionalised people) or habitually wearing clothing that covers most of the skin while outdoors and those from minority ethnic groups with dark skin". However, some of the studies used to form the recommendations considered at risk groups to also contain children aged 18m-3y, those aged 65y and over and women of child bearing age representing pregnant and breastfeeding women. Although a separate RNI is not required for these groups they are still at in need of supplementation and therefore they will remain the focus of this guidance.

		years and over. This is the amount needed for 97.5% of the population to maintain a serum 25(OH)D concentration of 25 nmol/L or above when UVB sunshine exposure is minimal. • The RNI of 10 µg/d proposed for the whole UK population includes individuals from minority ethnic groups with darker skin. • It is proposed that the RNI is applicable throughout the year, as a precautionary measure, to cover population groups in the UK identified to be at risk of minimal sunshine exposure as well as unidentified individuals in the population with minimal sunshine exposure who would be at risk of 25(OH)D concentrations below 25 nmol/L in summer. • Data are insufficient to set RNIs for infants and children aged 0-3 years. As a precaution, a 'Safe Intake' of vitamin D is therefore proposed for these ages: in the range 8.5-10 µg/d for ages 0 to < 1 year (including exclusively breast fed infants); and 10 µg/d for ages 1 to < 4 years. • Since it is difficult to achieve the RNI/Safe Intake from natural food sources alone, it is recommended that consideration is given to strategies for the UK population to achieve the RNI of 10 µg/d for those aged 4 years and older and for younger children to achieve a Safe Intake in the range 8.5-10 µg/d at ages 0 to < 1 year and 10 µg/d at ages 1 to < 4 years.	To address these issues we will alter the guideline's title to state that the guideline is for "increasing supplement use in specific population groups" and we will make amendments to the guideline's introductory sections and glossary to ensure readers are aware of SACN's advice on RNI for the whole population. .
Sheffield CCG	Agree		Thank you for your comment
Royal College of Nursing	Agree	The RCN welcomes to opportunity to comment on this public health guideline surveillance review on increasing Vitamin D supplements use in at risk group.	Thank you for your comments

		The RCN supports the decision that this guideline should not be updated at this time but just refreshed in line with the Scientific Advisory Committee on Nutrition (SACN) on Vitamin D and Health report. We agree that the guideline should be placed on the static list.	
Lactation Consultants of Great Britain	Disagree	I would ensure that the guideline clarifies the difference between D2 and D3 and the different metabolic effects and efficacy of the two forms of supplement. From reading the recommendations, it is not clear which type of supplement would be used – simply the desired outcome to maintain a serum 25(OH)D concentration ≥ 25 nmol/L. Please see research below.	Thank you for your comments. It is beyond the remit of this guideline to differentiate between D2 and D3. The guideline's remit is to focus on safely implementing existing evidence-based recommendations on preventing vitamin D deficiency and increasing uptake of vitamin D supplement use.
	Page 5 section 2.3	*'The two major forms of vitamin D are vitamin D3 (also referred to as cholecalciferol) and vitamin D2 (also referred to as ergocalciferol). In this report, the term vitamin D refers to both vitamin D3 and D2 unless the specific form is indicated.'* I think this statement is inconsistent in the light of some of the research quoted. The metabolic effectiveness of the two are significantly different, according to the comments in the original guidelines, see the reference P8 section 2.29 below.	Thank you for your comment. We are unable to amend or respond to comments on the SACN Vitamin D and Health report as NICE is only responsible for the publication of its own guidance.
	P8, 2.29	*'Although vitamin D2 undergoes similar metabolic transformations to vitamin D3, it is unclear if all details of regulation and biological activity are identical to those of vitamin D3 (Henry, 2011). Vitamin D2 and its metabolites have a lower binding affinity to DBP than vitamin D3 and its metabolites (Houghton & Vieth, 2006).'* Houghton and Vieth suggest that there are several biological mechanisms that contribute to the superior absorbability and	Thank you for your comment. We are unable to amend or respond to comments on the SACN Vitamin D and Health report as NICE is only responsible for the publication of its own guidance.

