Memorandum

Date: February 2, 2005

From: Division of Petition Review (HFS-265)
Chemistry Review Team

Subject: FAP 4A4758; (MATS# 1161, M2.0 & 2.1) Kraft, submissions of 7/23/2004, 10/15/2004, 10/26/2004, and 12/23/2004. Petition for the use of vitamin D_3 as a nutrient supplement in select cheese and cheese products.

To: Division of Petition Review (HFS-265)
Regulatory Group I
Attention: J. Kidwell

Introduction

Kraft Foods Global, Inc. (Kraft) is petitioning to amend 21 CFR 172.380 to allow for the safe use of vitamin D_3 as a nutrient supplement in select cheese and cheese products. Currently, cheese and cheese products may be fortified with vitamin D at a level of 89 International Units (IU)[1] per 100 g based on 21 CFR 184.1950.[2] The current petition requests fortification of natural and processed cheeses having a reference amount customarily consumed (RACC) of 30 g at levels not to exceed 81 IU vitamin D_3 per RACC.

Vitamin D (in the form of crystalline vitamin D_2, crystalline vitamin D_3, vitamin D_2 resin, and vitamin D_3 resin) is affirmed as generally recognized as safe (GRAS) under §184.1950 for use with specific limitations in breakfast cereals, grain products and pastas, milk, milk products, infant formula, and margarine. As established in §184.1(b)(2), any new use of an ingredient affirmed as GRAS with specific limitations shall require a food additive regulation. Consequently, the most recent approval of vitamin D_3 for use as a nutrient supplement in calcium-fortified fruit juices and juice drinks resulted in the regulation listed under §172.380(c) and (d).[3] The FDA is also currently reviewing a petition for the use of vitamin D_3 in certain dietary/weight control and meal replacement products.[4]

Following a preliminary review of the original submission dated 7/23/04, a letter was sent to Kraft (9/2/2004, J. Kidwell to Kraft) requesting further chemistry information regarding manufacturing of [redacted] analytical results for vitamin D_3 in representative cheeses, including validation data; and further intake estimates. Responses to these requests were provided in submissions from Kraft dated 10/15/2004 and 10/26/2004.

---

[1] One IU of vitamin D is equivalent to 0.025 µg of vitamin D.
[2] Cheese is not specifically listed in §184.1950; however, it has been interpreted by FDA that cheese and cheese products are considered as milk products in §184.1950 for vitamin D fortification at levels up to 89 IU per 100g.
[3] 68 FR 9000 (February 27, 2003). Regulation resulted from FAP 2A4734.
[4] 68 FR 50541 (August 21, 2003). See FAP 3A4746.

2004F-0374

BKF 1

Identity

Vitamin D_3

The Food Chemicals Codex, fifth edition (FCC V) and §184.1950 recognize 2 forms of crystalline vitamin D: vitamin D_2 and vitamin D_3. Vitamin D_2 is produced commercially by ultraviolet (UV) irradiation of ergosterol isolated from yeast and related fungi. Vitamin D_3 is produced endogenously in the skin (by the photochemical reaction of sunlight with the precursor sterol 7-dehydrocholesterol, which is present in the epidermis). §172.380 and the subject submission note that vitamin D_3 is produced commercially by isolation from fish liver oils and by the UV irradiation of 7-dehydrocholesterol derived from cholesterol. FAP 4A4758 specifically petitions for the use of vitamin D_3.

Name: Vitamin D_3

CAS Name: (3β,5Z,7E)-9,10-Secocholesta-5,7,10(19)-trien-3-ol

Chemical Names: 9,10-seco(5Z,7E)-5,7-10(19)-cholestatrien-3ol

Common Names: Vitamin D, calciol, cholecalciferol, activated 7-dehydrocholesterol, oleo-vitamin D

Trade Names: Duphafral D_3 1000, Delsterol, Deparal, Ebivit, Micro-Dee, Neo Dohyfral D_3, Provitina, Ricketon, Trivitan, D_3-Vicotrat, Vigantol, Vigorsan

