NATURAL RESOURCES DEFENSE COUNCIL

SENT BY EMAIL AND MAIL

November 22, 2013

Dr. Antonia Mattia
Office of Food Additive Safety
U.S. Food and Drug Administration
Mail Stop HFS-255
College Park, MD 20740
Email: antonia.mattia@fda.hhs.gov

Re: Comments on GRN#474: GRAS exception notification for black pepper extract (Bioperine®) for use as a flavoring agent.

Dear Dr. Mattia:

NRDC respectfully submits these observations on FDA's Generally Recognized as Safe (GRAS) exception notification for BioPerine®, an extract from black pepper which principal ingredient is piperine at concentrations greater than 95%.[1]

Sabinsa intends to use BioPerine as a flavoring agent (flavor enhancer) in "Baked Goods, Breakfast Cereals, Milk Products, Cheese, Egg Products, Processed Vegetables, Soft Candy, Soups, Snack Foods, Beverages Type I - Non-alcoholic, Imitation Dairy Products, Hard Candy, Chewing Gum, Granulated Sugar, Seasonings & Flavors" at levels up to 15 part per million (ppm). The intended use is estimated to result in a maximum daily intake of 13.70 mg/person.[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 Sabinsa has used to justify its claim that BioPerine is GRAS for its intended uses. Chief among our concerns is the company's apparent selective use of available evidence and flawed exposure and hazard assessments. Specifically:

- Failing to mention that the European Food Safety Authority (EFSA) concluded that additional toxicology and use levels are needed to determine if piperine is safe as a flavor.[3]

[1] GRN #474. GRAS Notification for Black Pepper Extract (Bioperine®). Received June 17, 2013. U.S. Food and Drug Administration Office of Food Additives Safety. Page 13. See http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=grasListing&id=474

[2] GRN #474, page 4.

[3] Scientific Opinion on Flavouring Group Evaluation 86, Revision 1 (FGE.86Rev1). Consideration of aliphatic and aromatic amines and amides evaluated by JECFA (65th meeting). EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). 2011. European Food Safety Authority. EFSA Journal 9(4):1926. Page 19.

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- Ignoring FDA exposure assessment guidance by using antiquated data, not considering impact on children or all sources of piperine. Specifically, Sabinsa:
    - Used a1965 Market Research Corporation of America (MRCA) report on frequency of eating and U.S. Department of Agriculture (USDA) mean portion size to estimate the *per capita* consumption to calculate the estimated daily intake (EDI). The notifier did not explain why it did not use the National Health and Nutrition Examination Survey (NHANES) 2-day food consumption survey data from the past ten years as recommended by FDA;
    - Did not provide an EDI for children; and
    - Did not calculate a cumulative EDI considering all sources of piperine, including dietary supplements (and more specifically the one they make) and natural sources.
- Lacking toxicology testing studies for BioPerine. The notifier:
    - Estimated an acceptable daily intake (ADI) based on a no observed adverse effect level (NOAEL) that EFSA said is based on inappropriate studies;
    - Did not consider studies showing immunotoxicity and reproductive toxicity, or human studies showing piperine interferes with drug metabolism; and
    - Relied on studies the majority of which did not perform toxicological testing but rather "were undertaken to evaluate its efficacy for different health conditions" and tested different black pepper-derived compounds.[4]

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 Sabinsa saying that BioPerine is not GRAS and should not be used until FDA approves a food additive petition for its use.

Notice expands the existing allowed uses of additive

Sabinsa states that BioPerine is GRAS under the conditions of intended use as an ingredient in "Baked Goods, Breakfast Cereals, Milk Products, Cheese, Egg Products, Processed Vegetables, Soft Candy, Soups, Snack Foods, Beverages Type I - Non-alcoholic, Imitation Dairy Products, Hard Candy, Chewing Gum, Granulated Sugar, Seasonings & Flavors" at a maximum intake of 13.7mg per person per day.[5]

Sabinsa reports that there are additional GRAS exemptions for ingredients containing piperine, the main constituent of BioPerine, or for piperine itself. It noted that the Flavor and Extract Manufacturer Association (FEMA) has determined the use of black pepper (FEMA No. 2844), black pepper oil (FEMA No. 2845) and black pepper oleoresin (FEMA No. 2846, and piperine (FEMA No. 2909) as GRAS.

