U.S. FOOD & DRUG ADMINISTRATION

Memorandum

Date: October 14, 2022

From: Division of Food Ingredients
Toxicology Review Branch-Team 1

To: Division of Food Ingredients
Regulatory Review Branch-Team 2
Attention: Lane Highbarger, PhD

Subject: FAP 9A4823: Hogan Lovells US LLP on behalf of Kellogg Company: Use of Vitamin D_3 in breakfast cereals and grain-based nutrition bars.

Introduction

The purpose of this memorandum is to provide a safety review and evaluation of the petition request by the Kellogg Company for the use of vitamin D_3 as a nutrient supplement in breakfast cereals and grain-based nutrition bars. The petition requests the use of vitamin D_3 at levels of up to 560 international units (IU) vitamin D_3 per 100 grams (g) in breakfast cereals, as defined in 21 CFR § 170.3(n)(4), and up to 400 IU vitamin D_3 per 100 g in grain-based nutrition bars[1] (e.g., granola bars).

The petitioner indicates that the intended uses of vitamin D_3 proposed in the submitted food additive petition (FAP) do not pose any human safety concern and meet the "reasonable certainty of no harm" safety standard required for food additives. This safety determination was based on the findings of the 2011 Institute of Medicine (IOM) report on the Dietary Reference Intakes[2] (DRI) for vitamin D.[3]

The safety analysis provided by the petitioner for added exposure to vitamin D_3 from consumption of supplemented breakfast cereals and grain-based bars is based on the following considerations. First, the IOM has established a tolerable upper intake level (UL) for vitamin D for all age groups in 2011. The petitioner also noted that the Food and Drug Administration (FDA) indicated in a 2014 Federal Register Notice (21 CFR Part 172: Federal Register, Vol 79 No 155 pp 46993-46996, August 12, 2014) for vitamin D_3 as a food additive in certain meal replacement beverages that these ULs can serve as the basis for acceptable

[1] While petition uses "grain-based nutrition bars," 21 CFR 172.780 and 101.12 use "grain-based bars" (e.g., breakfast bars, granola bars, rice cereal bars). We consider these terms to refer to the same category of food products. Therefore, for consistency of terminology, we are using "grain-based bars."
[2] The dietary reference intakes (DRI) are a family of established nutrient reference values for "normal healthy persons" in the North American population. These values include the Estimated Average Requirement (EAR), Recommended Dietary Allowance (RDA), tolerable upper intake level (UL) and possibly an adequate intake level.
[3] This 2011 IOM report also included a DRI determinations for calcium.

daily intakes (ADIs) for vitamin D in FAPs.[4] Second, the petitioner identified and reviewed relevant scientific literature published since the 2011 IOM DRI determinations for vitamin D[5] and reported that none of these recently published papers questioned the basis and validity of the IOM-established ULs for vitamin D (studies published between January 1, 2011 through February 25, 2019). Third, the petitioner's estimated daily intakes (EDI) associated with 90th percentile total intake of vitamin D are below its noted ADIs for vitamin D for all age groups. In summary, the petitioner stated that they "determined that there are no new findings that would change IOM's conclusions regarding adverse effects of excessive vitamin D, or that would call the vitamin D UL's established by IOM in 2011 into question."

Safety Evaluations

2011 IOM Vitamin D Safety Determination

In 2011, IOM published a report with updated nutrient reference values for vitamin D (in addition to calcium) (IOM, 2010; IOM, 2011a-d, Ross et al., 2011).[6] To make this determination, IOM conducted a comprehensive examination of available scientific evidence on the association between vitamin D exposure and a range of health outcomes. IOM found a sound scientific basis for the relationship between vitamin D and bone health outcomes, and it served as the foundation for the development of DRIs for vitamin D. However, the role for vitamin D in other chronic health outcomes or conditions could not be established from the available information. Hence, the IOM determined dietary intake guidance levels based on nutrient requirements and limits for vitamin D for bone health for several age and gender life-stage groups. The IOM Recommended Daily Allowance (RDA) or adequate intake (AI),[7] and UL values for vitamin D for various age groups[8,9] are depicted in Table 1. The RDA is the average daily dietary intake level that meets the vitamin D nutrient needs of at least 97.5% of healthy individuals in a population group. The UL is considered the maximum chronic daily intake of vitamin D that is likely to pose no health hazard risk for almost all individuals[10] in the general population.[11,12]

IOM DRI values were developed for the population of "normal healthy persons" in North America and not intended for individuals with specific disease states. Also, the DRIs for vitamin D assume that individuals experience minimal or no sun exposure.

[4] This point reflects the petitioner's interpretation of this 2014 Federal Register Notice discussion of ADIs and ULs.
[5] The 13 references identified by the petitioner as published after the IOM report on DRIs for vitamin D are listed in Appendix 2.
[6] Information on references cited in the main text of this memorandum is located in Appendix 1.
[7] An AI level is estimated rather than an RDA because of limited or insufficient evidence available to development an RDA for an age group. This was the case for vitamin D in infants aged 0 to 12 months.
[8] The UL for vitamin D in infants is based on considerations with respect to the AI exposure estimate, which is a less scientifically rigorous standard than used for an RDA estimate.
[9] The ULs for vitamin D in age groups between 1 to 8 years old, and 9 years old to adults are based on separate considerations with respect to the corresponding RDAs for these groups.
[10] The gender life stages of pregnancy and lactation were considered for females in certain age groups.
[11] The UL typically represents total intake from food, water, and dietary supplements (unless otherwise specified by IOM).
[12] The UL is not intended as a target intake level but as a risk level.