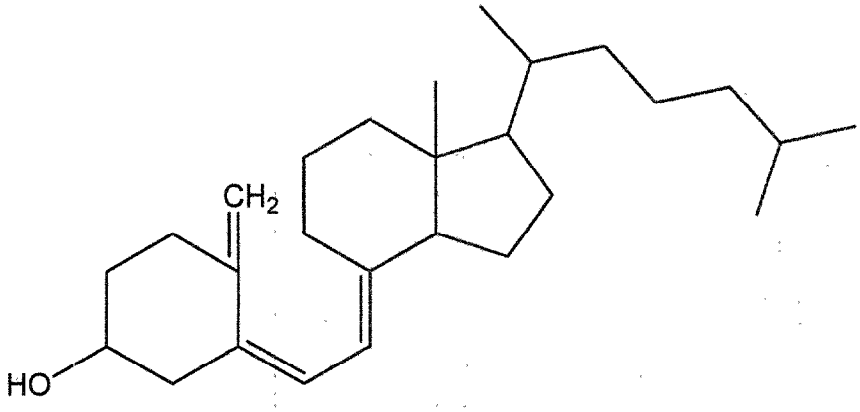
CAS Reg. No.: 67-97-0

Molecular Formula: $C_{27}H_{44}O$

Molecular Weight: 384.65

Solubility: Soluble in alcohol, chloroform, and fatty oils.

Structure:



...

We have no questions with regards to identity.

Manufacturing

Information regarding the manufacture of vitamin D_3, ... and cheese fortified with vitamin D_3 is included in Section A.4 of the original submission.

Vitamin D_3

...

...

...

...

	±

Stability

The stability of vitamin D_3 in cheese is discussed in Section A.6 and Appendix IV of the original submission, as well as Appendix VI of the 10/26/04 submission. Kraft states that minimal degradation of vitamin D_3 is expected in natural and processed cheeses over their expected shelf life (approximately 4 months and 7 months, respectively). In Appendix IV, Kraft has summarized data from a 5 month vitamin D_3 stability study on two types of processed cheese: Kraft American Singles (KAS), and Kraft 2% Singles (K2S). A more complete set of data for the same stability study is included in Appendix VI of the 10/26/04 submission. The study in Appendix VI contains summarized stability data over 7 months, as well as all raw data and chromatograms. Two samples of KAS and three samples of K2S were examined over the 7 month period.[8] The initial measured vitamin D_3 concentrations were 196 and 195 IU/100 g for the KAS samples, and were 248, 346, and 460 IU/100 g for the K2S samples. We note that both samples of KAS are fortified below the petitioned fortification level (270 IU/100 g), whereas for the K2S samples, two are fortified above, and one is fortified approximately at the petitioned fortification level. In all five samples, over the 7 month period, the level of fortification remained essentially constant. However, the level of vitamin D_3 in the two KAS samples appears to increase over time. The increase is likely due to variation associated with the analytical method and sampling of the cheese matrix. The

...

data appear to adequately demonstrate stability of vitamin D_3 in processed cheese over the shelf life of the product.

Kraft also references (Section A.6 of the original submission) a storage and heat stability study performed by Upreti *et al.* on pasteurized processed cheese fortified with vitamin D_3 at a level of 100 IU/28 g (approximately 357 IU/100 g).[9] In this study, no loss of vitamin D_3 was observed over a 9 month period in refrigerated samples or samples stored at room temperature. However, a loss of 25-30% vitamin D_3 was observed in processed cheese samples heated for 5 minutes at 232°C. Kraft notes that most processed cheese in the United States is consumed in a refrigerated form or after heating at moderate temperatures for short periods of time. These data adequately support the shelf life stability of fortified processed cheese.