		efficacy of Vitamin D3. In the liver, thanks to a particular hepatic enzyme, Vitamin D3 is more readily metabolized into a bioactive form of D that is easily converted to its hormone form in the kidneys. It takes much longer to make this hepatic conversion with Vitamin D2. D2 and D3 are metabolized so differently that they result in “the production of unique biologically active metabolites.” These forms of Vitamin D are not the same, hence this study’s conclusion that ergocalciferol should not be used as a supplement. A study that would have been included in the earlier guidelines is shown below. This also highlights the difference in types of supplementation. Cochrane Database Syst Rev. 2011 Jul 6;(7):CD007470. doi: 10.1002/14651858.CD007470.pub2. **Vitamin D supplementation for prevention of mortality in adults.** Bjelakovic G[1], Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, Bjelakovic M, Gluud C. **Conclusions** (extract) When the different forms of vitamin D were assessed separately, only vitamin D(3) decreased mortality significantly (RR 0.94, 95% CI 0.91 to 0.98, I(2) = 0%; 74,789 participants, 32 trials) whereas vitamin D(2), alfacalcidol, or calcitriol did not. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2173541 There appears to have been an additional significant shift in understanding since all the research quoted above was written. See reference below. This seems to address the research lines of enquiry that were requested in the original guidelines.	

		This is one reference I have found (below), but there may be others that describe the subtlety in dosing and other differentiators.	
		Differential effects of vitamin D2 and D3 supplements on 25-hydroxyvitamin D level are dose, sex, and time dependent: a randomized controlled trial. Hammami MM[1,2], Yusuf A[3]. Conclusions: Effects of D2 and D3 supplements on 25 (OH)D level may be dosing-schedule and sex-dependent. D2-associated reduction in 25(OH)D3 level may be related to total 25(OH)D level rather than being D2-specific. D2 may be 25-hydroxylated faster than D3. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28231782	Thank you for your comment.
	General	I have not seen any recommendations for those individuals with poor fat absorption? Vitamin D may be deficient in those with gluten-sensitive enteropathies and irritable bowel disease, who may have additional requirements for supplementation or a different route of administration. *(Clinical Nutrition – a Functional Approach 2nd edition p139-40)*	Thank you for your comments. Sources of evidence for this guideline are existing evidence-based guidelines and studies that assess the implementation of these recommendations. As there is currently little published evidence around how to implement existing evidence-based recommendations on preventing vitamin D deficiency in this population group we will not be able to add this group at this time.
	General	Calcitriol (D_3) is prescribed for those with renal disease, since such patients are unable to convert D_2 to this active form (ibid)	Thank you for your comment.
	General	Boron may be important in converting 25-(OH)D_3 to 1,25-$(OH)_2D_3$ (ibid)	Thank you for your comment.
		An additional point on **water soluble** Vitamin D.	Thank you for your comments.

		This vitaminer is formed in the skin of their mothers (and in the babies if allowed a little sunshine exposure). This is not widely recognised or communicated. Breastfed babies are uniquely able to access this water-soluble form of Vitamin D that their mother produces, through their mother's breastmilk, in addition to the much more commonly measured fat-soluble form. This may partly explain why the levels of **fat-soluble** Vitamin D in breastmilk appear low, because mothers also provides a water-soluble version to their babies that is not measured currently. (The fat-soluble forms of Vitamin D that the mother produces are also absorbed very efficiently and optimally by the baby.) The inference that breastmilk may not contain "sufficient" vitamin D may not be valid, if the water-soluble fraction is not also taken into account. My concern is that we are not measuring the water soluble fraction, and making recommendations on this basis. If NICE guidelines are not more carefully worded, it may be implied in delivering the recommendations - that breastmilk does not contain sufficient Vitamin D as a whole. My related concern is that this may undermine mothers' confidence in their breastmilk so they may choose to switch to artificial breastmilk substitutes (formula).	This guideline is focusing on safely implementing existing evidence-based recommendations on the prevention of vitamin D deficiency. NICE is not currently aware of any recommendations that exist on water soluble fraction measurement that would help to implement existing recommendation and therefore this will not affect the recommendations at this time. In order to ensure good health among pregnant and breastfeeding women it is felt important that they remain within the guideline. In order for the recommendations to be removed there would need to be published good quality evidence indicating that recommending vitamin D supplementation has an unintended consequence of leading women to switch from breastfeeding to using formula milk. NICE is clearly supportive of the importance of breastfeeding in their guideline CG37 Postnatal care up to 8 weeks after birth and in PH11 Maternal and Child Nutrition which is also highlighted in the "Related NICE guidance" section of the guideline. It is hoped that breastfeeding women could consult such guidelines if concerned about their choice in regard to breastfeeding. According to the original scope of this guideline NICE will not be considering recommendations that cover the fortification of food and drinks with Vitamin D or the relative contribution of dietary and cutaneous vitamin D synthesis to the vitamin D status of the UK population. However it is noted in the guideline that dietary sources of vitamin D are limited and the SACN report notes that it is difficult to achieve the RNI/Safe Intake from natural food sources alone.