Table 1: Vitamin D IOM RDAs (or AIs) and ULs for All Age Groups[a]		
Age Group	**RDA[b] (or AI)**	**UL**
Infants 0 to 6 Months	400 IU/day[c]	1,000 IU/day
Infants 6 to 12 Months	400 IU/day[c]	1,500 IU/day
Children 1 to 3 Years	600 IU/day	2,500 IU/day
Children 4 to 8 Years	600 IU/day	3,000 IU/day
Children 9 to 13 Years	600 IU/day	4,000 IU/day
Adolescents 14 to 18 Years[d]	600 IU/day	4,000 IU/day
Adults 19 to 70 Years[d]	600 IU/day	4,000 IU/day
Adults 71+ Years	800 IU/day	4,000 IU/day

[a] The RDA values presented are based on the dietary requirements for bone health which was used as the health outcome or indicator of focus.
[b] IOM states that the serum 25-hydroxyvitamin D (25-(OH)D) level corresponding to these vitamin D RDA levels and covering the requirements of at least 97.5% of all the population is 20 ng/ml (or 50 nmol/L). Serum 25-(OH)D specified for children and adolescents (1 to 18 years) are 16 ng/mL (or 40 nmol/L) and 20 ng/ml (or 50 nmolL), respectively.
[c] Reflects AI reference value rather than RDA. RDAs have not been established for infants. IOM states that the AI for infants is based on the desire to maintain serum 25-(OH)D levels in the 16-20 ng/mL (or 40-50 nmol/L) range in addition to other available data.
[d] Group includes females in life stages of pregnant and lactating.

FDA Vitamin D Safety Evaluations

Subsequent to the IOM's revision of the DRIs for vitamin D in 2011, the FDA has performed two extensive safety evaluations of vitamin D. These assessments performed by the Office of Food Additive Safety (OFAS), Division of Petition Review are found in a memorandum dated February 11, 2014, that reviewed FAP 2A4788,[13] and a memorandum dated February 10, 2016, that reviewed FAP 3A4801.[14] The documents described in detail the basis of the IOM determination of and related calculations for the vitamin D UL values. The FDA documents were prepared after the availability of the 2011 IOM Report on vitamin D intake and included the review of references published after 2010[15] to determine if the findings of the more recent studies would call into question the conclusions of the IOM on the UL values for vitamin D exposure. The 2014 and 2016 FDA memoranda concluded that the available scientific literature published after 2010 did not demonstrate any new toxicological concerns regarding vitamin D_3 and D_2, and it was appropriate to rely on the IOM's safety evaluation in the vitamin D report.

[13] The subject of this 2014 OFAS Division of Petition Review, Toxicology Team, memorandum was "Use of vitamin D_3 as a nutrient supplement in meal replacement products, and as a sole source of nutrition for enteral tube feeding."
[14] The subject of this 2016 OFAS Division of Petition Review, Toxicology Team, memorandum was "FAP 3A4801: Safety of Vitamin D_3 as a Nutrient Supplement in Milk and Vitamin D_2 as a Nutrient Supplement in Plant-Based Beverages and Plant-Based Yogurts."
[15] The references reviewed and included in the 2011 IOM vitamin D DRI document were comprised of references with publication dates up to 2010.

Safety Review for FAP 9A4823

The present evaluation identified and reviewed additional references on the effects of vitamin D exposure that either were not included in the previously noted OFAS FAP memoranda or were not included in the petitioner's submission. This included references that examined both skeletal and extraskeletal (e.g., diabetes, asthma, cancer) health outcomes.[16] The references reviewed for skeletal health effects information also encompassed those that contained vitamin D supplementation dose-response information and/or that examined the skeletal-related outcome of falls and bone fractures. These topic areas were considered necessary to the review of bone-related references for the sake of completeness. Because vitamin D facilitates the efficient absorption of calcium which in turn allows calcium to build and maintain bones, considering the role of vitamin D in several aspects of bone health including these noted ones (like fractures) is important. A reference list of all the supplemental references identified via a literature search, reviewed, and evaluated for the present analysis is found in Appendix 3. See Appendix 3 for additional details on the literature search performed.

This analysis focused on references that contain information and data such as exposure-response relationship findings that potentially would contribute to an update of current vitamin D dietary reference values (e.g., RDA, ULs established by IOM in 2011). The relevant available references for this evaluation were found to be only studies that examined skeletal health outcomes. References that examined other health outcomes (i.e., extraskeletal ones) were determined not to be relevant or not to serve to update current IOM vitamin D reference values. The identified references of focus used in this analysis are listed in Appendix 1. The safety review and evaluation were based on studies that examined the effects of chronic dietary vitamin D exposure[17] in healthy individuals with normal vitamin D nutritional status, and not individuals in a state of vitamin D insufficiency or deficiency, or in a disease state[18]. Thus, the findings of this analysis of the safety of exposure to vitamin D are applicable to the population of healthy, disease-free individuals with normal vitamin D nutritional status. This is in line with the population of individuals for which the IOM DRI values for vitamin D were developed.

At this time, the best biomarker of clinical and nutritional vitamin D status is serum 25-(OH)D level. It is considered a useful measure of vitamin D exposure from endogenous and exogenous sources. The 2011 IOM Committee Report concluded that a serum 25-(OH)D level of 20 ng/mL (or 50 mmol/L) is needed for good bone health in the majority of individuals in the population. They considered a sufficient or "normal" 25-(OH)D levels for bone health to be in the range of 20-50 ng/mL (or 50-125 mmol/L) (Looker et al., 2011; IOM, 2011b and d). The various IOM categories for vitamin D status and the associated 25-(OH)D levels are presented in Table 2. IOM also states that serum 25-(OH)D level of 20 ng/mL corresponds to

[16] In IOM's 2011 recommendation on the dietary reference intakes for calcium and vitamin D, the Committee opined that the available evidence supported a consistent and reliable link between these nutrients and bone health but not for other health conditions. The Committee further noted that there is emerging evidence that too much of these nutrients may be harmful to bone health. In addition, excessive vitamin D intake has been reported to be associated with several adverse health conditions, such as hypercalcemia and hypercalciuria, and possibly decreased renal function and increased cardiovascular risk.

