January 24, 2008

Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852.

Preliminary Statement

The Cornucopia Institute and the National Alliance for Breastfeeding Advocacy submit this petition under section 4(d) of the Administrative Procedure Act (5 U.S.C. § 553(e)[i]) and sections 201(n)[ii], 402(a)(1)[iii], 402(f)(1)(B)[iv], 403(a)(1)[v], and 701(a)[vi] of the federal Food, Drug, and Cosmetic Act (FFDCA), (21 U.S.C. §§ 342(a)(1), 342(a)(2)(A), 342(f)(1)(B) and 371(a)) to request the Commissioner of Food and Drugs to revise the labeling requirements for infant formulas that contain DHA and ARA from algal and fungal sources, respectively. We specifically request a notice on the label of infant formula with DHA- and ARA-containing oils to warn parents of the possibility of adverse reactions to these novel ingredients.

Incidences of infants experiencing adverse reactions, including diarrhea, vomiting, bloating, and gastrointestinal distress, have been reported to the FDA's MedWatch system. These reports suggest that a subset of the population reacts adversely to the DHA and ARA oils that have been added to infant formula since 2002. Cornucopia and NABA request that the FDA conduct an investigation of adverse reactions in infants to DHA and ARA oils in infant formula, including a thorough investigation of any postmarket surveillance performed by formula manufacturers. If, as a result of such investigations, the FDA finds that a subset of the infant population does indeed react adversely to infant formula with DHA and ARA oils, Cornucopia and NABA request a regulatory change in labeling requirements for infant formula to warn parents of the possibility of adverse reactions.

Action Requested

Cornucopia and NABA request that the FDA take regulatory action to revise the existing regulation by requiring a label notice for all infant food products containing DHA and ARA oils. The proposed regulation should prescribe the following (or similar) language: "NOTICE: This products contains DHA oil from algal microorganisms and ARA oil from fungal microorganisms, which have been linked to diarrhea, bloating, vomiting, and other gastrointestinal problems in some infants. Discontinue usage and seek medical help if your infant

reacts adversely to this formula and symptoms do not immediately resolved upon switching to and alternative formula without DHA/ARA oils."

Factual Grounds for Action

Since 2002, infant formula manufacturers have produced formula with DHA/ARA by adding the novel ingredients DHASCO and ARASCO to formula. DHASCO stands for docosahexaenoic acid single cell oil and ARASCO stands for arachidonic acid single cell oil. These oils are produced and marketed by Martek Biosciences Corporation.

Docosahexaenoic acid (DHA) and arachidonic acid (ARA) are naturally present in human breast milk—a breastfeeding mother acquires these fatty acids from sources such as fatty fish or synthesizes them from other omega-3 fatty acid sources like walnuts, flaxseed, and eggs. Given their presence in breast milk, DHA and ARA are believed to be highly beneficial to an infant's development.

Martek's DHASCO and ARASCO are novel foods. They are extracted with the use of a solvent (hexane) from fermented algae and soil fungus. Moreover, DHASCO and ARASCO contain DHA and ARA triglycerides that are not identical to those found in human milk. These structural differences should be investigated as a possible cause of the gastrointestinal distress that some infants experience after ingesting formula supplemented with DHASCO and ARASCO.

Scientists have conducted numerous studies that question long-term benefits to an infant's development from adding DHA and ARA to infant formula. Overall, research results are inconsistent and inconclusive. The scientific community does not agree that DHA and ARA added to formula confer proven benefits to an infant's development and well-being.

DHASCO and ARASCO are considered Generally Recognized as Safe (GRAS), although FDA officials reviewing the GRAS notice by Martek never affirmed the safety of DHASCO and ARASCO. In their letter to Martek, FDA officials wrote:

> "Some studies have reported *unexpected deaths* among infants who consumed formula supplemented with long-chain polyunsaturated fatty acids. These unexpected deaths were attributed to Sudden Infant Death Syndrome (SIDS), sepsis or necrotizing enterocolitis. Also, some studies have reported adverse events and other morbidities including *diarrhea, flatulence, jaundice, and apnea* in infants fed long-chain polyunsaturated fatty acids."[vii] [emphasis added]

Parents of infants reacting adversely to formula supplemented with DHASCO and ARASCO oils have reported adverse reactions to the FDA. *These reports, along with anecdotal evidence from health care professionals, reveal that a subset of the population experiences pain and distress from consuming DHA/ARA formula.* Premarket safety tests did not reveal these adverse reactions, which could be due to the fact that ethical guidelines require the withdrawal of infants reacting negatively, or due to the fact that rare adverse reactions are only revealed once hundreds of infants consume the formula. If that is the case, then adverse reactions would come to light only after the product reaches the market.

A total of 98 adverse reaction reports submitted to the FDA's MedWatch program could reasonably be linked to the DHA and ARA oils in infant formula. While 98 adverse reaction reports may seem like a low number, we feel the need to point out that this does not justify a dismissal of the severity of the problem. First, parents are currently left in the dark about the possibility that DHA and ARA oils in formula could be the cause of their infant's diarrhea or other adverse reactions. Physicians and other healthcare providers might assume that the widely marketed brands of infant formula are not the root cause when examining patients or consulting with worried parents over the phone.