Kraft did not present data to support the claim of stability of vitamin D_3 in natural cheeses over their anticipated 4 month shelf life. However, Kraft stated that "due to the lower level of oxygen in natural cheese packages, the oxidative degradation of vitamin D_3 in well-packaged natural cheese is assumed to be less than that for processed cheese." An article referenced in the Upreti paper by Banville *et al.*, however, observed degradation of vitamin D_3 in cheddar cheese ripened for longer than 5 months.[10] Banville studied the stability of vitamin D during the ripening process of vacuum-sealed cheddar cheese fortified with vitamin D by three different methods (encapsulation in lipososomes, addition of a commercially available water soluble vitamin D formulation, addition of crystalline vitamin D). [redacted] by Kraft; however, the addition of the commercially available water soluble form and the addition of crystalline vitamin D are most relevant. Banville noted that vitamin D levels in cheddar cheese fortified by these two methods were stable over a 5 month ripening period. After 7 months of ripening, however, there was a decrease in vitamin D concentration of approximately 11% for cheese made with the commercially available water soluble vitamin D formulation, and 16% for cheese made with crystalline vitamin D. The data presented in the Banville paper appear to contradict Kraft's assumption that degradation of vitamin D in natural cheese would be less than that of vitamin D in processed cheese. Kraft has stated that natural cheese has a shelf life of 4 months, but has not commented on the length of the ripening process, which appears to have an effect on vitamin D stability, according to the Banville paper. We would presume that, based on the Banville paper, any degradation of vitamin D_3 in natural cheese would likely be small. **Therefore, in light of the Banville paper, we request that Kraft comment on the stability of vitamin D_3 in natural cheeses and, in particular, with regard to the vitamin D_3 levels in fortified natural cheeses after 5-7 months of curing.**

Uses, Use Level, and Technical Effect

---

[9] Upreti, P., V.V. Mistry, and J.J. Warthesen. 2002. Estimation and fortification of vitamin D_3 in pasteurized process cheese. *J. Dairy Sci.* 85:3173-3181.

[10] Banville, C., J.C. Vuillemard, C. Lacroix. 2000. Comparison of different methods for fortifying Cheddar cheese with vitamin D. *Int. Dairy J.* 10:375-282.

Kraft proposes to use vitamin D_3 as a nutrient supplement at a concentration of 81 IU per 30 gram RACC (270 IU/100 g) in cheese and cheese products. The targeted cheese and cheese products are those with a RACC of 30 g under 21 CFR §101.12, including standardized and non-standardized natural cheese, processed cheese, cream cheese, and cheese spreads and dips. Hard grated cheeses with smaller reference amounts, such as Parmesan and Romano, are not included, nor are cheeses with larger reference amounts, such as cottage cheese or ricotta cheese. Cheese-like products made from non-dairy starting materials (e.g. soy-based products), which are not considered to be cheese within the meaning of §170.3(n)(5), are not included. Cheese and cheese products subject to a standard of identity under §133 may be fortified only if such fortification complies with §130.10 such that the requirements for the establishment of a nutrient content claim (such as "good source" under §101.54(c)) are met.

Kraft states that vitamin D is a critical nutrient which plays an important role in calcium metabolism and homeostasis, bone health, and other bodily functions. Kraft states that the primary biologic function of vitamin D in humans is to enhance the efficiency of the small intestine to absorb calcium and phosphorous, thereby helping to maintain serum calcium and phosphorus concentrations within normal ranges. Kraft points to the Institute of Medicine's 1997 report[11] to support their belief that the fortification of cheese and cheese products at increased levels is prudent to help ensure that the U.S. population is getting enough vitamin D. Kraft states that cheese is a good choice for increased vitamin D fortification because it is already a permitted vehicle for fortification, it is a food consumed in significant quantities by a majority of the U.S. population, and as a milk product, it is expected to have a bioavailability similar to that of fluid milk.

We have no questions with regard to use and technical effect.

Analytical Method

Kraft has provided (Appendix V of the original submission) a copy of the Association of Official Analytical Chemists (AOAC) Method 982.29 (from AOAC Official Methods of Analysis 2000, "vitamin D in mixed feeds, premixes, and pet foods") for detection and quantification of vitamin D in cheese. Briefly, the AOAC method involves weighing a vitamin D-containing cheese sample followed by saponification with potassium hydroxide over a steam bath to break down fat and release vitamin D. The digest is then extracted with ether to recover unsaponifiable material. Interfering substances are removed from the extract using open column chromatography on alumina. The extract is further cleaned up on a reverse phase high performance liquid chromatography (HPLC) column. Finally, the eluted fraction from the clean up column that contains vitamin D is injected on normal phase HPLC column for quantitative determination of vitamin D.