[17] Like the 2011 IOM evaluation for vitamin D exposure for the derivation of DRIs, this safety review only considers the effects of dietary exposure to vitamin D and assumes no to minimal sun exposure occurs. Also, the key studies in this review limited excessive sun exposure, such as excluding those who use tanning salons.

[18] Examples of disease states include osteoporosis, diabetes, and obesity.

the RDA exposure for all age groups and covers the requirements of at least 97.5% of the population. However, it is important to note that the common criteria for defining normal, insufficient, and deficient vitamin D levels for diagnostic purposes (Alshahrani and Aljohani, 2013; Taylor and Davies, 2018) differ from the IOM levels[19] depicted in Table 2.

Table 2: IOM Thresholds and Categories for 25-(OH)D Levels[a, b]

25-(OH)D Level (ng/mL)	25-(OH)D Level (nmol/L)	Category for Vitamin D Status
<12	<30	At Risk of Vitamin D Deficiency
12 - 19	30 - 49	At Risk of Vitamin D Inadequacy
20 - 50	50 - 125	Sufficient in Vitamin D
>50	>125	Possibly Harmful Vitamin D Level

[a] The 25-(OH)D levels and associated IOM categories characterizing vitamin D status are derived from Looker et al. (2011) and IOM (2011b; 2011d).
[b] To convert serum 25-(OH)D levels expressed as the units of nmol/L to ng/mL, the nmol/L value is divided by 2.496.

In this safety review, vitamin D status reflective of good bone health is defined based on the IOM determination of a sufficient vitamin D level (i.e., serum 25-(OH)D of 20-50 ng/mL or 50-125 mmol/L). Thus, for the most part, only studies that begin with healthy subjects[20] in good bone health with baseline serum 25-(OH)D levels considered sufficient by IOM were included in the analysis,[21, 22] and subsequently described in detail in the literature review below. In addition, to examine the effects of chronic exposure, the selected studies only included those that orally administered vitamin D in a repeated fashion[23] over an extended time.[24]

[19] The baseline vitamin D status of subjects described in a particular study often depended on which 25-(OH)D classification system was applied in characterizing the state of bone health of subjects. As a result, in some instances, this led to the appearance of inconsistent and/or conflicting characterizations of the bone health status of subjects between vitamin D studies.
[20] Again, this means that vitamin D studies were reviewed and assessed for an inclusion vs. exclusion determination. The findings of studies that were from subjects in a disease state or with clinical conditions subsequently were not included in the final literature review presented in this memorandum. See Appendix 3 for a complete list of assessed references.
[21] The baseline vitamin D status of subjects in each study was evaluated with respect to the 25-(OH)D categories promulgated by the IOM. As a result, in some cases, study subjects fell into a different vitamin D status category than originally determined by the study authors if they had employed the diagnostic-based vitamin D status categories. For instance, subjects considered as being "insufficient" in vitamin D (i.e., 20-30 ng/mL 25-(OH)D) under the diagnostic classification system would be considered be "sufficient" in vitamin D (i.e., 20-50 ng/mL) with respect to the IOM classification system.
[22] Sometimes this vitamin D status was determined based on a mean value for 25-(OH)D for an experimental group.
[23] The experimental design of the principal studies selected for evaluation involved daily administration of vitamin D over an extended period (e.g., chronic exposure). However, some studies that were used as supportive evidence for the effects of vitamin D administered several large doses of vitamin D intermittently over an extended time. In the latter case, the average daily exposure levels were considered.
[24] This means that references that assessed the effect of acute experimental exposure to vitamin D, or the outcome of acute poisoning cases were not included in the literature review.

Literature Review of Recent Vitamin D Publications

As stated in the previous section (i.e., see "*Safety Review for FAP 9A4823*" above) that outlined and described the literature review and reference study selection procedures and criteria, it was found that only studies that examined the effects of vitamin D exposure on bone health outcomes in contrast to other health outcomes were determined to be relevant to this analysis. The published studies identified to contain relevant findings are reviewed below. This included several recently published studies and a few earlier published studies that contained information that fell within the topics and criteria considered of significance to the study review and selection process described above.

- McCullough P, Amend J. Results of daily oral dosing with up to 60,000 international units (iu) of vitamin D3 for 2 to 6 years in 3 adult males. J Steroid Biochem Molec Biol 173: 308–312, 2017

In this publication, challenge tests involving the ingestion of high amounts of vitamin D_3 daily for prolonged time periods in 3 healthy adult male volunteers are described.[25] The volunteers consumed over-the-counter vitamin D_3 gel caps or powder capsules. Subject 1 was a 50-year-old male who gradually increased oral dosages of vitamin D_3 in successive steps from 6500 IU/day to 60,000 IU/day over 6 years. Subject 2 was a 50-year-old male who consumed vitamin D_3 for successive periods at dosages ranging from 10,000 to 30,000 IU/day for approximately 3.5 years. Subjects 3 was a 20-year-old male who took vitamin D_3 supplements at doses from 10,000 to 20,000 IU/day for about 1.5 years. Serum 25-(OH)D was measured periodically at intervals that ranged from 2-6 months to 3 years depending on the subject and were somewhat associated with the timing of changes in the dosages administered. Calcium (mg/dl), intact parathyroid hormone (iPTH), and albumin levels were measured sporadically. No overt adverse events or toxicity related to vitamin D exposure were reported by the 3 study participants. Values for calcium, iPTH, and albumin were within the normal range at various time points where measurements were available. Serum 25-(OH)D levels rose above 150 ng/mL in all 3 subjects and above 200 ng/mL in one participant (Subject 1). These 25-(OH)D levels are considered at levels of concern with respect to the IOM 25-(OH)D categories of vitamin D status (see Table 2 and discussion above). From their findings along with their review of available studies, the authors suggest that long-term vitamin D_3 supplementation at the level of 10,000 to 25,000 IU/day is safe. However, a major limitation of this paper was that a small number of only male subjects were tested.