It is precisely for this reason that we request a warning label on formula. Formula labels and manufacturers' websites or advertisements do not currently point to any possibility that an infant's diarrhea or other problems may be caused by the DHA and ARA oils in formula. As a result, parents and health providers are unlikely to identify DHA and ARA oils as a possible cause of their infant's problems, and these adverse reactions will go unreported. Second, parents whose infants react adversely may not be aware of the FDA's MedWatch program, which contributes to possible underreporting of this problem.

Legal Grounds for Action

Our petition is submitted based on sections 201(n), 402(a)(1), 402(f)(1)(B), 403(a)(1) and 701(a) of the Federal Food, Drug and Cosmetics Act. Section 402(a)(1) determines that a food shall be deemed to be adulterated if it bears or contains any poisonous or deleterious substance which may render it injurious to health. To at least a subset of the infant population, Martek's DHASCO and ARASCO in infant formula appear to be injurious to health by causing adverse reactions such as diarrhea, vomiting, and gastrointestinal distress.

In addition, according to section 402(f)(1)(B) a food shall be deemed to be adulterated if it contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. FDA's GRAS Notice 000041 states that the agency has not made its own determination regarding the GRAS status of the subject use of ARASCO and DHASCO. We believe that inadequate information regarding the safety of DHASCO and ARASCO was available when DHA/ARA-supplemented formula came on the market, and that reports of adverse reactions demonstrate a lack of reasonable assurance that these ingredients do not present an unreasonable risk of illness or injury to infants.

Under section 201(n), FDA determines whether labeling is misleading by examining, among other things, the extent to which the labeling *fails to reveal facts* material as to consequences that may result from use of the product under conditions of use prescribed in the labeling or under customary or usual conditions of use. We believe that the lack of information regarding the possibility of adverse reactions in infants from the consumption of DHA/ARA-supplemented formula constitutes misleading labeling.

Section 403(a)(1) states that a food is misbranded if its labeling is false or misleading in any particular. Section 701(a) generally authorizes FDA to issue regulations for the efficient enforcement of the FFDCA. FDA has relied upon its authority under those sections of the FFDCA to require label notices that alert consumers to the potential health hazards posed by certain foods and food ingredients.[viii]

Environmental Impact

This petition is categorically excluded from the requirement for an environmental assessment under 21 C.F.R. § 25.30(k), because it requests the "[e]stablishment or repeal by regulation of labeling requirements for marketed articles" for which "there will be no increase in the existing levels of use or change in the intended uses of the product or its substitutes." In any event, Cornucopia and NABA do not believe that the actions requested in this petition would have any environmental impact.

Conclusion

The lack of labeling of infant formula with DHA- and ARA-containing oils does not adequately protect the health and well being of infants who experience adverse reactions, such as diarrhea, bloating, vomiting, and gastrointestinal distress from the consumption of formula with DHA and ARA oils. Currently, no labeling or warning is required, and formula manufacturers are not voluntarily warning parents of the possibility of adverse reactions. Parents are unaware that the simple switch to a non-DHA/ARA-supplemented formula may relieve their infant's pain and suffering from adverse reactions to Martek's DHASCO and ARASCO. Taking the action urged by Cornucopia and NABA would alert parents and caregivers of formula-fed infants to the possibility of adverse reactions caused by algal DHA and fungal ARA, providing them with knowledge that may help them end their infants' pain and distress.

Cornucopia and NABA request that the FDA determine whether such a warning label is warranted. We especially urge the FDA to undergo an investigation of the adequacy and results of post-market surveillance by formula manufacturers. If deemed necessary, the FDA should revise its existing regulations to require a label notice alerting parents to the possibility of adverse reactions.

Certification

The undersigned certify, that, to our best knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petition which are unfavorable to the petition.

Respectfully submitted,

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[i] Each agency shall give an interested person the right to petition for the issuance, amendment, or repeal of a rule.

[ii] 201(n) If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.

[iii] SEC. 402. [21 U.S.C. 342] A food shall be deemed to be adulterated— 1 (a)(1) If it bears or contains any poisonous or deleterious substance which may render it injurious to health; but in case the substance is not an added substance such food shall not be considered adulterated under this clause if the quantity of such substance in such food does not ordinarily render it injurious to health.

[iv] A food shall be deemed to be adulterated if it is a dietary supplement or contains a dietary ingredient that is a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury

[v] Sec 403. A food shall be deemed to be misbranded (a) False or misleading label. If (1) its labeling is false or misleading in any particular.

[vi] The authority to promulgate regulations for the efficient enforcement of this Act, except as otherwise provided in this section, is hereby vested in the Secretary.

[vii] United States Food and Drug Administration. GRAS Notice 000041. Available online at http://www.cfsan.fda.gov/~rdb/opa-g041.html.

[viii] U.S. Department of Health and Human Services, Food and Drug Administration. Food labeling: warning and notice statements; labeling of juice products; proposed rule. *Federal Register*, Vol. 63, No. 79, 1998, p. 20487.