In the 9/2/04 letter, Kraft was requested to provide analytical data for vitamin D_3 in 5 representative lots of cheese. Appendix IV of the 10/26/04 submission contains vitamin D_3 concentration data for 6 lots of cheese.[12] The Appendix contains raw and summary data

[11] Institute of Medicine. 1997. *Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride*. National Academy Press. Washington, DC. pp. 250-287.

[12]

collected from two separate studies[13] on cheese fortified with vitamin D_3 at a level of 285 IU/100 g.[14] While each study analyzed all 6 of the sample lots, only the study designated as 9/7/04 was performed in triplicate for each sample lot. Appendix V of the 10/26/04 submission contains a statistical analysis of the results of the 9/7/04 study. Averaging the results from the triplicate analysis of the 6 sample lots, Kraft reports a mean vitamin D_3 concentration of 279 IU/100g, a standard deviation of 26.3 IU/100 g, and a coefficient of variation of 9.4%.

Validation

In the 9/2/04 letter, Kraft was requested to validate the submitted AOAC method 982.29 for use in cheese. Kraft has supplied validation information in Appendices I-III of the 10/26/04 submission. Appendix I provides a brief description of the validation testing performed. Appendix II provides raw and summary data (including chromatograms and calibration curves) for the spiking studies as well as data used to determine the limit of detection (LOD) and the limit of quantitation (LOQ) for the analytical method. Appendix III provides sample calculations.

A non-fortified cheese lot with low levels of natural vitamin D_3 was used to determine an LOD of <13 IU/100 g, and an LOQ of <42 IU/100 g based on a triplicate analysis of 5 samples from the lot. All raw data, chromatograms and a calibration plot were provided.

Kraft states that the method was validated by spiking cheese at levels of 135, 270, and 540 IU/100 g followed by analysis of the spiked samples for percent recovery of vitamin D_3. Kraft reports percent recoveries of 85.8%, 95.6%, and 92.9% at the spiking levels of 135 IU/100 g, 270 IU/100g, and 540 IU/100 g, respectively. However, upon further inspection of the data, it appears that the samples were actually spiked at lower levels than reported. It appears that the spiking was carried out at levels of 100, 200, and 400 IU/100 g.[15] Although the reported spiking levels appear to be incorrect, the percent recovery values are correct since they were calculated on a total IU basis. While different than originally reported, the actual spiking levels of 100, 200, and 400 IU/100 g still bracket the petitioned level of 270 IU/100 g. Thus, we conclude that the method is properly validated.

...

[14] Kraft states that cheese was fortified at a level of 285 IU/100g rather than the petitioned 270 IU/100 g to allow for losses due to manufacturing.

[15] Kraft spiked samples using a standard solution with a vitamin D_3 concentration of 33.6 IU/ml. Three sets of samples were spiked with the following amounts of the standard: 0.3 ml, 0.6 ml, and 1.2 ml, which correspond to vitamin D_3 amounts of 10.08, 20.16, and 40.32 IU. On average, Kraft spiked cheese samples that had a mass of 10 g. As shown in the example below, taking into account the amount of vitamin D_3 with which the cheese was spiked, this yields spiking levels of approximately 100, 200 and 400 IU/100 g.

$$\text{spiking level} = 0.3\,\text{ml} \times \frac{33.6\,\text{IU}}{\text{ml}} \times \frac{1}{10\,\text{g}} = \frac{1\,\text{IU}}{\text{g}} \times \frac{100}{100} = \frac{100\,\text{IU}}{100\,\text{g}}$$

Based on the calculations provided for determination of vitamin D from the chromatographic results, it appears that Kraft has used a modification of AOAC method 982.29. AOAC method 982.29 includes a correction for the formation of pre-vitamin D during the saponification step, whereas Kraft does not. It appears that Kraft's method employs a lower temperature in the saponification step, which does not require correction for pre-vitamin D_3 formation. It is also likely that other modifications have been made to the AOAC method due to the complexities presented by the cheese matrix. Such modifications to AOAC method 982.29 were seen in another vitamin D petition which presented a complex matrix for analysis.[16]

We request that Kraft comment on whether a modified version of AOAC method 982.29 was used to generate the submitted analytical data. If a modified version of the method was used, we request that they provide a list of modifications made to AOAC method 982.29.