- Burt LA, Billington EO, Rose MS, Raymond DA, Hanley DA, Boyd SK. Effect of high-dose vitamin D supplementation on volumetric bone density and bone strength: A randomized clinical trial. JAMA 322(8): 736 - 745, 2019

This study was conducted to experimentally evaluate the measurement of bone density and bone strength. In a double-blind, placebo-controlled, randomized clinical trial conducted in healthy older male (53%) and female (47%) adults (mean: 62.2 years old) living in North America, study subjects (n=311) ingested daily amounts of vitamin D_3 supplements at the levels of 400 IU (n=109), 4000 IU (n=100) or 10,000 IU (n=102) daily for three years. This

[25] This study didn't provide baseline 25-(OH)D levels or bone density measures to confirm subjects' normal bone health. Because the study subjects were healthy, young, or middle-aged adult males, the study was reviewed and described assuming the subjects' initial bone health was normal. It was also considered a support study and not principal study in the safety review.

treatment was accompanied by instructions to keep intake of calcium supplements to less than 1200 mg/day and to take no more than 200 IU additional vitamin D per day from other sources. The selected study subjects were considered to have normal vitamin D nutritive status and bone health. The criteria for eligibility as a study participant include the following: normal serum calcium levels; no evidence of osteoporosis in dual x-ray absorptiometry (DXA) scans; no disorders that affect vitamin D metabolism in the last 2 years; no use of vitamin D_3 supplements at levels greater than 2000 IU within the past 6 months or bone active medication within the last 2 years; and no regular use of tanning salons. Several bone-related primary and secondary outcomes along with other safety outcomes were evaluated periodically (e.g., baseline, 6, 12, 24, and/or 36 months) during the experiment-related vitamin exposure. Some treatment-related changes were found after supplementation at daily doses of 4000 IU and/or 10,000 IU vitamin D_3. The mean baseline 25-(OH)D levels for the 3 treatment groups (400, 4000, 10,000 IU/day vitamin D_3) were at levels considered by IOM (2011b; 2011d) to represent sufficient levels of vitamin D. Significant increases in serum 25-(OH)D levels versus baseline levels were seen when tested periodically over the 3-year period of daily exposure in the 4000 IU (3 months: 32.6 - 46.2 ng/mL; 36 months: 52.9 ng/mL) and 10,000 IU (3 months: 31.4 – 75.3 ng/mL; 18 months: 80.3 ng/mL; 36 months: 57.9 ng/mL[26]) vitamin D_3 treatment groups, with greater increases associated with higher dose (see Table 2). In the primary outcome variables assessed, small significant and dose-related alterations in HR-pQCT bone mineral density (BMD) measures in the healthy adults were seen at the 4000 IU and 10,000 IU vitamin D_3 dose levels compared to the 400 IU dose group. At the end of the 3-year trial, -2.4% and -3.5% decreases in mean total volumetric BMD in the radius were seen in the 4000 IU and 10,000 IU vitamin D_3 dose groups, respectively, compared to the -1.2% decrease seen in 400 IU dose group. Small Vitamin D_3-related decreases in total volumetric BMD in the tibia were observed after three years (-0.4%, -1.0% and -1.7% in 400 IU, 4000 IU, 10,000 IU groups respectively). Small dose-related decrease in serum parathyroid hormone and increase in plasma marker of bone reabsorption (C-telopeptide of collagen 1 or CTx) accompanied these BMD effects. Small changes (e.g., losses) resulted in some measures of bone microarchitecture at the two higher vitamin D_3 doses but not in other measures of bone microarchitecture. As a comparison to the experimental results of the HR-pQCT methodology, a terminal DXA was taken. The DXA is a commonly used and well-characterized measure to assess bone density for general clinical diagnosis of bone disease (e.g., osteoporosis). The DXA measure of total hip areal BMD was stable over the trial showing no differences between groups. How BMD changes in the radius and tibia bones relate to those associated with the hip that is typically assessed is not clear. But, given the DXA findings, the changes found in BMD via the HR-pQCT assessment appear not to be associated with meaningful adverse clinical scenarios or outcomes (and thus are not of concern). Additionally, the study authors did not include data from a post-vitamin D treatment recovery period that provide information on the effects on bone measures after vitamin D exposure is removed. To summarize, some of the "significant" changes stated by Burt et al. were statistically significant but were not biologically relevant, that is, the changes remained within the range of normal BMD. This study utilized specific bone health-related endpoints and demonstrated that oral administration of a very high dose of vitamin D_3 (2.5-times the IOM UL) daily for 3 years to subjects aged 55 and 70 years did not produce adverse effects on bone health.

[26] During the study, there was a change in the manufacture of the experimental vitamin D treatment at this dose level. See source paper for details.

