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**Petition for the Addition of ARA Single-Cell Oil  
to the National List of Allowed and Prohibited Substances**

**NON-CBI COPY**

**Respectfully Submitted:**

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## Introduction

Martek Biosciences Corporation (“Martek”), pursuant to 7 U.S.C. §6517-18, and 7 C.F.R. §205.600-07, respectfully submits this Petition to the National Organic Standards Board (“NOSB”) and the National Organic Program (“NOP”) [*See also* 72 Fed. Reg. 2167-69 Overview of Petition Review by the NOSB (January 18, 2007)]. This Petition seeks the placement of Arachidonic Acid Single-Cell Oil (“ARA Single-Cell Oil”) on the National List of Allowed and Prohibited Substances (“National List”) under 7 C.F.R. § 205.605(a) or (b).<sup>1</sup>

The petitioned material has appeared as an ingredient in multi-ingredient organic food products for several years pursuant to an NOP letter ruling authorizing its use in handling as an allowed synthetic material falling under the “nutrient vitamin and minerals” category on the National List<sup>2</sup> [See 7 C.F.R. § 205.605(b)]. In April of 2010, the NOP revisited the issue of letter rulings on National List authorizations from a procedural perspective and determined that, “[T]he NOP will not be making policy decisions in letters.”<sup>3</sup> Pursuant to the change in the letter ruling policy, materials that were previously recognized by letter ruling, such as ARA Single-Cell Oil, are now procedurally required to be the subject of a Petition seeking NOSB review, and placement on the National List. The petitioned material is unchanged from that which was authorized previously.

## Executive Summary

This petition covers ARA Single-Cell Oil that is sourced from *Mortierella alpina*. Currently, Martek’s ARA Single-Cell Oil is included in organic infant formulas as a source of ARA.

ARA is an omega-6 long chain, polyunsaturated fatty acid. ARA is a primary structural component in the brain and retina. ARA is recognized by experts worldwide as playing a nutritional role in infant growth and neural development. The inclusion of ARA (and docosahexaenoic acid (DHA), which is covered by a separate petition) in infant formula is particularly important because studies have demonstrated that failure to provide ARA along with DHA erodes the neural developmental benefits of DHA and may adversely impact certain aspects of cognitive development. Infants receiving infant formulas without DHA and ARA perform more poorly on visual and cognitive tests than infants receiving breast milk or a formula supplemented with DHA and ARA. In addition to supporting neural development, ARA has also been demonstrated to support normal physical growth, particularly in preterm infants. Additionally, ARA from either human milk or long chain poly unsaturated fatty acid (LCPUFA)-enriched infant formula

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<sup>1</sup> Martek recognizes that the proper classification of a material, or class or category of materials, under the NOP is the subject of ongoing discussion. *See e.g.*; Classification of Materials--DRAFT Guidance document (Joint Materials and Handling Committee) (March 1, 2010)(hereinafter “Draft Guidance”); Addendum to November 6, 2009 Recommendation on Classification of Materials, (Joint Materials and Handling Committee)(March 1, 2010)(hereinafter “Recommendation”); Recommendation on Classification of Materials, (NOSB)(November 6, 2009); Recommendation on Classification of Materials (NOSB Joint Materials and Handling Committee)(September 9, 2009).

<sup>2</sup> *See* Appendix No. 1, Letter to Compliance Officer Amador from Assoc. Deputy Administrator Bradley (November 3, 2006)(approving DHA as an “accessory nutrient”); *see also* Appendix No. 2, The Use of Nutrient Supplementation in Organic Foods, National Organic Standards Board Recommendation, (October 31, 1995)(recognizing DHA as an “accessory nutrient”)

<sup>3</sup> *See* Appendix No. 3, Action Memorandum for the Chairman of the National Organic Standards Board: Scope of Nutrient Vitamins and Minerals in Organic Food, (April 26, 2010).

has been reported to support the development and function of the infant immune system (Field, 2005).

