NATURAL RESOURCES DEFENSE COUNCIL

SENT BY EMAIL AND MAIL

November 12, 2013

Dr. Antonia Mattia
Office of Food Additive Safety
U.S. Food and Drug Administration
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Email: antonia.mattia@fda.hhs.gov

Re: Comments on GRN#471: GRAS exception notification regarding annatto seed extract for use in all foods.

Dear Dr. Mattia:

NRDC respectfully submits these observations on FDA's Generally Recognized as Safe (GRAS) exception notification for DeltaGold®, a tocotrienol-rich extract derived from the annatto seed (*Bixa orellana*). The additive manufacturer describes DeltaGold as containing a minimum concentration of 70% tocotrienols, approximately 90% of which is δ-tocotrienol and 10% of which is γ-tocotrienol, and virtually free of the tocopherols form of vitamin E. [1] In GRN#471, American River Nutrition, Inc. notified the Office of Food Additive Safety that it had determined that the use of DeltaGold is GRAS for its intended use as an ingredient in any type of food.[2]

We appreciate FDA's practice of posting the additive manufacturer's notice on its website and hope it will consider these comments before taking final agency action. We have concerns with the scientific procedures American River Nutrition, Inc. has used to justify its claim that DeltaGold is GRAS for its intended use. Chief among our concerns is the company's flawed additive characterization, and exposure and hazard assessment. Specifically, it did:

- Not providing detailed descriptions of carotenoid content (specifically bixin and norbixin) in the raw material and the final product;
- Not considering dietary supplements, natural sources of tocotrienols in food, and uses of annatto seed extract as flavor [3] in its estimated daily intake (EDI) calculation.
- Not providing estimated 90th percentile and subpopulations EDI, unlike previous GRN #307 [4];

[1] GRN #471. Notice to US Food and Drug Administration that the use of DeltaGold® is Generally Recognized as Safe. Received May 13, 2013. U.S. Food and Drug Administration Office of Food Additives Safety. Page 7. See http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=graslisting&id=471

[2] GRN #471, page 5.

[3] Hall RL and Oser BL. 1965. Recent Progress in the Consideration of Flavoring Ingredients Under the Food Additives Amendment. III. GRAS Substances. Food Technology 19:2

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- Improperly using the cost of the additive as the "self-limiting" factor to establish use levels; and
- Not performing toxicology testing for DeltaGold where tocopherols are not present in detectable levels, and relying on studies that tested mixtures that may not be an accurate indication of the dose of tocotrienols that may cause harm.

This particular notice also has problems that are common to many in the program, including the fact that it ignores possible cumulative effects of the substance in the diet, does not reflect the minimum testing level that should be conducted according to FDA guidance, and suffers from possible financial conflicts of interest.

Therefore, FDA should issue a letter to American River Nutrition, Inc. saying that the notice does not provide a sufficient basis for a GRAS determination.

More details about our concerns are below.

Additive manufacturer's expanded use in notice?

American River Nutrition, Inc. states that DeltaGold is GRAS under the conditions of intended use as an ingredient in food at an exposure level of up to 212 mg tocotrienols per day.[5]

American River Nutrition, Inc. reports that there is an additional GRAS exemption notification for tocotrienols from palm oil for intended use in fats or oils, such as salad dressing, mayonnaise, margarine, and spread; potato chips and salty snacks; bakery products; ready-to-eat cereals; meal replacement and other functional beverages; meatless soups and soup mix; meatless gravies, sauces, and pasta sauces; processed juices, processed fruits, juice drinks, and punch; frozen dairy desserts; yogurt; pudding; gelatin products; chocolate milk and flavored milk; soy milk and products; chocolate, candy, confectionary, and sweets; beverages; and chewing gum.[6]

The notifier intends to use DeltaGold in all foods; however, it is unclear what the function of the ingredient would be since American River Nutrition, Inc. states that "DeltaGold does not add texture or taste to foods."[7]

NRDC is concerned that the notifier established its use level based on the inaccurate interpretation of the definition of "self-limiting level". According to the 1997 GRAS proposed rule [8] "if a substance is above its technologically self-limiting level, the food becomes unpalatable, unappealing or otherwise unfit for consumption." The notifier improperly used the cost of the additive as the "self-limiting" factor stating that "it would be cost-prohibited to add more than 100 mg of tocotrienols per serving to one particular food item."[9] We treat this 100 mg as the upper limit allowed in a serving of the food.