- Sanders KM, Stuart AL, Williamson EJ, JA, Kotowicz MA, Young D, Nicholson GC. Annual high-dose oral vitamin D and falls and fractures in older women: A randomized controlled trial. JAMA 303(18): 1815 - 1822, 2010

This study was a double-blind, placebo-controlled, randomized trial that assessed the occurrence of falls and fractures in community-dwelling, vitamin D-sufficient women aged 70 years or older administered vitamin D_3.[27] Vitamin D_3 was given as a single oral dose annually in the autumn or winter for 3 to 5 years. Subjects (n=2256) received a dose of 500,000 IU[28] or placebo and were followed monthly for falls and confirmed fractures. The rate of falls was significantly greater for women in the vitamin D_3 group than women in the placebo group (Rate: Vitamin D_3, 83.4 per 100-person-years vs. Placebo, 72.7 per 100-person-years).[29] In addition, the rate of fractures was significantly greater for women in the vitamin D_3 group than women in the placebo group (Rate: Vitamin D_3, 4.9 per 100-person-years vs. Placebo, 3.9 per 100-person-years). This effect included total fractures associated with and without falls. In a subset of subjects (n=133) in which serum 25-(OH)D levels were measured at several different times over the study's five treatment years, elevated 25-(OH)D levels were observed at each point in vitamin D_3-treated subjects in contrast to the levels found at baseline and in the placebo group. For instance, 25-(OH)D measures taken at 1 month after vitamin D treatment ranged from 49-51 ng/mL; those taken 3 months after this treatment ranged from 36-38 ng/mL; and those taken 12 months post-treatment ranged from 22-30 ng/mL in contrast to the subjects' baseline values or placebo treatment group (~21 ng/mL).[30] Finally, although this study administered vitamin D_3 in one high annual dose, it served to increase 25-(OH)D levels over the year that followed. This indicates that the corresponding treatment-related elevated vitamin D levels were maintained at some degree during the year after the single day consumption of the experimental vitamin D dose. This study has several issues that limit its applicability to a safety assessment of vitamin D_3 exposure through food for the general population, such as the women subjects being 70 years or older, and the study design involved a very large dose of vitamin D.

- Thanapluetiwong S, Chewcharat A, Takkavatakarn K, Praditpornsilpa K, Eiam-Ong S, Susantitaphong P. Vitamin D supplement on prevention of fall and fracture: A Meta-analysis of Randomized Controlled Trials. Medicine, 2020

Thanapluetiwon et al. (2020) conducted a meta-analysis of randomized control trials on the role of vitamin D supplements in preventing the fall and fracture outcome. The analysis showed that the results are still inconclusive, reporting either having effectiveness or no benefit. The authors concluded that the disparity in the results might be caused by differences in methodology, study quality, groups of population, calcium co-supplement, and

[27] This study was evaluated because the participating subjects had baseline 25-(OH)D values that were approximately within the range of values considered normal by the IOM. The median 25-(OH)D level at baseline was 49 nmol/L (or ~20 ng/mL). Selected subject consumed vitamin D doses of less than 400 IU/day prior to the study.

[28] This represents an average daily dose of 1370 IU/day.

[29] A "person-year" is a statistic for expressing incidence rates which is the sum of the results of events divided by time. A person-year reflects a period of observation or average population during a time interval. It represents a point prevalence or number of cases (new and pre-existing) at a specific point in time.

[30] These represent 25(OH)D values taken from subsets of study subjects over different treatment years. The 12-month post-dosing values were taken each year for 5 treatment years (n=133). The 1-month and 3-month post-dosing values were taken during treatment years 3 and 4.

details of vitamin D administration, including type, dose, frequency, and duration in these studies.

- Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, Staehelin HB, Meyer OW, Theiler R, Dick W, Willett WC, Egli A. Monthly high-dose vitamin D treatment for the prevention of functional decline: a randomized clinical trial. JAMA Intern Med 176: 175 – 183, 2016

This recent double-blind, placebo-controlled study administered vitamin D_3 to community-dwelling older men (33%) and women (67%). The subjects, 70 years of age or older, were assessed as having good mobility and mental status, along with supplemental vitamin D use below 800 IU/day. A group (n=67) that had a 20 ng/mL 25-(OH)D mean baseline level, which is considered a sufficient level for bone health by the IOM, was administered 60,000 IU vitamin D_3 orally once per month for 12 months.[31] The study investigators noted this amount represented an exposure of 2000 IU/day. The absolute mean 25-(OH)D levels significantly increased at 6 months and 12 months post-treatment to about 39 ng/mL and 40 ng/mL, respectively. After adjusting these absolute 25-(OH)D values for baseline 25-(OH)D level, age, sex, and body mass index (BMI), the corresponding adjusted 25-(OH)D levels are 57.3 and 59.2 ng/mL for these respective time points. There was an 18.7% probability of reaching 25-(OH)D levels as high as 44.7 – 98.9 ng/mL. The experimental vitamin D_3 exposure is associated with a 66.9% of subjects recording falls. This represents a mean of 1.47 falls in this group over 12 months of vitamin D treatment with a similar pattern observed during the first 6 months and the last 6-month period of treatment. The authors note a general relationship between the quartile level of 25-(OH)D reached and the odds of falling and number of falls. Subjects reaching the highest quartile levels at 12-months had the highest likelihood of and number of falls occurring compared to those reaching the lowest quartiles levels. The study findings provide general information on the relationship between exposure to vitamin D_3, the resultant 25(OH)D levels and the occurrence of falls in healthy, elderly adults. However, the control groups in this study had mean baseline levels below the level that IOM considers sufficient for good bone health and thus, didn't serve as adequate controls for the "normal" vitamin D-treatment group discussed above. The problems with the design of the study don't allow for a conclusive determination to be made about the association between vitamin D exposure and the occurrence of falls in a population of healthy elderly individuals.