ARA Single-Cell Oil is obtained from a naturally occurring, non-genetically modified microbial source. As will be explained in more detail in the following petition, the manufacturing process for ARA Single-Cell Oil uses an aerobic fermentation process followed by oil recovery from the fermentation broth. Because the ARA Single-Cell Oil is formed naturally within the microbial cell, the oil cannot be extracted using mere physical means such as that commonly used in the cold pressing of products such as olives, soy, and tree nuts. Fermentation of *M. alpina* results in a growth form that is a densely packed mass with sponge-like characteristics, which retains significant water during harvesting. As a result, the cell mass is very pliable and the cells are very difficult to break. Homogenization of the wet biomass may physically rupture the cells, but the resulting oil and water emulsion is difficult to break without the use of a non-polar solvent to extract the oil from the cells. The manufacturing process also utilizes non-organic processing aids such as food acids and antioxidants that are needed to maintain the stability of the oil, which is prone to oxidation. At this time, Martek has not been able to identify a functional organic alternative to these processing aids.

The Food and Drug Administration (FDA) has authorized the use of the ARA Single-Cell Oil from *M. alpina* for use in infant formulas. Unlike most foods, infant formulas are subject to FDA pre-market notification requirements prior to marketing, and must meet federal nutrient requirements and include minimum and maximum amounts of certain nutrients. The premarket notification typically must be supported by safety data and clinical studies demonstrating the new infant formula will support growth. Moreover, a modification of the oil extraction process for *M. alpina* could trigger the filing of a new infant formula notification. Inclusion of the solvent-extracted *M. alpina* on the National List will ensure infants receiving organic formulas will have the ARA that is needed to optimize growth and neural development.

The components of ARA Single-Cell Oil have a history of safe consumption. All ingredients used in the processing of ARA Single-Cell Oil are either food grade or of higher quality. The entire process meets the current Good Manufacturing Practices for foods. ARA Single-Cell Oil undergoes rigorous analytical and quality assurance testing and meets well-defined product specifications prior to release. Additionally, a large number of safety studies have been conducted using ARA Single-Cell Oil and no scientifically valid reports (published or unpublished) have suggested any safety issues associated with the use of this product.

Martek believes that ARA Single-Cell Oil is eligible under either category of allowed materials for handling under 7 C.F.R. § 205.605. ARA Single-Cell Oil may be classified under either 7 C.F.R. § 205.605 (a) or (b), and additionally may fall under an existing category of approved material, such as “microorganisms” or “nutrient vitamins and minerals” if the boundaries of that category are clarified.

## PETITION

### Item A

#### Category for inclusion on, or removal from, the National List

Martek is petitioning for the inclusion of ARA Single-Cell Oil on the National List under 7 C.F.R. §205.605 (a) or (b) for handling of multi-ingredient food products.

### Item B

**1. Common name of the substance.**

ARA Single-Cell Oil  
Single-Cell Oil

Martek's ARA Single-Cell Oil is currently marketed under the trade names *life'sARA*<sup>™</sup> and ARASCO<sup>®</sup>.

**2. Manufacturer's name, address and telephone number.**

Martek Biosciences Corporation  
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FAX: (410) 997-7789

**3. The intended or current uses of the substance.**

ARA Single-Cell Oil is intended to be used in organic handling operations as a source of ARA in infant formulas and growing-up milks. As discussed in more detail in section 8.d, below, ARA is a valuable omega-6 fatty acid that is the primary omega-6 fatty acid found in the brain and retina. Its presence in the diet is particularly important for infants and young children given the significant neural development that occurs during the first years of life.

**4. Source of the substance and a detailed description of its manufacturing or processing procedures from the basic component(s) to the final product.**

ARA Single-Cell Oil is obtained from *M. alpina*, a naturally occurring, non-genetically modified microbial source. *M. alpina* is a member of the Fungi kingdom and is a eukaryotic, non-photosynthetic single-celled organism.

ARA Single-Cell Oil is produced using traditional food fermentation techniques, followed by oil recovery and purification steps which utilize standard food-grade vegetable oil industry methods. As has been made clear in the recent descriptions of the National List evaluation processes, the use of synthetic solvents to facilitate the isolation or extraction of a component of an agricultural product or a product of a natural biological process, does not automatically render the extracted fraction of the product a “synthetic” substance as it is described in the OFPA. Here, the use of a common solvent does not change the original chemical composition of ARA Single-Cell Oil. In its March 2010 draft guidance, the NOSB noted that the use of an extraction solvent will not result in a material being classified as synthetic, “unless either the extraction resulted in a chemical change or the synthetic remained in the final product at a significant level,”<sup>4</sup> neither of which occurs here. The use of food acids and bases to adjust the pH during the manufacturing process similarly does not result in a chemical change to the ARA Single-Cell Oil.<sup>5</sup> Moreover, the antioxidants in the finished ARA Single-Cell Oil are not present at significant levels<sup>6</sup> and have no technical or functional effect in the finished foods that utilize ARA Single-Cell Oil.