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[4] GRN # 307. Generally Recognized as Safe (GRAS) Determination for the Use of Palm Tocotrienol Rich Fractions (TRF) as Ingredients in Food. Received October 23, 2009. U.S. Food and Drug Administration Office of Food Additives Safety. Page 4. See http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=grasListing&id=307

[5] GRN #471, page 5

[6] GRN # 307, page 4.

[7] GRN #471, page 15

[8] April 17, 1997 Federal Register, 62 Fed Reg. 18938

[9] GRN #471, page 15

Concerns with this notice that are common to others

NRDC has serious reservations about the GRAS program administered by FDA. First, we believe that Congress intended that the food additive petition, and not the GRAS exemption, should be the primary mechanism to determine the safety of new chemicals added to food under the Food Additives Amendment of 1958. The agency has wrongly allowed industry to expand the loophole so it has essentially swallowed the law.

Second, although we recognize the perceived benefits of agency review through the voluntary GRAS notification program, we think it is inappropriate for FDA to be running this program based on nothing more than a proposed rule. While the agency may describe its "no question" letters as informal opinions that are not agency actions, in practice, these letters are used as a stamp of FDA approval. The letters thus meet the definition of an agency action.

Finally, we urge FDA to proactively and formally invite comment to its proposed exemption notifications and to respond to concerns raised. The public, including competitors, academic researchers, non-governmental organizations, and other governments, can add value to this decision-making process and identify issues the agency might have missed. This is especially important given the conflicts of interest inherent in allowing additive manufacturers themselves to make safety decisions, and it will ameliorate to at least a small extent the reality that the agency is under-resourced and without sufficient expertise in its staff on the wide range of scientific issues often involved.

There are problems common to notices. These include:

1. Analysis ignores the Food Additives Amendment of 1958 clearly indicating that "the cumulative effect of the substance in the diet, taking into account any chemically of pharmacologically related substance or substances in such a diet" (21CFR §170.3(i)) is one of the factors to consider in determining whether a use is safe.
2. Analysis ignores FDA's guidance on the conduct of a proper safety assessment. Specifically, it does not assign a Concern Level that is essential to determining what minimum testing should be conducted according to FDA's recommendations.
3. NRDC questions the qualification of scientists making GRAS determinations because of financial conflicts of interest. [10] The science on conflicts of interest and the 2009 Institute of Medicine report make clear that regardless of professional expertise and the best of intentions, conflicted experts may not fully and objectively capture possible contradictory data, describe gaps or flaws in the available data, and fairly characterize the scientific community's assessment on the use of this additive in food. [11]. These conflicts of interest are severe enough that, based on FDA's guidance,[12] many scientists making GRAS determinations would have a disqualifying financial conflict that would render them ineligible to advise the agency if it sought guidance on the issue from outside experts. Therefore, a conflicted scientist should not be making the final safety decision.

Concerns with specific issues in this notice

American River Nutrition, Inc. did not assign a Concern Level to DeltaGold. Based on the information provided in the notice, the proper Concern Level would be 3—the highest level.

The president of American River Nutrition, Inc. appears to have made the safety assessment. [13] As president of the company, he is likely to have financially benefitted from the decision and the success of its company depends upon the sale of its products which include DeltaGold. Without a doubt, this is a severe conflict of interest.

Annatto extracts are approved color additives for use in foods. (21CFR 73.30) We have identified almost 12,000 products[14] currently in the U.S. market containing annatto as an ingredient. The products include baby food, bread and baking goods, cereal, candy, tea, condiments, processed meats and cheese, ice cream, dairy, salad dressing, frozen foods, snacks, isotonic, produce and nutrition food. In most cases, it is listed as "color." However, it is unclear if the ingredient has other function.

The annatto color pigment contains carotenoids, specifically bixin and norbixin. In 2004, the Joint WHO/FAO Expert Committee on Food Additives (JECFA) reviewed the acceptable daily intake (ADI) for annatto extract based on new toxicology data and established a range of temporary ADIs for different preparations of annatto extract based on various amounts of bixin and norbixin. Based on this information, it seems clear that the higher the content of norbixin, the lower the ADI.[15] American River Nutrition, Inc. did not report the amount of bixin and norbixin in its raw material annato seed oil or in the final product. This is important because:

1. there are a large number of products already in the market containing annatto extract as color additive;
2. DeltaGold may be added to all foods; and
3. the notifier did not report the amount of pigment in DeltaGold. Therefore, it is unknown whether the exposure to the pigment components will exceed the lowest temporary ADI of 0.4mg/kg body weight determined by JECFA.

Without this information, the company's GRAS determination is incomplete.