		The formula manufacturers will no doubt advertise that their formula contains lots of Vitamin D – even though the forms provided and therefore absorbability may vary widely. (For commercial reasons, formula ingredients tend to be juggled between the cheapest and with the longest shelf life, rather than the most bioavailable.) This is particularly concerning when considering the detrimental impact that artificial breastmilk substitutes have on the baby's immature gut wall and the gut enterocytes where absorption should take place, plus the negative impact on developing a healthy microbiome that would normally maintain and support the health of the enterocytes and immune system. Along with supplementation, as I mentioned in my comments on the first form I submitted, it would be worth providing some education to pregnant and lactating mothers to increase their food sources of Vitamin D. These tend to be nutrient dense but fairly inexpensive foods that provide many other These would provide the normal method of Vitamin D delivery, made much more bioavailable by being filtered optimally, metabolised optimally, dosed optimally and provided optimally to the baby through the mother's own body.	
	Disagree	Please see the detailed explanation of the function and complexity of measuring Vitamin D status and intake in **Marsha Walker: Breastfeeding Management for the Clinician – Using the Evidence. Fourth Edition 2017, pages 42-45.** This selection does not provide detail the water-soluble vitaminer I highlighted in comments form 2, but does provide much	Thank you for your comments. Please see the responses above.

		excellent detail on the complexities and drawbacks of supplementing every breastfed infant. A brief selection of examples include: • Breastfed infants with limited sun exposure have not been shown to develop rickets • The cost of averting a single case of rickets by universally dosing infants with Vitamin D could be between $252, 614 and $958,293 per case (Vitamin D Expert Panel, & Centres for Disease Control and Prevention 2001) **Figures today for the UK are likely to be far higher.** • Approximately 20% of the mothers circulating Vitamin D is transferred to the infant through the mother's milk. • Exclusive breastfeeding results in normal infant bone-mineral content when maternal vitamin D status is adequate; when neonatal stores are normal and when the infant is regularly exposed to sunlight. • Supplementing the mother also reduces the risk of any side-effects from supplementing the infant directly. • Supplementing the infant directly with standard vitamin D preparations (400 IU/day) was associated with a 76% increased risk in urinary tract infections. **I would continue to support recommendations to supplement breastfeeding mothers, but with D_3.** There are many other factors listed that interact and overlap that need to be considered for the mother/infant dyad. **Please refer to Marsha Walker: Breastfeeding Management for the Clinician – Using the Evidence. Fourth Edition 2017, pages 42-45** and take them into account before re-issuing the guidelines.	

		Many thanks.	

Do you have any comments on equalities issues or area excluded from the original scope?		
Stakeholder Organisation / PHAC member	**Comments**	**NICE response**
Queen Mary University of London	The original scope (to increase supplement use in 'at-risk groups') is now outdated, since the RNI of 10 micrograms (400 IU) vitamin D per day has been extended to the general population aged 4 years or more. The scope of this NICE committee therefore needs to be revised to consider what public health action should be taken in order to implement the new SACN recommendation of achieving a RNI of 10 micrograms (400 IU) vitamin D per day for the whole population aged 4 years or more, and achieving a 'safe intake' of 8.5-10 micrograms [340-400 IU] vitamin D in younger children. Given the literature indicating that uptake of over-the-counter supplements is very limited (e.g. Black LJ et al, J Nutr. 2015; 145(5): 969-76), the scope should include a specific remit to consider the case for voluntary / mandatory fortification of food and/or drinks with vitamin D so that the RNI / safe intakes recommended by SACN can be attained by all.	Thank you for your comment. The scope refers to developing guidance to help safely implement existing evidence-based recommendations on the prevention of vitamin D deficiency and goes on to say that it will focus on at-risk groups including infants and children aged under 5, pregnant and breastfeeding women, older people, people with dark skin and those who have limited exposure to the sun. It is beyond the remit of the department of health referral and outside of NICE's remit to make recommendations on mandatory fortification of food and/or drinks. Please note it is specified in the guideline that dietary sources of vitamin D are limited and the SACN report notes that it is difficult to achieve the RNI/Safe Intake from natural food sources alone.
Newcastle University	No comment	Thank you for your comment.
Royal College of Midwives	No comments to make	Thank you for your comment.
National Pharmacy Association	No comment	Thank you for your comment.
Public Health England	No comment	Thank you for your comment.