- Smith LM, Gallagher JC, Suiter C. Medium doses of daily vitamin D decrease falls and higher doses of daily vitamin D_3 increase falls: A randomized clinical trial. J Steroid Biochem Molec Biol 173: 317-322, 2017

The study was a 12-month double-blind, placebo-controlled, randomized prospective clinical trial in elderly Caucasian and African American women conducted over 2 years. It evaluated the effects of a year-long vitamin D_3 supplementation on serum 25-(OH)D and parathyroid hormone levels and on the occurrence of falls. Inclusion criteria used in subject selection included baseline serum 25-(OH)D levels of < 20 ng/mL, postmenopausal stage, age range of 57 to 90 years and no conditions or use of medication that might affect calcium and vitamin D metabolism. The study participants (Caucasian, n = 147; African American, n = 91) with a mean age of 66 years, were administered capsules of vitamin D_3 daily in one of 7

[31] Only the study experimental group with a 25-(OH)D mean baseline level considered sufficient for bone health by the IOM was evaluated. This was in line with the subject and study criteria for inclusion in this review and assessment outlined above.

different doses ranging from 400 to 4800 IU or placebo capsules. The subjects were instructed to avoid other vitamin D supplementation and to maintain a total calcium intake of between 1200 and 1400 mg per day. In subjects that reached sufficient vitamin D status or higher after 12 months of supplemental vitamin D intake, the relationship between the final study serum 25-(OH)D quartiles and fall rate was a U-shaped curve. The fall rate ranged from a low of 21-33% (32-41 ng/mL 25-(OH)D quartile) and highs of 45-72% in the other serum 25-(OH)D quartiles (25-35 ng/mL, 38-49 ng/mL, and >45-49 ng/mL).[32] The mixed results from this study makes drawing meaningful information about daily exposure to vitamin D in this population of older adult women difficult.

- Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ 326: 469-474, 2003

In a double-blind community trial study of healthy men (n= 2037) and women (n= 649) aged from 65 to 85 years, a 100000 IU vitamin D_3 capsule or a placebo capsule was taken by selected study participants[33] every 4 months for 5 years. This reflects an average daily vitamin D_3 exposure of about 833 IU. This exposure resulted in a significant decrease in total fractures (20%) and in fractures at major bone sites (30%) in the treatment group in contrast to the placebo control group. From about month 5 of treatment, the cumulative probability of any first fracture was significantly elevated in the placebo group over the vitamin D_3-treatment group. The positive treatment effect on bone status was accompanied by a 40% increase in mean 25-(OH)D level to 29.8 ng/mL in vitamin D-supplemented participants compared to the 21.4 ng/mL mean level found in the placebo-treated participants. The fracture-related effect was more prominent in the female over the male study subjects. The results of this study indicate that in older adults that are considered by IOM to have good bone health status (e.g., 25-(OH)D levels ≥ 20 ng/mL) and that are chronically supplemented with vitamin D_3 in amounts that don't elevate their 25-(OH)D levels beyond 30 ng/mL, beneficial bone affects (i.e., decrease in fractures) over adverse bone affects (i.e., increase in fractures) result after this regimen of vitamin D_3 exposure. It is not clear how 3 exposures per year to large amounts of vitamin D compares to long-term daily dietary exposure to this nutrient.

In summary, from the additional studies reviewed and the additional health effects data assessed, no substantial adverse effects emerged from daily vitamin D_3 exposures at or above IOM UL levels. This included daily exposure to levels as high as 10,000 IU/day in healthy older adults. Thus, it is still appropriate to rely on the existing IOM DRI values for vitamin D (see Table 1) for evaluating the safety of daily vitamin D intake in normal, healthy individuals.

[32] The range of values noted for 25-(OH)D levels and percentage of falls reflect the results from 2 two different methods used to measure serum 25-(OH)D. These methods were RIA Diasorin kits and liquid chromatography mass spectrophotometry (LCMS).

[33] The study participants were assumed to be of normal bone health status based on the results of a pre-study disease questionnaire and the normal 2-(OH)D levels found in the placebo controls.

Dietary Exposure Estimations

Estimations of chronic dietary exposure to vitamin D were performed by FDA Chemists in the OFAS DFI Chemistry Review Branch and described in detail in a DFI memorandum.[34] Briefly, mean and 90th percentile exposure estimates for the combined intake of vitamin D_3 from the proposed uses in breakfast cereals and grain-based bars were determined. Similar exposure estimates were derived for cumulative intake of vitamin D from background sources in addition to the proposed uses for vitamin D_3. These estimates were determined for specific ages within population groups for infants, children, adolescents, teenagers, adults, and elderly adults in addition to estimates for total US populations groups. Tables depicting these findings are presented in the noted DFI Chemistry memorandum.

Summary Safety Assessment Findings

The petitioner proposed maximum use levels for vitamin D_3 of 560 IU per 100 g food and 400 IU per 100 g food in breakfast cereals and grain-based bars, respectively. FDA has estimated that the daily exposure[35] to vitamin D_3 from the proposed uses in breakfast cereals and grain-based bars[36], containing the proposed maximum amounts of vitamin D_3, at the mean or 90th percentile intake levels result in daily vitamin D_3 exposures that are below the IOM-established ULs for vitamin D (see Table 1). This holds for the vitamin D daily exposure estimates associated with each age subgroup category and their respective UL values. Thus, chronic exposure to vitamin D from only the combined ingestion of breakfast cereal and grain-based bars that contain this nutrient at the proposed levels has a reasonable certainty of no harm to consumers.

The mean and 90th percentile cumulative daily vitamin D exposure estimates from all current existing background food sources of vitamin D in addition to the two proposed uses for vitamin D_3[37] found for each age subgroup category are above each respective age-specific RDA or AI value (see Table 1). This means the proposed vitamin D exposure meets the nutrient needs of at least 97.5% of the population. Next, the mean and 90th percentile cumulative daily vitamin D exposure estimates from the intake of all the described food sources combined for each age subgroup category were below their respective UL values. Thus, the daily intakes of vitamin D found for each age subgroup from this cumulative exposure estimate are below IOM's established UL health risk levels for all the population subgroups. Therefore, the cumulative chronic dietary exposures to vitamin D at the levels described has a reasonable certainty of no harm to consumers.