Exposure calculations are also of concern. Specifically, the calculation of the EDI for uses described in this notification and the calculation of the cumulative EDI is flawed and confusing. Specifically:

1. Calculation of EDI did not follow FDA's guidance. The notice neither provides information on average and 90th percentile exposure nor identifies the high consumer group. It did not use the most recent NHANES 2-day intake survey that better reflects changes in dietary consumption. Instead it chose the outdated 1992-1994 Market Research Corporation of America Information Services data. Then, it identified the greatest total number of servings of food estimated by USDA, 18.2 daily servings, and divided it by 10 solely on the basis that "it is reasonable to assume that due to the high cost of this specialty ingredient, DeltaGold would not be present in all servings of food consumed in a day."[16] Therefore, it concluded that daily exposure would be 212 mg for 2 servings of food. Unlike GRN #307, there is no evidence that American River Nutrition, Inc. performed a dietary exposure assessment to calculate the 90th percentile exposure as

[13] GRN #471, page 5.
[14] Based on proprietary database by the Gladson, Inc. using the March 15, 2013 version. See http://www.gladson.com.
[15] GRN #471, pages 30-31
[16] GRN #471, page 34

recommended by the FDA.[17] The company's approach is inconsistent with FDA's guidance and provides no explanation for the variance.

2. Calculation of EDI did not properly consider exposure to children: Unlike some previous GRAS notices such as GRN #307 [18], there is no evidence that American River Nutrition, Inc. estimated the exposure of children to DeltaGold. It also did not follow FDA's recommended "conservative assumptions", namely the assumption that the additive saturates the market, the additive is used at the anticipated maximum allowed levels for all uses and the estimate should be based on the 90th percentile of individuals eating the food. [19] American River Nutrition did not provide an explanation for overlooking exposure to subpopulations even though the company intends to use DeltaGold in all foods.
3. Calculation of cumulative EDI was flawed: The law clearly states that all dietary sources of an ingredient must be considered when calculating the cumulative EDI. That includes natural food sources of tocotrienols such as rice bran oil, corn, oats, wheat and other grains, and dietary supplements which are considered food per 21 CFR §1.328. It appears that American River Nutrition, Inc. did not include these sources in its EDI. More importantly, it did not include the contribution of the dietary supplement the company itself makes and markets (also called DeltaGold),[20] or any of its competitors' listed on Table 5 of the GRN. [21] It is worth noting that NHANES collects data on dietary supplement consumption and are available to estimate their contribution to a total daily intake.

Beyond the concerns with the EDI, NRDC questions some of the toxicology data presented in this notice. It appears, American River Nutrition, Inc. did not perform new toxicology testing. Rather it relied upon published studies the majority of which tested mixtures of tocopherols and tocotrienols. This is of particular concern because DeltaGold is described as virtually free of tocopherols and containing 90% of δ-tocotrienol.

1. On page 9 of the GRN the notifier states δ-tocotrienol's biological activity is unknown and "have not been formally accepted by a government agency," and that α-tocopherol is the vitamin E component with the highest biological activity. The majority of the studies cited by American River Nutrition, Inc. were done using mixtures of tocopherols and tocotrienols and few reported adverse effects.
2. In the two cases where tocotrienol-rich extracts (their percentage of tocotrienols was similar to DeltaGold) were tested, the toxicology data were a) obtained not following FDA's recommended testing; or b) misinterpreted. For instance, one study tested the anti-tumor activity of two doses of 97% δ-tocotrienol supplement using immunocompromised mice carrying a pancreatic tumor.[22] The second study [23] tested a rice bran extract

[17] U.S. Food and Drug Administration. Guidance for Industry: Estimating Dietary Intake of Substances in Food. Section IV. Modeling Intake Analysis, Subsection E. Upper Percentile Estimates. August 2006. See http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm074725.htm#chro

[18] GRN #307 reported an EDI of 28.6mg/day for children 1-3 years and 49.2mg/day for the entire population

[19] GRN #307, page 43

[20] American River Nutrition, Inc. now offering DeltaGold Annatto-tocotrienol, a vitamin E supplement associated with breast health benefits. August 13, 2013. Press release. See http://www.prweb.com/releases/2013/8/prweb11015014.htm

[21] GRN #471, page 30

[22] Hussain K et al. Vitamin E delta-tocotrienol levels in tumor and pancreatic tissue of mice after oral administration. 2009. *Pharmacology* 83:157-163

containing 98.7% tocotrienols (2.5% α, 92% γ and 4.2% δ). The study authors described that diets were supplemented with 0.02, 0.06 or 0.20% of the tocotrienols, which corresponded to mean exposures of 4.7, 14.6 and 42.2 mg/rat/day, respectively. The results showed that the lowest intake of 4.7 mg/rat/day caused significantly higher relative liver weight compared to those in the 14.6 and 42.2 mg/rat/day groups "for unknown reasons." Although a NOAEL was not determined, the authors suggested a safe dose of less than 0.20% of the diet. This dose response finding is relevant and requires investigation or an explanation. Although γ was the most abundant tocotrienol tested, the study used "a pure tocotrienol product" with negligible tocopherols, similar to DeltaGold.