FDA has also designated black pepper, its essential oil, oleoresin, and natural extractives (21 CFR 182.20) as GRAS and has approved the use of piperine as a synthetic flavoring substance (21 CFR 172.515)[6] under its food additive regulations.[7] Oleoresin is the approved GRAS substance

[4] GRN #474, page 20.
[5] GRN #474, page 4.
[6] GRN #474, page 17.
[7] We do not understand how a use of an additive can be both a food additive and GRAS under the law.

containing the highest percentage of piperine, approximately 40%. In contrast, BioPerine contains >95% of piperine.[8] This very high concentration of piperine makes BioPerine a unique ingredient.

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 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. It will also 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 which clearly indicates 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" (21 U.S.C. 348(c)(5)(B) and 21 CFR §170.3(i)) is one of the factors that must be considered in determining whether an additive's 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.[9]
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

[8] GRN #474, page 15, Table 3.

[9] FDA, Guidance for Industry: Summary Table of Recommended Toxicology Testing for Additives Used in Food, 2006. See http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/ingredientsadditivesgraspackaging/ucm054658.htm.

[10] Neltner, TG et al. Conflicts of Interest in Approvals of Additives to Food Determined to Be Generally Recognized as Safe. Out of Balance. Journal of the American Medical Association. Internal Medicine. 2013. Published online August 07, 2013. doi:10.1001/jamainternmed.2013.10559

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

Sabinsa states that "[a]lthough some foods with standard of identity are included in the list of foods, at present the use of BioPerine is intended for foods without a standard of identity."[13] Since many of these products have recognized standards of identity, is Sabinsa really intending it not to be used in those foods?

Sabinsa arranged for an expert panel of three scientists to review the "publicly available data summarized" in the GRN. Their conflicts of interest are not disclosed in the notice. One of them is the president of the consulting firm hired as the agent for Sabinsa Corporation. He is likely to financially benefit from a positive decision.

A. Failure to mention that the EFSA concluded that additional toxicology and use levels information to finalize its safety evaluation of piperine

NRDC is concerned that the notifier did not include the 2011 Scientific Opinion by EFSA's Flavoring Group stating that it did not agree with the World Health Organization/ Food and Agriculture Organization Joint Expert Committee on Food Additives (JECFA) that "appropriate studies are available for deriving NOAELs."[14] The EFSA panel of independent scientists concluded that additional toxicity data are required for piperine.[15] The report also stated that use levels are needed to develop "a more refined exposure assessment and to finalise the evaluation."[16]

Therefore, it seems that there is not an established acceptable daily intake (ADI) since EFSA expert panel rejected JECFA's no observed adverse effect level (NOAEL) of 20 mg/kg/day. In NRDC's opinion, the concerns of EFSA's panel of scientists indicate that there is no consensus in the scientific community that the use of piperine as flavor is safe.

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[11] Conflicts of interest in medical research, education and practice. Institute of Medicine. 2009. National Academies Press

[12] U.S. Food and Drug Administration. Guidance for the public, FDA advisory committee members, and FDA staff on procedures for determining conflicts of interest and eligibility for participation in FDA advisory committees. 2008. See http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125646.pdf

[13] GRN #474, page 18.

[14] Scientific Opinion on Flavouring Group Evaluation 86, Revision 1 (FGE.86Rev1). Consideration of aliphatic and aromatic amines and amides evaluated by JECFA (65th meeting). EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). 2011. European Food Safety Authority. EFSA Journal 9(4):1926. Page 19.

[15] FL-no.14.003

[16] Scientific Opinion on Flavouring Group Evaluation 86, Revision 1 (FGE.86Rev1). Consideration of aliphatic and aromatic amines and amides evaluated by JECFA (65th meeting). EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). 2011. European Food Safety Authority. EFSA Journal 9(4):1926. Page 19.

B. Ignoring FDA exposure assessment guidance by using antiquated data, not considering impact on children or all sources of piperine.