Health Food Manufacturer's Association	No further comments, other than agreement with the need to update the guidance in line with the 2016 SACN report.	Thank you for your comment.
Royal College of Physicians	No comment	Thank you for your comment.
Sheffield CCG	No comment	Thank you for your comment.
Royal College of Nursing	No comment	Thank you for your comment.
Lactation Consultants of Great Britain	How much training in functional nutrition do the targeted health professionals receive who will be administering these supplements? I do not see any encouragement anywhere for health professionals to recommend adding good sources of Vitamin D3 such as oily fish and meat into their patients' family diet. I understand that these foods would be an issue for vegetarian communities, some of whom may often be at additional risk if they also cover up from the sun or spend little time outdoors, so supplementation in these cases may be essential. However, vegan D3 sources are available.	Thank you for your comment. NICE do not specify the exact level of training that will be needed, however they do list information that should be included in relevant training in Recommendation 9. According to the original scope of this guideline NICE will not be considering recommendations that cover the fortification of food and drinks with Vitamin D or the relative contribution of dietary and cutaneous vitamin D synthesis to the vitamin D status of the UK population. However it is noted in the guideline that dietary sources of vitamin D are limited and the SACN report notes that it is difficult to achieve the RNI/Safe Intake from natural food sources alone.

	Families on very low incomes may also struggle, but nevertheless, cheap, nutrient-dense sources of D3 such as tinned sardines, fresh mackerel fillets, eggs or liver could be suggested. They may not be the most popular foods, which is probably an additional reason why many people are deficient. However, a little education and some user-friendly ways to encourage cooking these foods, would simultaneously increase the target population's wider macro and micronutrient intake, as well as their D3. Is it beyond the scope of NICE to suggest this?	
	Similarly, while it may be a lifestyle approach, might it be helpful for physicians to recommend ten minutes a day in the summer sunshine without sunscreen with face and hands exposed at least (if no history of melanoma), and more minutes in the winter? For individuals with darker skin, the recommendation might be for 20 minutes? This would promote an individual's better understanding of their own natural and effective Vitamin D production; its impact on promoting good health and reducing the risk of a wide range of conditions. An interesting point to note is that when exposed to sunshine, skin also synthesizes vitamin D3 sulfate. This form of vitamin D is water soluble, unlike oral vitamin D3 supplements, which is unsulfated. The water-soluble form can travel freely in thebloodstream, whereas the unsulfated form needs LDL (the so-called "bad" cholesterol) as a vehicle of transport. There is reason to believe that many of the profound benefits of vitamin D are actually due to the vitamin D sulfate. As a result, the oral non-sulfated form of vitamin D might not provide all of the same benefits, because it cannot be converted to vitamin D sulfate Dermatoendocrinol. 2012 Apr 1; 4(2): 109–117. doi: 10.4161/derm.20013 PMCID: PMC3427189	Thank you for your comment. According to the original scope of the guideline NICE will not be considering recommendations that cover length and intensity of sun exposure for different population groups in this guideline. Please note that this is covered in NG34 Sunlight Exposure: risks and benefits which is highlighted under the Related NICE Guidance section.

	Beneficial effects of UV radiation other than via vitamin D production Asta Juzeniene [1, *] and Johan Moan [1, 2] Author information ► Copyright and License information ► Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3427189/	

References

1. Au L; Harris S; Jacques P; Dwyer J; Sacheck J: Adherence to a Vitamin D supplement intervention in urban schoolchildren (2014) Journal of the Academy of Nutrition and Dietetics Volume 114 pp86-90