DeltaGold is described as "virtually free of the tocopherols form of vitamin E." Therefore, the notifier should have tested the effect of DeltaGold in the absence of potentially beneficial effects of tocopherols, especially considering the effects observed at doses lower than the proposed exposure level of up to 212 mg tocotrienols per day.

In its guidance for industry,[24] FDA lists studies it recommends for Concern Level 3 additives such as DeltaGold. In Appendix A we compared the studies recommended by FDA to those described in the GRAS notification. Based on the scarcity of information provided, we were unable to identify the information needed to complete it. Therefore, we included question marks since the notice is insufficient to determine whether the minimum toxicology testing recommended by FDA was completed.

We also note that the notifier only mentioned one three-generation rat study for consumption of rice bran oil. The composition of the oil is believed to be 13% α, 79% γ, and 7.6% δ-tocotrienols, which is also different from DeltaGold. This data gap is particularly important because American River Nutrition, Inc. intends to use DeltaGold as an ingredient in all food and DeltaGold "is intended to replace consumption of vitamin E added to foods in the same respective food categories"[25] as listed in GRN #307.

Similarly, American River Nutrition, Inc. listed the number of human studies using supplements containing tocotrienols. The great majority of the studies tested mixtures of tocopherols and tocotrienols, only 26% tested δ-tocotrienol and for no longer than two months.

Conclusion

It is clear that DeltaGold is a tocotrienol-rich extract that is sold as dietary supplement by the notifier. With the GRAS notification, American River Nutrition, Inc. intends to expand the market to all conventional foods. However, this unique extract has been neither adequately tested nor adequately evaluated to determine its uses are safe at this time. FDA should notify the company that its claim that DeltaGold is GRAS is insufficient.

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[23] Shibata A et al. Physiological effects and tissue distribution from large doses of tocotrienol in rats. *Biosci Biotechnol Biochem*. 2012. 76:1805-1808

[24] FDA. 2006. Guidance for Industry. Summary table of recommended toxicological testing for additives used in food. See http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm054658.htm

[25] GRN #411, page 36

Please do not hesitate to call or email with questions. I can be reached at 202-513-6244 and mmaffini@nrdc.org.

Thank you for your prompt attention to this request.

Sincerely,

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Appendix A: Comparison of studies recommended by FDA for Concern Level 3 additives to those described in the GRAS notification

Appendix A

Comparison of studies recommended by FDA for Concern Level 3 additives to those described in the GRAS notification

FDA recommend type of study	Type of publication[2]	Year of publication	Year study conducted	Study details available	Redbook compliant[3]	GLP compliant[4]
Genetic toxicity tests	?	?	?	?	?	?
Short-term toxicity tests with rodents[5,6]	?	?	?	?	?	?
Subchronic toxicity studies with rodents[5,6]	?	?	?	?	?	?
Subchronic toxicity studies with non-rodents[5,6]	?	?	?	?	?	?
One-year toxicity studies with non-rodents[6]	?	?	?	?	?	?
Chronic toxicity or combined chronic toxicity/carcinogenicity studies with rodents[6]	?	?	?	?	?	?
Carcinogenicity studies with rodents	Not found	Not found	Not found	Not found	Not found	Not found
Reproduction studies[6]	?	?	?	?	?	?
Developmental toxicity studies[6,7]	?	?	?	?	?	?
Metabolism and pharmacokinetic studies[7]	?	?	?	?	?	?
Humans studies[7]	?	?	?	?	?	?

[1] FDA. 2006. Guidance for Industry. Summary table of recommended toxicological testing for additives used in food. See http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm054658.htm

[2] (A) unpublished, (B) published but not peer reviewed, (C) peer-reviewed and published, or (D) conducted by a government agency

[3] FDA. 2000. Toxicological principles for the safety assessment of food ingredients. See www.**fda**.**gov**/downloads/**Food**/GuidanceRegulation/UCM222779.pdf.

[4] 21 C.F.R. Part 58.

[5] If needed as preliminary to further study.

[6] If indicated by available data or information.

[7] Including screens for neurotoxicty and immunotoxicty (available in 1993 Draft Redbook II).