[34] The FDA OFAS DFI Chemistry Review Branch (Team 2), Chemistry memorandum dated October 13, 2022, is titled "FAP 9A4823: Hogan Lovells US LLP, on behalf of Kellogg Company: Use of vitamin D_3 in breakfast cereal and grain-based nutrition bars. Submissions dated June 4, 2019, February 27, 2020, and March 4, 2021."

[35] The exposure estimates for the evaluation of vitamin D effects reflect those for chronic exposure (which corresponds to the focus on the chronic effect of bone health), not for acute or subchronic Vitamin D exposures.

[36] See presentation on daily exposure estimates for the proposed uses of vitamin D_3 in breakfast cereals and grain-based bars on pp 9-10 and in Table 6 in the FAP 9A4823 Chemistry memorandum.

[37] See presentation on daily exposure estimates for the cumulative exposure to vitamin D from background sources and the proposed uses of vitamin D_3 in breakfast cereals and grain-based bars on pp 11-12 and in Table 7 in the FAP 9A4823 Chemistry memorandum.

Conclusion

DFI Toxicology evaluated the available information and data on the potential health effects of chronic exposure to vitamin D from the proposed dietary uses described in FAP 9A4823. We conclude that the proposed intended use levels of vitamin D_3 of 560 IU/100 g in breakfast cereals, and of 400 IU/100 g in grain-based bars raise no current safety concerns.

Sue A. Assimon -S Digitally signed by Sue A. Assimon -S Date: 2022.10.14 12:44:25 -04'00'

Sue Anne Assimon, MS, PhD

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F/T:SAAssimon:10/14/2022

Appendix 1:

Reference List of Publications Cited in the Main Text of Memorandum for FAP 9A4823

Alshahrani F, Aljohani N. Vitamin D: Deficiency, Sufficiency and Toxicity. Nutrients 5:3605-3616, 2013

Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, Staehelin HB, Meyer OW, Theiler R, Dick W, Willett WC, Egli A. Monthly high-dose vitamin D treatment for the prevention of functional decline: a randomized clinical trial. JAMA Intern Med 176: 175 – 183, 2016

Burt LA, Billington EO, Rose MS, Raymond DA, Hanley DA, Boyd SK. Effect of high-dose vitamin D supplementation on volumetric bone density and bone strength: A randomized clinical trial. JAMA 322(8): 736 - 745, 2019

IOM. Dietary Reference Intakes: Calcium and Vitamin D. Chapter 1 - Introduction. Washington, DC: The National Academies Press, pp 15-34, 2011a

IOM. Dietary Reference Intakes: Calcium and Vitamin D. Chapter 5 – Dietary Reference Intakes for Adequacy: Calcium and Vitamin D. Washington, DC: The National Academies Press, pp 345-402, 2011b

IOM. Dietary Reference Intakes: Calcium and Vitamin D. Chapter 6 – Tolerable Upper Intake Levels: Dietary Reference Intakes for Adequacy: Calcium and Vitamin D. Washington, DC: The National Academies Press, pp 403-455, 2011c

IOM. Dietary Reference Intakes: Calcium and Vitamin D. Summary. Washington, DC: The National Academies Press, pp 1-14, 2011d

IOM. Report Brief: Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: Institute of Medicine of The National Academies, November 2010

Looker AC, Johnson CL, Lacher DA, Pfeiffer CM, Schleicher RL, Sempos CT. Vitamin D Status: United States, 2001–2006. US Department of Health & Human Services, Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS) Data Brief. No. 59, March 2011

McCullough P, Amend J. Results of daily oral dosing with up to 60,000 international units (iu) of vitamin D3 for 2 to 6 years in 3 adult males. J Steroid Biochem Molec Biol 173: 308–312, 2017

Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, DA RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS, Mayne ST, Rosen CJ, Shapes SA. The 2011 Report on Dietary Reference Intakes for Calcium and Vitamin D from the Institute of Medicine: What Clinicians Need to Know. J Clin Endocrinol Metab 96 (1): 53 – 58, 2011

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Smith LM, Gallagher JC, Suiter C. Medium doses of daily vitamin D decrease falls and higher doses of daily vitamin D3 increase falls: A randomized clinical trial. J Steroid Biochem Molec Biol 173: 317 –322, 2017

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Thanapluetiwong S, Chewcharat A, Takkavatakarn K, Praditpornsilpa K, Eiam-Ong S, Susantitaphong P. Vitamin D supplement on prevention of fall and fracture: A Meta-analysis of Randomized Controlled Trials. Medicine http://dx.doi.org/10.1097/MD.0000000000021506, 2020

Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ 326: 469-474, 2003

Appendix 2:

List of 13 Relevant Safety-Related References Submitted by Petitioner for FAP 9A4823

Apaydin M, et al. The effects of single high-dose or daily low-dosage oral cholecalciferol treatment on vitamin D levels and muscle strength in postmenopausal women. BMC Endocrine Disorders 18 (1): 48, 2018

Cho SY, Park H-K, Lee HJ. Efficacy and safety of early supplementation with 800 IU of vitamin D in very preterm infants followed by underlying levels of vitamin D at birth. Italian J Pediatr 43(1): 45, 2017

Gallagher JC, Yalamanchili V, Smith LM. The effect of vitamin D on calcium absorption in older women. J Clin Endocrinol Metab 97(10): 3550-3556, 2012

Ginde AA, et al. High-dose monthly vitamin D for prevention of acute respiratory infection in older long-term care residents: A randomized clinical trial. J Am Geriatrics Soc 65(3): 496-503, 2017

