

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 172

[Docket No. 2003F–0370]

Food Additives Permitted for Direct Addition to Food for Human Consumption; Vitamin D₃

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the food additive regulations to provide for the safe use of vitamin D₃ as a nutrient supplement in meal replacement bars, other-type bars, and soy-protein based meal replacement beverages represented for special dietary use in reducing or maintaining body weight. This action is in response to a petition filed by Unilever United States, Inc. (Unilever).

DATES: This rule is effective [*insert date of publication in the **Federal Register***]. The Director of the Office of the Federal Register approves the incorporation by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51 of certain publications in 21 CFR 172.380 as of [*insert date of publication in the **Federal Register***]. Submit written or electronic objections and requests for a hearing by [*insert date 30 days after date of publication in the **Federal Register***]. See section VI of this document for information on the filing of objections.

ADDRESSES: You may submit written objections and requests for a hearing, identified by Docket No. 2003F–0370, by any of the following methods:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.
- Agency Web site: <http://www.fda.gov/dockets/ecomments>. Follow the instructions for submitting comments on the agency Web site.
- E-mail: fdadockets@oc.fda.gov. Include Docket No. 2003F-0370 in the subject line of your e-mail message.
- FAX: 301-827-6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD-ROM submissions]:
Division of Dockets Management (HFA-305), Food and Drug Administration,
5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the agency name and docket number for this rulemaking. All objections received will be posted without change to <http://www.fda.gov/ohrms/dockets/default.htm>, including any personal information provided. For detailed instructions on submitting objections, see the “Objections” heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or objections received, go to <http://www.fda.gov/ohrms/dockets/default.htm> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Judith L. Kidwell, Center for Food Safety and Applied Nutrition (HFS-265), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, 301-436-1071.

SUPPLEMENTARY INFORMATION:

I. Introduction

In a notice published in the **Federal Register** of August 21, 2003 (68 FR 50541), FDA announced that a food additive petition (FAP 3A4746) had been filed by Unilever United States, Inc., 390 Park Ave., New York, NY 10022–4698. The petition proposed that the food additive regulations be amended in § 172.380 *Vitamin D₃* (21 CFR 172.380) to provide for the safe use of vitamin D₃ as a nutrient supplement in certain foods for special dietary use, such as meal replacement products and snack replacement products. Foods specifically identified in the petition were meal replacement bars, other-type bars, and soy-protein based meal replacement beverages that are represented for special dietary use in reducing or maintaining body weight.

Vitamin D₃ currently is approved for use as a nutrient supplement in calcium-fortified fruit juice and fruit juice drinks under § 172.380. Vitamin D¹, including vitamin D₃, also is affirmed as generally recognized as safe (GRAS) for use in food under § 184.1950 (21 CFR 184.1950) with the following limitations:

Category of Food	Maximum Levels in Food (as served)
Breakfast cereals	350 International Units (IU)/ 100 grams (g)
Grain products and pasta	90 IU/100 g
Milk	42 IU/100 g
Milk products	89 IU/100 g

Additionally, under § 184.1950(c)(2) and (c)(3) vitamin D is affirmed as GRAS for use in infant formula and margarine, respectively.

¹ Vitamin D comprises a group of fat-soluble seco-sterols and comes in many forms. The two major physiologically relevant forms are vitamin D₂ and vitamin D₃. Vitamin D without a subscript represents either D₂ or D₃. Section 184.1950 includes crystalline vitamin D₂, crystalline vitamin D₃, vitamin D₂ resin, and vitamin D₃ resin. Section 172.380 includes only crystalline vitamin D₃.

Vitamin D₃, also known as cholecalciferol, is the chemical 9,10-seco(5Z,7E)-5,7,10(19)-cholestatrien-3-ol. Humans synthesize vitamin D₃ in skin from its precursor, 7-dehydrocholesterol under exposure to ultraviolet B radiation in sunlight. Vitamin D₃ does not accumulate significantly in the body as a result of sun exposure because it is metabolized and removed during normal skin cell turnover. Other sources of naturally occurring vitamin D are foods such as butter, buttermilk, cheese, cream, eggs, fish, goat milk, meat fats and organ meats, and mushrooms.