The EDI calculation for uses described in this notification and the calculation of the cumulative EDI are flawed and confusing. For instance:

1. The notifier used antiquated data: Sabinsa did not use the most recent NHANES 2-day intake food survey that better reflects changes in dietary consumption. Instead it calculated the EDI[17] using the 1965 mean consumption estimates of designated food categories based on MRCA mean frequency of eating and USDA mean portion size. The mean EDI was calculated as 6.85mg BioPerine/person; then it multiplied by two to estimate the 90th percentile exposure of 13.7mg/person. Sabinsa did not provide any explanation for using this outdated method, except that "FDA historically relied on MRCA survey data to determine consumption estimates."[18] Also, the notice does not identify the subpopulation that is above 90th percentile. In addition, we do not understand why the notifier did not use the maximized survey-derived intake (MSDI) approach.[19] Although both JECFA and EFSA recognized that the MSDI may underestimate normal intake, it is still considered a relevant estimation in the absence of use levels.
2. Calculation of EDI did not properly consider exposure to children: There is no evidence that Sabinsa estimated the exposure of children to BioPerine, even though the intended uses include foods widely consumed by children such as cereal, candy, soups, snacks, and chewing gum. The notifier did not provide an explanation for overlooking exposure to children.
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 (21 U.S.C. 348(c)(5)(B) and 21 CFR §170.3(i)). This includes natural food sources of piperine and dietary supplements which are considered food per 21 CFR §1.328. It appears that Sabinsa 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 BioPerine).[20] Note that NHANES collects data on dietary supplement consumption and are available to estimate their contribution to a total daily intake.

C. Lacking toxicology testing studies for BioPerine

NRDC questions some of the toxicology data presented in this notice. Sabinsa did not appear to perform new toxicology testing and its interpretation of the referenced studies is of great concern.

In addition, Sabinsa did not assign a Concern Level to BioPerine. Based on the information provided in the notice, the proper Concern Level would be 3—the highest level. In its guidance for industry,[21] FDA describes studies it recommends for Concern Level 3. In Appendix A, we compared the studies recommended by FDA to those described in the GRAS

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[17] GRN #474, page 19-20

[18] Id. at 19

[19] Scientific Opinion on Flavouring Group Evaluation 86, Revision 1 (FGE.86Rev1). Consideration of aliphatic and aromatic amines and amides evaluated by JECFA (65th meeting). EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). 2011. European Food Safety Authority. EFSA Journal 9(4):1926. Page 6.

[20] See Disclaimer at http://www.bioperine.com/clinical.html

[21] 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

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.

NRDC has the following specific concerns"

1. Estimated an acceptable daily intake (ADI) based on a no observed adverse effect level (NOAEL) that EFSA said is based on inappropriate studies: The subchronic study cited as the source of the NOAEL of 20mg/kg/day was conducted in a single species and using a single sex (male rats). Sabinsa notes that "JECFA also considered this dose the NOAEL." However, it failed to report that EFSA disagreed and rejected the study as "appropriate." NRDC believes that it is inappropriate for Sabinsa to estimate its own ADI when the scientific community clearly stated that the available scientific information is insufficient and more is needed before concluding that piperine use as a flavor is safe.
2. Did not consider studies showing immunotoxicity and reproductive toxicity, or human studies showing piperine interferes with drug metabolism:
    a. The notifier described a study showing that piperine resulted in immunotoxicity[22] at all dose levels by suppressing "the cellular population of lymphoid organs except for the spleen" where the two lower doses caused an increase. Sabinsa dismissed the results stating that the results "do not show a dose-related effects of piperine as several parameters showed an increase at low dose and a decrease at high dose."[23] This dose response finding is relevant and requires investigation or an explanation, instead of referring to it as "difficult to interpret."[24]
    b. Sabinsa mentioned a few reproductive and developmental toxicity studies testing both exposures *in vitro* and *in vivo*. It stated that the piperine concentrations used in the *in vitro* hamster egg fertilization study that reduced both the percentage of fertilized eggs and sperm secretion "seems very high"[25] without providing details of how the experimental concentrations compared to the intended use level. Regarding the *in vivo* study, both doses tested (10mg/kg and 20mg/kg) had profound effects on embryo implantation, as well as decreased mating performance and fertility. The notifier acknowledges a "lack of dose-related effects on implantation" [26] and claim that the difficulty in explaining the results is because the "study was not conducted according to standard guidelines." [27] These findings are relevant and require investigation or an explanation.
    c. Similarly, Sabinsa listed a few human studies showing that piperine affects the metabolism of other compounds, including drugs by increasing their bioavailability. These studies seem to support the data described on page 23 of the GRN. These findings are important because the addition of piperine to common foods, especially those widely consumed by children, could potentially increase the bioavailability of drugs in a manner not anticipated by healthcare professionals prescribing the drug. The notifier must provide an explanation for why the studies are not relevant. It is noteworthy that Sabinsa advertises