**a) Fermentation** – *M. alpina* are grown utilizing an aerobic fermentation process followed by recovery from the fermentation broth. Fermentation media consists of a carbon source (e.g., glucose), a nitrogen source (e.g., yeast extract), bulk nutrients (e.g., magnesium sulfate), and trace minerals (e.g., iron, zinc). Fermentation is monitored and controlled for process conditions. The fermentation is performed under aseptic conditions, and post-fermentation the broth is pasteurized and safe and suitable food-grade antioxidants, such as tocopherols and ascorbic acid, may be added to the fermentation broth to protect any free oil that may be released from the microbes during fermentation (the long chain omega-6 fatty acids are easily oxidized and need to be protected from oxidation). The biomass is recovered from the fermentation broth via filtration, followed by drying.

**b) Oil Recovery** – Following fermentation, oil is recovered from the biomass utilizing established food-grade vegetable oil industry methods, such as solvent extraction. The dried biomass is combined with solvent. After sufficient residence time, the majority of the ARA is released out of the biomass. The resulting oil/solvent mixture is sent through a series of evaporators which utilize heat and vacuum to remove the solvent from the oil. No detectable residues of solvent remain in the final product. Hexane is undetectable at a detection limit of <0.3 ppm. The solvent is recovered for re-use through a series of condensers, separators, and an oil scrubber. See Figure 1 for an overview of the ARA Single-Cell Oil extraction process.

The composition of the biomass requires the use of a solvent extraction process. ARA Single-Cell Oil is derived from *M. alpina*, which have a vegetative structure known as a mycelium, consisting of multi-branched intertwined thread-like filaments called hyphae. The mycelium of

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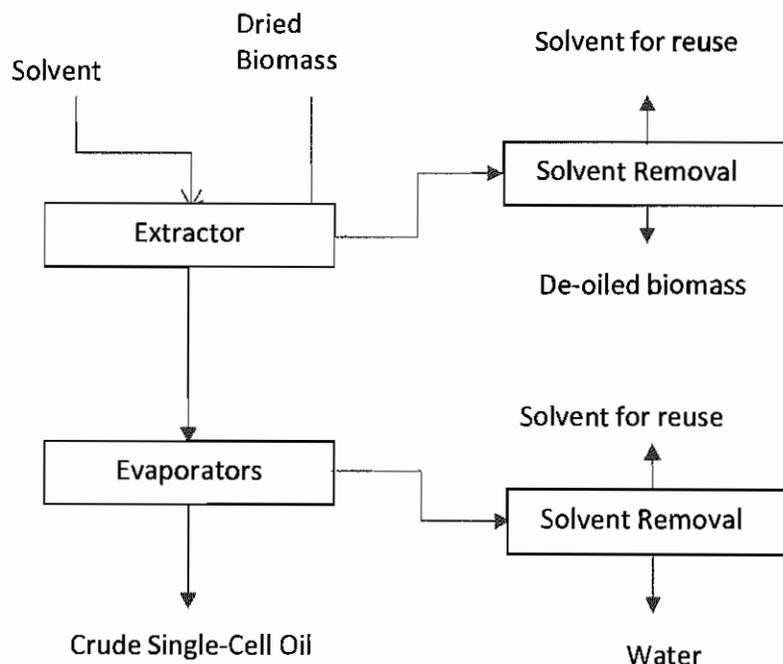
<sup>4</sup> National Organic Standards Board – Joint Materials and Handling Committee Classification of Materials,” Draft Guidance, Question 3, pg 6 (March 1, 2010).

<sup>5</sup> In its draft Guidance, NOSB recognized the use of an acidification and neutralization step in the isolation of soy protein from soybeans does not, standing alone, result in a “chemical change” determination under the National List analysis because the soy protein at the end of the process was restored to the same chemical identity as the soy proteins in the source soybeans. *Id.*

<sup>6</sup> See, *id.*, Draft Guidance, Question 4, pg. 7 (*de minimis* presence is below the level of regulatory significance under the NOP).