Exposure

Kraft has estimated the intake of vitamin D from all current and proposed uses. A summary of the intake estimate is provided in Section E.3 of the original submission, along with a detailed report in Appendix VII. In the letter dated 9/2/2004 (J. Kidwell to Kraft), Kraft was asked to provide vitamin D intake estimates for breast-fed infants 0-11 months of age. The additional intake data for breast-fed infants was provided in Appendix II of the 10/15/04 submission. All intake estimates performed by Kraft employed data from the USDA Continuing Survey of Food Intake by Individuals (CSFII, 1994-1996 and 1998 Supplemental Children's Survey).

Intake Estimate for Fortified Cheese

Kraft provided an intake estimate for vitamin D from cheese fortified at the petitioned level of 270 IU/100 g for 18 different population groups. All cheese and cheese products with a RACC of 30 g were assumed to be fortified at the maximum petitioned level. The estimate did not include imitation cheese, cottage cheese or ricotta cheese, which are not requested for fortification.[17] Additionally, the estimate did not take into consideration cheese used in commercial products (e.g., frozen entrees, canned soups and snack chips). USDA food codes used in the estimate are included in Appendix A of the intake estimate report provided in Appendix VII of the petition. The intakes are presented below in Table 4.

Table 4. Estimated intake of vitamin D_3 from proposed fortification of cheese[18]

Population	Survey Population	Percent Eaters	Vitamin D intake from fortified cheese (IU/p/d)

[16] See point 7 of the 2/19/04 chemistry memorandum from D. Folmer to J. Kidwell regarding FAP 3A4746.
[17] The intake estimate does appear to include Parmesan cheese. Hard grated cheese such as Parmesan are not requested for fortification in the current petition.
[18] Taken in part from Appendix II, Table 1 of the 10/15/04 submission.

			Mean	90th Percentile
M/F, 0 through 11 months, breast-fed	421	5	18	57
M/F, 0 through 11 months, non breast-fed	1065	14	30	61
M/F, 1 through 3 years, non breast-fed	3777	72	47	101
M/F, 4 through 8 years	3769	80	58	120
M, 9 through 13 years	569	83	78	158
M, 14 through 18 years	446	86	108	210
M, 19 through 30 years	854	84	109	218
M, 31 through 50 years	1684	76	96	197
M, 51 through 70 years	1606	66	71	156
M, 71 years and older	674	54	55	111
F, 9 through 13 years	580	83	65	140
F, 14 through 18 years	436	80	69	135
F, 19 through 30 years	760	80	72	153
F, 31 through 50 years	1614	75	65	130
F, 51 through 70 years	1539	62	52	110
F, 71 years and older	623	54	45	99
F, Pregnant/Lactating	112	72	82	183
M/F, 2 years and older	18071	74	75	159

Estimation of vitamin D intake for eaters of cheese for four fortification scenarios

Kraft performed four different vitamin D intake estimate scenarios for cheese consumers. The scenarios begin with background vitamin D intake only, and culminate in a cumulative intake that includes background intake plus intake from all currently-regulated and proposed uses of vitamin D.

Scenario 1: Background intake of vitamin D for cheese consumers

Kraft determined background vitamin D levels in foods from a proprietary database developed by ENVIRON Health Sciences Institute. This database was initially compiled in the year 2000 from the following sources: the USDA Nutrient Database for Standard Reference, Standard Release 13; the Nutrient Data System for Research version 4.02-30 (a proprietary database developed by the Nutrition Coordinating Center of the University of Minnesota); published literature; product information collected from manufacturers; information collected on internet searches; and product labels observed in the Washington, DC area between June and August, 2000. The database comprises foods which naturally contain vitamin D, as well as foods that have been fortified with vitamin D (not including fruit juices and juice drinks). Foods contained in the database include fatty fish (at levels ranging from 100 to 1600 IU/100 g depending on the type of fish); lean fish, whole eggs and mushrooms (at levels ranging from 10 to 100 IU/100 g); ready-to-eat breakfast cereals (brand-specific, but most commonly 133 IU/100 g); infant cereals and cookies (286 to 600 IU/100 g); fluid milk (41 IU/100 g); dried milk (89 IU/100 g); dairy-based beverages and beverage mixes (37 to 67 IU/100 g); margarine (440 IU/100 g); ricotta and cottage cheese (89 IU/100 g); infant formulas (40 IU/100g); soymilk[19]; and yogurt (36 IU/100 g). The USDA foodcodes for the foods in the database were not provided. Mean and 90th percentile vitamin D intake from background sources are listed