[22] Dogra, RK, Khanna, S, Shanker, R. Immunotoxicological effects of piperine in mice. 2004. *Toxicology* 196:229-236
[23] GRN #474, page 25
[24] Id.
[25] Id. at 31
[26] Id.
[27] Id.

BioPerine "for its ability to increase the bioavailability of nutritional compounds."[28]

3. Relied on studies the majority of which did not perform toxicological testing: On page 21 of the GRN the notifier states that "[t]he majority of the experimental *in vitro*, animal or human studies conducted with black pepper or its preparations, including piperine, were undertaken to evaluate its efficacy for different health conditions."[29] Clearly, these are not toxicology testing studies as recommended by the FDA. The definition of safety at 21 CFR 170.3 does not include consideration of the potential benefits of an additive.

   Also, the studies tested other black pepper-derived substances. Experts in the field of dietary supplements maintain that there is a big difference between botanical materials and a nearly pure compound obtained from the botanical or a synthetic identical compound. And that it is hard to draw any conclusions when the toxicology studies are done on botanical extracts as a whole and not for the purified ingredient alone.[30] The typical composition of BioPerine is described as ~95-99% piperine, a nearly pure compound.[31] Therefore, the notifier should have tested the effect of BioPerine, especially considering that there is not an established ADI. The existent literature on black pepper-derived chemicals is deficient and many reported findings are inconclusive for the tested compounds.

   Of the few toxicology studies referenced in the GRN, the notifier's interpretation of the data is unclear. For instance, it cited an "extensive and critical review article"[32] on black pepper and piperine indicating no adverse effects caused by the ingredients although "additional details of the study were not available."[33] NRDC questions how Sabinsa judged the quality of the unavailable data it cites as relevant. The notifier also listed a chemoprevention study[34] as carcinogenicity-related study associated with piperine. The notifier did not cite any carcinogenicity study, as described by FDA in its "Redbook."

Conclusion

It is clear that BioPerine is a highly concentrated extract from black pepper that is sold as dietary supplement by the notifier. With the GRAS notification, Sabinsa intends to expand the market to conventional foods. However, this unique extract containing >95% piperine has been neither adequately tested nor adequately evaluated to determine its uses are safe at this time. FDA should notify the company that the notice does not provide a sufficient basis for a GRAS determination and that it should submit a food additives petition for BioPerine.

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

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[28] See http://www.bioperine.com/

[29] GRN #474, page 21

[30] See http://www.nutraingredients-usa.com/Research/Are-bael-and-its-aegeline-content-set-for-intense-analytical-safety-scrutiny

[31] GRN #474, page 15.

[32] Id. at 21

[33] Id.

[34] Selvendiran, K, Selvendiran, P, Magesh, V, Sakthisekaran, D. Modulatory effect of piperine on mitochrondiral antioxidant system in Benzo(a)pyrene-induced experimental lung carcinogenesis. 2004. *Phytomedicine* 11:85-89.

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]	Not found	Not found	Not found	Not found	Not found	Not found
One-year toxicity studies with non-rodents[6]	Not found	Not found	Not found	Not found	Not found	Not found
Chronic toxicity or combined chronic toxicity/carcinogenicity studies with rodents[6]	Not found	Not found	Not found	Not found	Not found	Not found
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).