Vitamin D is essential for human health. The major function of vitamin D is the maintenance of blood serum concentrations of calcium and phosphorus by enhancing the absorption of these minerals in the small intestine. Vitamin D deficiency can lead to abnormalities in calcium and bone metabolism such as rickets in children or osteomalacia in adults. At high levels, vitamin D may be toxic. Excessive intake of vitamin D elevates blood plasma calcium levels by increased intestinal absorption and/or mobilization from the bone.

To ensure that vitamin D is not added to the U.S. food supply at levels that could raise safety concerns, FDA affirmed vitamin D as GRAS with specific limitations, as listed in § 184.1950. Under 21 CFR 184.1(b)(2), an ingredient affirmed as GRAS with specific limitations may be used in food only within such limitations, including the category of food(s), functional use(s), and level(s) of use. Any addition of vitamin D to food beyond those limitations set out in § 184.1950 requires either a food additive regulation or an amendment of § 184.1950.

To support the safety of the proposed uses of vitamin D₃, Unilever submitted dietary intake estimates from current and proposed uses and

naturally occurring sources of vitamin D and compared these exposure estimates to the tolerable upper intake level (UL) for vitamin D established by the Institute of Medicine (IOM) of the National Academies. The petitioner also submitted a number of publications pertaining to human clinical studies on vitamin D. Based on this information, which is discussed in section II of this document, the petitioner concluded that the proposed use of vitamin D₃ in meal replacement bars and other-type bars represented for special dietary use in reducing or maintaining body weight at levels not to exceed 100 IU per 40 g product is safe. The petitioner also concluded that the proposed use of vitamin D₃ in soy-protein based meal replacement beverages represented for special dietary use in reducing or maintaining body weight at levels not to exceed 140 IU per 240 milliliter product is safe.

II. Evaluation of Safety

To establish with reasonable certainty that a food additive is not harmful under its intended conditions of use, FDA considers the projected human dietary exposure to the additive, the additive's toxicological data, and other relevant information (such as published literature) available to the agency. FDA compares an individual's estimated daily intake (EDI) of the additive from all sources to an acceptable intake level established by toxicological data. The EDI is determined by projections based on the amount of the additive proposed for use in particular foods and on data regarding the consumption levels from all sources of the additive.

A. Acceptable Daily Intake for Vitamin D for Adults and Children

In 1997, the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board at IOM conducted an extensive review of toxicology and metabolism studies on vitamin D published

through 1996. The IOM published a detailed report that included a UL for vitamin D for infants, children, and adults. The IOM UL for vitamin D for children 1 to 18 years of age and adults is 2,000 IU per person per day (IU/p/d). The UL for infants is 1,000 IU/p/d.

The IOM considers the UL as the highest usual intake level of a nutrient that poses no risk of adverse effects when the nutrient is consumed over long periods of time. The UL is determined using a risk assessment model developed specifically for nutrients and considers intake from all sources: Food, water, nutrient supplements, and pharmacological agents. The dose-response assessment, which concludes with an estimate of the UL, is built upon three toxicological concepts commonly used in assessing the risk of exposures to chemical substances: No-observed-adverse-effect level, lowest-observed-effect level, and an uncertainty factor.

B. Estimated Daily Intake for Vitamin D

The petitioner provided average and 90th percentile vitamin D intake estimates for consumers of meal replacement bars, other-type bars, and soy-protein based meal replacement beverages represented for special dietary use from the following: (1) The proposed food uses, (2) current food uses (including naturally occurring sources of vitamin D), (3) current and proposed food uses, and (4) current and proposed food uses and dietary supplements. The proposed uses are for foods intended for use by adults as part of a weight control diet. Although these special dietary foods are not intended for use by children, the petitioner acknowledged that some sporadic use by children may occur, especially among older children. Therefore, intake estimates for adults and children over the age of 9 years were provided. The agency has determined that the methodology used to calculate these estimates is appropriate.