[19] Although no current regulation allows for the fortification of soymilk with vitamin D, fortified soymilk is available commercially, and thus it is prudent to include it in the background intake estimate.

below in Table 5 for all 18 population groups.

Scenario 2: Intake of vitamin D from background foods plus fortified juice and juice drinks

Kraft prepared a vitamin D intake estimate for cheese consumers from consumption of background foods and fortified juice and juice drinks. This estimate assumes that all juice and juice drink products are fortified at the maximum regulated level of 100 IU/240 ml. Mean and 90th percentile vitamin D intake estimates for this scenario are provided below in Table 5.

Scenario 3: Intake of vitamin D from background foods, fortified juice and juice drinks, and cheese fortified with vitamin D at requested levels

Kraft prepared a vitamin D intake estimate for cheese consumers from consumption of background foods, fortified juice and juice drinks (100 IU/240 ml), and cheese identified in the petition at fortification levels of 270 IU/100 g. Mean and 90th percentile vitamin D intake estimates for this scenario are provided below in Table 5.

Scenario 4: Intake of vitamin D from all natural, currently-regulated and proposed food sources

Kraft prepared a vitamin D intake estimate for cheese consumers from consumption of background foods, fortified juice and juice drinks (100 IU/240 ml), fortified cheese (270 IU/100 g), soy protein-based meal replacement beverages (140 IU/240 ml), and meal replacement bars and snack replacement bars (100 IU/40 g).[4] As a result, this scenario provides a cumulative intake estimate for cheese consumers of all natural, currently-regulated and proposed food sources of vitamin D. Mean and 90th percentile vitamin D intake estimates for this scenario are provided below in Table 5.

Table 5. Estimated intake of vitamin D from four fortification scenarios[20]

Population	Percent eaters	Scenario 1 (background only) (IU/p/d)		Scenario 2 (background and fortified juice and juice drinks) (IU/p/d)		Scenario 3 (background, fortified juice and juice drinks, and fortified cheese) (IU/p/d)		Scenario 4 (background, fortified juice and juice drinks, fortified cheese, and fortified meal/snack replacements) (IU/p/d)	
		Mean	90th %	Mean	90th %	Mean	90th %	Mean	90th %
M/F, 0 through 11 months, breast-fed	5	143	267	162	267	180	322	180	322
M/F, 0 through 11 months, non breast-fed	14	382	577	414	643	442	696	443	696
M/F, 1 through 3 years, non breast-fed	72	243	411	335	518	380	580	383	583
M/F, 4 through 8 years	80	237	388	316	490	372	559	376	568
M, 9 through 13 years	83	273	457	346	561	420	638	425	640
M, 14 through 18 years	86	287	585	376	674	480	859	484	865
M, 19 through 30 years	84	200	427	272	540	377	664	384	687
M, 31 through 50 years	76	216	413	267	500	359	619	363	627
M, 51 through 70 years	66	219	407	270	467	338	542	341	542
M, 71 years and older	54	230	397	275	465	327	524	328	527
F, 9 through 13 years	83	212	366	285	477	347	561	351	563
F, 14 through 18 years	80	162	330	241	473	308	540	311	560
F, 19 through 30 years	80	147	295	195	364	264	461	268	463
F, 31 through 50 years	75	159	305	198	383	260	463	263	468
F, 51 through 70 years	62	168	321	209	386	258	448	261	454
F, 71 years and older	54	182	331	226	373	269	421	273	435
F, Pregnant/Lactating	72	243	427	312	558	390	660	392	660
M/F, 2 years and older	74	201	385	259	482	331	576	335	582

[20] Data in this table are taken from Tables 2 and 3, Appendix II of the 10/15/04 submission.