Haines N, et al. The effect of a single early high-dose vitamin D supplement on fracture union in patients with hypovitaminosis D: a prospective randomized trial. Bone Joint J 99(11): 1520-1525, 2017

IOM. Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D and Fluoride. Washington, DC: The National Academies Press, 1997

Leidig-Bruckner G, et al., Are commonly recommended dosages for vitamin D supplementation too low? Vitamin D status and effects of supplementation on serum 25-hydroxyvitamin D levels—an observational study during clinical practice conditions. Osteoporos Int 22(1): 231-240, 2011

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Nygaard B, et al. Effects of high doses of cholecalciferol in normal subjects: a randomized double-blinded, placebo-controlled trial. PLOS One 9(8): e102965, 2014

Radhakishun NNE, et al. Efficacy and tolerability of a high loading dose (25,000 IU weekly) vitamin D3 supplementation in obese children with vitamin D insufficiency/deficiency. Hormone Res Pædiatr 82(2): 103-106, 2014

Roth DE, et al. Randomized placebo-controlled trial of high-dose prenatal third-trimester vitamin D3 supplementation in Bangladesh: the AViDD trial. Nutr J 12(1): 47, 2013

Sansanayudh N, et al. Comparative efficacy and safety of different doses of ergocalciferol supplementation in patients with metabolic syndrome. International J Clin Pharm 36(4): 771-778, 2014

Takács I, et al. Randomized clinical trial to comparing efficacy of daily, reference list weekly and monthly administration of vitamin D3. Endocrine 55(1): 60-65, 2017

Wallace RB, et al. Urinary tract stone occurrence in the Women's Health Initiative (WHI) randomized clinical trial of calcium and vitamin D supplements. Am J Clin Nutr 94(1): 270-277, 2011

Appendix 3:

Recent References Reviewed by OFAS/DFI for Toxicology Evaluation for FAP 9A4823

To perform an updated toxicology safety analysis, literature searches were performed using PubMed and Google Scholar to identify references published after 2010 that contained information on adverse effects, adverse health outcomes or toxicity responses associated with vitamin D exposure. The identified published studies that were reviewed and evaluated included those that examined skeletal and extraskeletal adverse effects or health outcomes and are listed below. The specific studies that were determined potentially to be relevant and to contribute to a toxicology analysis update and were described in the safety evaluation in this memorandum are listed in Appendix 1.[38]

Alshahrani F, Aljohani N. Vitamin D: Deficiency, Sufficiency and Toxicity. Nutrients 5:3605-3616, 2013

Avenell A, Mak JC, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. Cochrane Database Syst Rev 14(40): 2014

Barbarawi M, Kheiri B, Zayed Y, Barbarawi O, Dhillon H, Swaid B, Yelangi A, Sundus S, Bachuwa G, Alkotob ML, Manson JE. Vitamin D supplementation and cardiovascular disease risks in more than 83000 individuals in 21 randomized clinical trials: A meta-analysis. JAMA Cardio 4(8): 765 - 775, 2019

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Chausmer AB. Letters – Comments and Responses: Dose response to vitamin D supplementation in postmenopausal women. Ann Intern Med 157(5): 384, 2012

Cummings SR, Kiel DP, Black DM. Vitamin D Supplementation and Increased Risk of Falling: A Cautionary Tale of Vitamin Supplements Retold. JAMA Internal Medicine 176(2): 171-172, 2016

Dawson-Hughes B, Harris SS. High-dose vitamin D supplementation: Too much of a good thing? JAMA 303(18): 1861-1862, 2010

Gallagher JC. Vitamin D and falls – the dosage conundrum. Nature Rev Endocrinol 12: 680-684, 2016

[38] The list of references in Appendix 3 represent the references reviewed and evaluated for the safety analysis performed in the memorandum for FAP 9A4823 that were not included in the OFAS/DFI memoranda associated with the previous OFAS/DPR memoranda for vitamin D petitions FAP 2A4788 (2014) and FAP 3A4801 (2016). The findings of some of the listed references were determined not to be relevant or to contribute to the final safety analysis for vitamin D exposure and thus, were not included as citations in the final FAP 9A4823 memorandum listed in Appendix 1.

Gallagher JC, Sai A, Templin T, Smith L. Dose response to vitamin D supplementation in postmenopausal women: A randomized trial. Ann Intern Med 156(6): 425-437, 2012

Gallagher JC, Sai A. Letters – Comments and Responses: Dose response to vitamin D supplementation in postmenopausal women. Ann Intern Med 157(5): 384-385, 2012

Hibbs AM, Ross K, Kerns LA, Wagner C, Fuloria M, Groh-Wargo S, Zimmerman T, Minich N, Tatsuoka C. Effect of vitamin D supplementation on recurrent wheezing in black infants who were born preterm: The D-wheeze randomized clinical trial. JAMA 319(20):2086-2094, 2018

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Institute of Medicine (IOM). Dietary Reference Intakes: Calcium and Vitamin D. Chapter 1 - Introduction. Washington, DC: The National Academies Press, pp 1-14, 2011

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National Institute of Health (NIH), Office of Dietary Supplements, Fact Sheet for Health Professionals: Vitamin D. www.NIH.gov, Last Updated November 9, 2018

Nørrisgaard PE, Haubek D, Kühnisch J, Chawes BL, Stokholm J, Bønnelykke K, Bisgaard H. Association of high-dose vitamin D supplementation during pregnancy with the risk of enamel defects in offspring: A 6-year follow-up of a randomized clinical trial. JAMA Pediatr 2545, published online August 5, 2019

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US Preventive Services Task Force. Vitamin D, calcium, or combined supplementation for the primary prevention of fractures in community-dwelling adults: US Preventive Services Task Force recommendation statement. JAMA 319(15): 1592-1599, 2018