For the proposed food uses, dietary intake of vitamin D₃ for 90th percentile consumers of meal replacement bars, other-type bars, and soy-protein based meal replacement beverages was estimated to be 215 IU/p/d for consumers 9 years of age and older. The corresponding mean intake was estimated to be 127 IU/p/d.

For currently regulated uses in conventional foods (under § 184.1950 and § 172.380) and naturally occurring sources, mean dietary exposure to vitamin D for consumers of meal replacement bars, other-type bars, and soy-protein based meal replacement beverages was estimated to be 470 IU/p/d for consumers 9 years of age and older. Intake at the 90th percentile was estimated to be 957 IU/p/d. For consumers 9 years of age and older, mean and 90th percentile dietary intakes from current (including naturally occurring sources) and proposed food uses of vitamin D were estimated to be 565 IU/p/d and 995 IU/p/d, respectively.

The petitioner also considered the intake of vitamin D from dietary supplements. The National Health and Nutrition Examination Survey III (NHANES III) data indicate that approximately 40 percent of the U.S. population 2 months of age and older take dietary supplements. The NHANES III data also show that, when vitamin D is taken as a dietary supplement, the most frequent level is 400 IU/p/d. As a conservative estimate of intake of vitamin D from dietary supplements and food uses, the petitioner assumed that all consumers of meal replacement bars, other-type bars, and soy-protein based meal replacement beverages represented for special dietary use would take dietary supplements containing 400 IU of vitamin D. They then added this value to the mean and 90th percentile intake estimates from current and proposed food uses. For consumers of meal replacement bars, other-type bars,

and soy-protein based meal replacement beverages, mean and 90th percentile dietary intakes from current and proposed food uses and dietary supplements were estimated to be 965 IU/p/d and 1,395 IU/p/d for consumers 9 years of age and older, respectively. FDA concurs with these exposure estimates.

C. Safety Assessment

To support the safety of their proposed uses for vitamin D₃, Unilever submitted 16 scientific articles published subsequent to the IOM report and issuance of the 2003 final rule permitting the use of vitamin D₃ in calcium-fortified fruit juices and fruit juice drinks within the prescribed limitations (68 FR 9000, February 27, 2003). Unilever concluded that the recent publications continue to support the safe use of vitamin D supplementation in both animals and humans. FDA concurs with Unilever's conclusions.

FDA considered the UL established by IOM for children and adults relative to the intake estimates provided by the petitioner as the primary basis for assessing the safety of the proposed use of vitamin D₃ in meal replacement bars, other-type bars, and soy-protein based meal replacement beverages represented for special dietary use. For all children and adults 9 years of age and older, mean and 90th percentile intake estimates from current and proposed food uses of vitamin D are well below the IOM UL of 2,000 IU/p/d. Additionally, when dietary supplements are included in the calculations, intake estimates remain below the UL.

Because the EDI of vitamin D from all sources is less than the UL, the agency concludes that dietary exposure of vitamin D₃ from its use as a nutrient supplement in meal replacement bars, other-type bars, and soy-protein based meal replacement beverages represented for special dietary use in reducing or maintaining body weight will not pose a safety concern.

III. Conclusion

Based on all data relevant to vitamin D₃ reviewed by the agency, FDA concludes that there is a reasonable certainty that no harm will result from the use of vitamin D₃ as a nutrient supplement in meal replacement bars, other-type bars, and soy-protein based meal replacement beverages represented for special dietary use in reducing or maintaining body weight. Thus, vitamin D₃ is safe for its proposed use and the agency concludes that the food additive regulations should be amended as set forth in this document. To ensure that only food grade vitamin D₃ is used in food, the additive must meet the specifications set forth in this document.