*M. alpina* results in a growth form that is a densely packed mass with sponge-like characteristics, which retains significant water during harvesting. As a result, the cell mass is very pliable and the cells are very difficult to break. Homogenization of the wet biomass may physically rupture the cells, but the resulting oil and water emulsion is difficult to break without the use of a non-polar solvent to extract the oil from the cells. Removing the water via drying makes the cells brittle and easier to break, releasing the oil. Since water is not compatible with handling of the harvested mycelium, the use of non polar solvents is the preferred extraction method.

**Figure 1. Overview of the extraction process for ARA Single-Cell Oil**

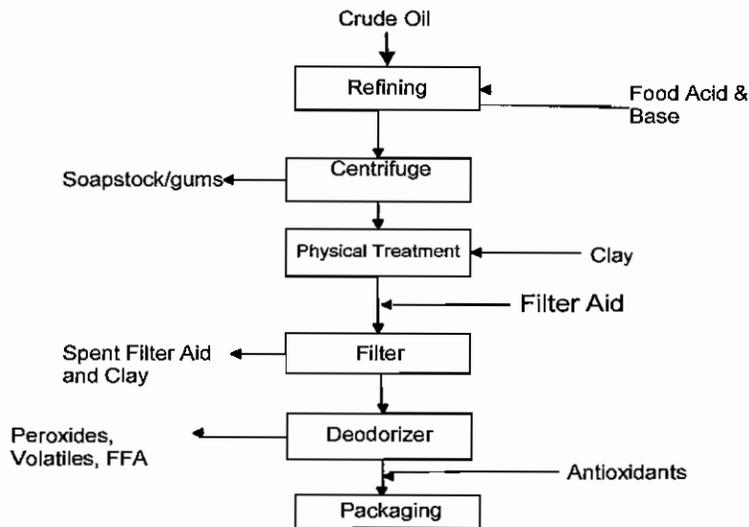


**c) Oil Purification** – The crude oil needs to be further purified to neutralize free fatty acids and naturally occurring trace metals (e.g., copper, iron and phosphorous). The purification is accomplished by adjusting the pH, which causes the formation and precipitation of the undesirable residues in the crude oil so they can be easily separated and removed. The crude oil is heated, followed by the addition of an acidulated solution (e.g., citric acid). After treatment, the pH of the oil is then raised through the addition of sodium hydroxide. These changes in the pH cause the formation of “soaps,” “gums,” and water that will be present in the “heavy phase”. The oil is then reheated and centrifuged to separate the heavy phase from the refined oil. After alkali refining, the oil is treated with adsorbents and chelators (e.g., citric acid, silica, clay, filtration) to remove through physical means the remaining residual levels of polar compounds

(e.g., soaps), trace metals (e.g., copper, iron and phosphorus), and oxidation products from the refined oil.

After adsorbent treatment, a deodorizer, operated under elevated temperature and vacuum, is used to remove peroxides and any remaining low molecular weight compounds naturally found in the oil (e.g., carbonyls and aldehydes) that may cause off-odors and flavors. The oil is cooled under a nitrogen blanket at the end of the deodorization cycle and safe and suitable antioxidants, such as tocopherols and ascorbyl palmitate, are added to the oil to provide oxidative stability. High oleic sunflower oil may be added to the oil to provide a product with a consistent ARA potency. The finished oil is then packaged and stored. Figure 2 provides an overview of the refining and downstream processing of the oil.

**Figure 2. Overview of the refining process of ARA Single-Cell Oil**



**d) Manufacturing Overview** - All processes are set up using a Hazard Analysis Critical Control Point (HACCP) approach. They are documented according to current Good Manufacturing Practices regulation (cGMP) for foods and the identified critical control points (CCPs) are monitored. Quality Control (QC) personnel record the results of laboratory tests as well as sterility checks. Production personnel record the continuous batch monitoring results within the batch records, according to cGMP. Quality Assurance personnel monitor the production records to ensure that batch process changes have been properly authorized, documented, and recorded in the records for each batch.

Martek's ARA Single-Cell Oil has no detectable residues of extraction solvents, pesticide residues, PCB's or any heavy metals such as arsenic, mercury, cadmium and lead. Product information can be found in Appendix 4.