Vitamin D intake from dietary supplements

Kraft has provided information on the intake of dietary supplements for 16 age-sex groups taken from the 1999-2000 National Health and Nutrition Examination Survey (NHANES). This data is included below in Table 6. Kraft reports that based on the data, the median intake of a vitamin D supplement for all 16 of the age groups is 400 IU. They also note that the 90th percentile vitamin D intake for persons aged 2 and over is 400 IU. Based on the data in the NHANES report, Kraft concludes that it is reasonable to assume that dietary supplements provide 400 IU of vitamin D per day for vitamin D-containing supplement users.

Table 6. Use of vitamin D containing supplements in the U.S. from NHANES data[21]

Population	**Survey Population**	**Number of respondents reporting intake of vitamin D supplements**	**Percent of the population taking vitamin D containing supplements**
M/F, 0 through 11 months	471	31	7
M/F, 1 through 3 years	711	174	29
M/F, 4 through 8 years	939	283	33
M, 9 through 13 years	595	92	22
M, 14 through 18 years	742	76	12
M, 19 through 30 years	524	85	21
M, 31 through 50 years	731	200	34
M, 51 through 70 years	708	217	39
M, 71 years and older	439	126	34
F, 9 through 13 years	606	105	21
F, 14 through 18 years	733	119	19
F, 19 through 30 years	707	269	31
F, 31 through 50 years	828	305	39
F, 51 through 70 years	717	296	49
F, 71 years and older	488	200	48
M/F, 2 years and older	9207	2506	33

Estimation of vitamin D intake for cheese consumers from all natural sources, fortified sources, and proposed fortification sources of vitamin D containing foods and dietary supplements

While Kraft discussed the appropriateness of including vitamin D obtained from dietary supplements in the vitamin D intake estimate, they did not provide a revised estimate for all populations that includes the use of dietary supplements. Rather, they focused on the broad category population of persons over 2 years of age (M/F, 2 years and older), and non-breastfeeding infants (M/F, 0 through 11 months, non breast-fed). They note that the use of a 400 IU vitamin D containing supplement results in a vitamin D intake for persons 2 years and above of 731 IU/p/d at the mean, and 976 IU/p/d at the 90th percentile.[22] They chose not to add a value of 400 IU from supplement use to non breast-fed infants (0 to 11 months), noting that the mean of 442 IU/p/d and 90th percentile of 696 IU/p/d are reflective of vitamin D intakes for most infants (i.e., as shown in Table 6, only 7% of infants were shown to receive

[21] Data in this table is taken from Table 4, Appendix VII of the original submission.

[22] These estimates are generated by adding a value of 400 IU to the mean and 90th percentile from Scenario 3 for persons aged 2 and above. As a result, this value does not incorporate the use of soy protein meal replacement beverages and meal and snack replacement bars.

dietary supplements according to the NHANES report).

FDA comments on the Kraft vitamin D intake estimate

We agree with the methods used and the results of the intake estimates provided by Kraft for the intake of fortified cheese alone, as well as Scenarios 1-4. We believe that the most relevant intake scenario for use in gauging potential intake of vitamin D by cheese consumers is Scenario 4. We prefer, however, to revise Kraft's final intake estimates in order to provide an intake based on Scenario 4 that also takes into consideration the intake of vitamin D from supplement use. For completeness, we will provide a revised intake estimate for all 18 population groups rather than only for the two population groups (persons aged 2 and over, and non breast-fed infants) provided by Kraft.

In previous intake estimates for expanded vitamin D uses (juices and juice drinks, and special dietary/weight control and meal replacement products), we chose to assume a vitamin D intake of 400 IU/p/d from supplements for all population groups. While we do not agree with Kraft's choice to not include supplement use in the final vitamin D intake for non breast-fed infants, we believe that, in light of recent recommendations from the American Academy of Pediatrics (AAP)[23], a supplement intake of 200 IU/p/d may be more appropriate than 400 IU/p/d for infants. The AAP recommends a daily vitamin D supplement of 200 IU for the following groups:

1. All breastfed infants unless they are weaned to at least 500 mL per day of vitamin D-fortified formula or milk.

2. All non-breast-fed infants who are ingesting less than 500 mL per day of vitamin D-fortified formula or milk.

3. Children and adolescents who do not get regular sunlight exposure, do not ingest at least 500 mL per day of vitamin D-fortified milk, or do not take a daily multivitamin supplement containing at least 200 IU of vitamin D.