Based on a request by the petitioner, FDA also is updating § 172.380 by citing the 5th edition of the *Food Chemicals Codex* rather than the 4th edition. Section 172.380(b) currently states that vitamin D₃ must meet the specifications of the *Food Chemicals Codex*, 4th ed., 1996. The agency compared specifications for vitamin D₃ in the 4th and 5th editions and found them to be identical. Therefore, the agency is making this requested editorial change. In addition, the agency is making an editorial update to § 172.380(b) to reflect the new address for the National Academy Press. The agency also is making editorial changes to § 172.380(c) for clarification.

In accordance with § 171.1(h) (21 CFR 171.1(h)), the petition and the documents that FDA considered and relied upon in reaching its decision to approve the petition are available for inspection at the Center for Food Safety and Applied Nutrition by appointment with the information contact person (see **FOR FURTHER INFORMATION CONTACT**). As provided in § 171.1(h), the agency will delete from the documents any materials that are not available for public disclosure before making the documents available for inspection.

IV. Environmental Effects

The agency has previously considered the environmental effects of this rule as announced in the notice of filing for FAP 3A4746 (68 FR 50541). No new information or comments have been received that would affect the agency's previous determination that there is no significant impact on the human environment and that an environmental impact statement is not required.

V. Paperwork Reduction Act of 1995

This final rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VI. Objections

Any person who will be adversely affected by this regulation may file with the Division of Dockets Management (see **ADDRESSES**) written or electronic objections. Each objection shall be separately numbered, and each numbered objection shall specify with particularity the provisions of the regulation to which objection is made and the grounds for the objection. Each numbered objection on which a hearing is requested shall specifically so state. Failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held. Failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. Three copies of all documents are to be submitted and are to be identified with the docket number found in brackets in the heading of this document. Any objections received in response

to the regulation may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 172

Food additives, Incorporation by reference, Reporting and recordkeeping requirements.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act, authority delegated to the Commissioner of Food and Drugs, 21 CFR part 172 is amended as follows:

PART 172—FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION

■ 1. The authority citation for 21 CFR part 172 is amended to read:

Authority: 21 U.S.C. 321, 341, 342, 348, 371, 379e.

■ 2. Section 172.380 is amended by revising paragraph (d) to read as follows:

§ 172.380 Vitamin D₃.

* * * * *

(b) Vitamin D₃ meets the specifications of the *Food Chemicals Codex*, 5th ed. (2004), pp. 498–499, which is incorporated by reference. The Director of the Office of the Federal Register approves this incorporation by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. You may obtain copies from the National Academy Press, 500 Fifth St. NW., Washington, DC 20001 (Internet address <http://www.nap.edu>). Copies may be examined at the Center for Food Safety and Applied Nutrition’s Library, Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, or at the National Archives and Records Administration (NARA). For information on

the availability of this material at NARA, call 202-741-6030, or go to: http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.

(c) The additive may be used as follows:

(1) At levels not to exceed 100 International Units (IU) per 240 milliliters (mL) in 100 percent fruit juices (as defined under § 170.3(n)(35) of this chapter) that are fortified with greater than or equal to 33 percent of the reference daily intake (RDI) of calcium per 240 mL, excluding fruit juices that are specially formulated or processed for infants.

(2) At levels not to exceed 100 IU per 240 mL in fruit juice drinks (as defined under § 170.3(n)(35) of this chapter) that are fortified with greater than or equal to 10 percent of the RDI of calcium per 240 mL, excluding fruit juice drinks that are specially formulated or processed for infants.

(3) At levels not to exceed 140 IU per 240 mL (prepared beverage) in soy-protein based meal replacement beverages (powder or liquid) that are represented for special dietary use in reducing or maintaining body weight in accordance with § 105.66 of this chapter.

(4) At levels not to exceed 100 IU per 40 grams in meal replacement bars or other-type bars that are represented for special dietary use in reducing or maintaining body weight in accordance with § 105.66 of this chapter.

Dated: June 20, 2005.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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