Food-grade oils with high amounts of long chain polyunsaturated fatty acids, such as ARA Single-

Cell Oil, are highly susceptible to oxidation without the addition of antioxidants. Antioxidants are therefore added during processing to delay the oxidation of the oil which can result in palatability, functionality, shelf-life and nutritional quality issues. Tocopherols alone cannot be used to protect the oil from oxidation due to naturally present compounds, such as trace metals, ketones and aldehydes, and manufacturing processes that expose the oil to oxygen, heat, and light. As such, antioxidant mixtures are utilized which allows several compounds to work synergistically to delay the onset of oxidation.

Tocopherols are added to remove free radicals from the oil. Food acids, such as citric, are added to minimize the amount of naturally-occurring trace metals from the oil, while ascorbyl palmitate, the fat soluble form of vitamin C, serves primarily as an oxygen scavenger. Alternatives to ascorbyl palmitate, such as ascorbic acid, have limited applicability in Martek's ARA Single-Cell Oil due to the inability to uniformly disperse and dissolve in an oil matrix. Martek is continually evaluating the use of antioxidant mixtures to improve the quality and stability of our oil. At this time, we have not been able to identify an effective combination of alternative antioxidant blends. The antioxidants utilized by Martek are processing aids that scavenge oxygen that may be introduced during the manufacturing process and neutralize the trace minerals and other substances that can oxidize the oils. The antioxidants are used at the minimum level to accomplish their functional effect during processing. These processing aids do not have any functional effect in the foods that are made with the ARA Single-Cell Oil. In other words, while the processing aids promote stability during the manufacture of the ARA Single-Cell Oil, they do not function as antioxidants in the foods that are formulated with the ARA Single-Cell Oil.

High oleic sunflower oil is added to ARA Single-Cell Oil to provide a product with a consistent ARA potency to customers, as the amount of ARA can vary due to its natural source. High oleic sunflower oil is used for its fatty acid profile, stability and sensory profile. The high oleic sunflower oil does not provide a functional or technical effect in the foods that are formulated with ARA Single-Cell Oil.

Outside of the processing methods utilized by Martek, a review of publicly available information (e.g., GRAS notifications and patent applications) indicates that the ARA Single-Cell Oils commercially available today utilize organic solvents, such as hexane, to extract the oil from the microbial source.

Martek continues to investigate alternative food-grade extraction technologies. To date, a commercially feasible process, resulting in a stable, high-quality oil equivalent to the ARA Single-Cell Oil offered today has yet to be identified.

**5. A summary of any previous reviews of the petitioned substance by State or private certification programs, or other programs.**

- ARA Single-Cell Oil has previously been considered an accessory nutrient and utilized in "organic" and "made with organic" products under the Nutrient Vitamins & Minerals category of the National List (7 C.F.R. §205.605 (b)).
- Martek's ARA Single-Cell Oil is certified Kosher by the Orthodox Union.
- Martek's ARA Single-Cell Oil is certified Halal by the Islamic Food and Nutrition Council of America.

See Appendix 5 for a summary of regulatory approvals and market data for ARA Single-Cell Oil.

## 6. Information regarding EPA, FDA, and State Regulatory authority registrations.

### *FDA*

ARA Single-Cell Oil from *M. alpina* was the subject of a GRAS Notification (GRN000041) submitted by Martek Biosciences Corporation to the U.S. Food and Drug Administration (U.S. FDA) in 2000. The Agency responded with no objection regarding Martek's conclusion that ARA-rich Single-Cell Oil from *M. alpina* is GRAS when added to infant formulas at a level up to 1.25 percent of the total dietary fat and at a ratio of DHA to ARA of 1:1 to 1:2.

<http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=grasListing&id=41>

### *EPA*

The facilities where the extraction of ARA Single-Cell Oil occurs are regulated by the Environmental Protection Agency (EPA) and each facility has existing operating approvals from the EPA.

## 7. The Chemical Abstract Service (CAS) number of the substance and labels of products that contain the petitioned substance.

There is no Chemical Abstract Service (CAS) registry number for ARA Single-Cell Oil; however the CAS number for ARA, the primary component of this substance, is 506-32-1.

Sample labels for products containing ARA Single-Cell Oil can be found in Appendix 6.