Therefore, in light of the AAP recommendations, we will assume a vitamin D intake of 200 IU from supplement use for all infants (ages 0 to 11 months). However, we will use our previous intake of 400 IU from supplement use for all other populations (including children and adolescents). Table 7 presents a revised vitamin D intake estimate for 18 population groups taking into account Kraft's Scenario 4 intake estimate and our revised intakes for supplement use.

Table 7. Revised FDA vitamin D intake estimate based on Kraft's Scenario 4 intake estimate,

[23] See the clinical report "Prevention of rickets and vitamin D deficiency: new guidelines for vitamin D intake," from the American Academy of Pediatrics in: *Pediatrics* Vol. 111 No. 4 April 2003, pp. 908-910.

and the use of vitamin D-containing dietary supplements

Population	Percent eaters	Intake from vitamin D dietary supplements (IU/p/d)	Vitamin D intake based on Kraft Scenario 4 plus intake from dietary supplements (IU/p/d)	
			Mean	90th Percentile
M/F, 0 through 11 months, breast-fed	5	200	380	522
M/F, 0 through 11 months, non breast-fed	14	200	643	896
M/F, 1 through 3 years, non breast-fed	72	400	783	983
M/F, 4 through 8 years	80	400	776	968
M, 9 through 13 years	83	400	825	1040
M, 14 through 18 years	86	400	884	1265
M, 19 through 30 years	84	400	784	1087
M, 31 through 50 years	76	400	763	1027
M, 51 through 70 years	66	400	741	942
M, 71 years and older	54	400	728	927
F, 9 through 13 years	83	400	751	963
F, 14 through 18 years	80	400	711	960
F, 19 through 30 years	80	400	668	863
F, 31 through 50 years	75	400	663	868
F, 51 through 70 years	62	400	661	854
F, 71 years and older	54	400	673	835
F, Pregnant/Lactating	72	400	792	1060
M/F, 2 years and older	74	400	735	982

Proposed Regulation

Kraft has proposed wording for the regulation to amend 21 CFR §172.380 to allow for the use of vitamin D_3 in cheese and cheese products as defined in §170.3(n)(5), excluding cottage cheese, ricotta cheese, and grated hard cheese. We suggest that Kraft's proposed wording be revised to include the size of the RACC for the cheese of interest (30 g), so as to avoid any confusion with the RACC for other cheeses listed in §101.12. We propose the following modified language:

> Vitamin D_3 may be added, at levels not to exceed 81 IU per 30 gram reference amount customarily consumed provided in §101.12 of this chapter, to cheese as defined under §170.3(n)(5) of this chapter, excluding cottage cheese, ricotta cheese, and grated hard cheese.

Conclusion

Kraft proposes to amend §172.380 to provide for the safe use of vitamin D_3 as a nutrient supplement in cheese and cheese products at a concentration of 81 IU per 30 g RACC (270 IU/100 g). Kraft has determined the mean and 90th percentile intakes for vitamin D_3 from the petitioned use (Table 4) as well as provided cumulative intake from a number of different fortification scenarios (Table 5). We used the results from their most comprehensive intake scenario (Scenario 4) and combined them with intake from dietary supplements to yield a final mean and 90th percentile vitamin D cumulative intake for cheese consumers (Table 7).

As discussed above, Kraft should provide:

1. certificates of analysis for five lots of [redacted]
2. a discussion on the stability of vitamin D in natural cheeses
3. a comment on any modifications made to the analytical method used to determine vitamin D amounts in cheese (AOAC method 982.29).

When these requests have been addressed, we shall continue our review of the chemistry-related materials in the petition.

Daniel E. Folmer, Ph.D.

[redacted]