## 8. Physical properties of the substance and chemical mode of action: including environmental impacts, interactions with other materials, toxicity and persistence, effects on human health, effects of soil organisms, crops or livestock:

### *a. Physical properties and mode of action*

- ARA Single-Cell Oil is derived from a natural, single celled, non-genetically modified microbial source.
- ARA Single-Cell Oil is a yellow liquid oil that is composed predominantly of triglycerides, and contains approximately 40% ARA.
- Ingested long chain polyunsaturated fatty acids (LCPUFA) are found circulating in the blood, either as a constituent of red blood cell (RBC) membranes, or in non-cellular forms either as triglyceride, plasma phospholipids, or steryl esters. A number of studies have demonstrated increased blood levels of LCPUFA following ingestion of ARA from single cell oil among normal, healthy children ages 0 – 12 months (Auestad et al., 2001; Birch et al., 1998; Birch et al., 2000; Birch et al., 2002; Birch et al., 2005; Clandinin et al., 2005; Hoffman et al., 2000; Hoffman et al., 2003; Hoffman et al., 2004; Makrides et al., 2002
- ARA and DHA from single-cell oils have been demonstrated to promote growth of preterm

infants compared to non-LCPUFA formula or formula supplemented with DHA/EPA from fish oil (Clandinin et al., 2005).

**b. Chemical interactions with other substances**

No distinct chemical interactions are known to occur.

**c. Toxicity and environmental persistence**

ARA Single-Cell Oil from *M. alpina* is fully biodegradable and does not persist in the environment. There is no environmental risk or toxicity associated with the use or disposal of Martek's ARA Single-Cell Oil. See MSDS in Appendix 7.

**d. Effects on Human Health**

ARA is a normal component of the human diet and a precursor for many important eicosanoids, such as prostaglandins, thromboxanes, and leukotrienes. ARA plays an important role in infant growth and neural development. See Appendix 8 for a detailed discussion of the role of ARA in human health and recommendations of regulatory and expert organizations.

- ARA is typically only found in animal products and is often abundant in the diet of adults. Although breast milk and ARA/DHA supplemented formulas are good sources of ARA, the introduction of complementary foods, which are typically low in ARA, adversely impacts the availability of ARA to infants and children greater than 6 months of age (Luukkainen et al., 1996).
- The frequent practice of early cessation of breastfeeding (prior to 6 months) also limits ARA availability and necessitates the addition of ARA to infant formula to adequately maintain infant tissue ARA at a level comparable to that of an exclusively breastfed infant.
- Birch et al. (2005) reported significant visual improvement in response to LCPUFA supplementation throughout the first year of life of healthy term infants from day 5 of age with 0.36% DHA and 0.72% ARA as compared to non-LCPUFA formula.
- With regard to cognitive function, a recent meta-analysis indicates that plasma phospholipid ARA levels of children and adults with learning disorders are significantly depressed suggesting that suboptimal ARA intake during critical periods of growth may adversely impact brain development (Morse 2009).
- ARA from either human milk or LCPUFA-enriched infant formula has been reported to support the development and function of the infant immune system (Field, 2005).

**e. Environmental impacts from its use or manufacture**

There are no known negative environmental impacts resulting from the use or disposal of ARA Single-Cell Oil as a food ingredient. ARA Single-Cell Oil has no effect on soil organisms, crops or livestock. The source organism for Martek's ARA Single-Cell Oil is considered suitable for the

production of single-cell oils for use in foods. The organism is not toxigenic, pathogenic, or genetically modified.

ARA Single-Cell Oil is produced by fermentation under closed, aseptic conditions. ARA Single-Cell Oil is extracted, refined, treated, and deodorized in a process that is similar to that used for food-grade edible vegetable oils. ARA Single-Cell Oil offers a viable and sustainable source of dietary ARA.

Oil waste (e.g., cell debris, water) from the manufacturing process is treated on-site prior to being sent to a public wastewater treatment facility. Solvents used in processing are managed in a closed system, and captured utilizing scrubbers and condensers for subsequent re-use in production. The facilities where the extraction of ARA Single-Cell Oil occurs are regulated by the Environmental Protection Agency (EPA) and each facility has existing operating approvals from the EPA.

**9. Safety information about the substance.**

The components of ARA Single-Cell Oil have a history of safe consumption. The fatty acids present in ARA Single-Cell Oil are components of a normal diet or normal metabolites of fatty acids. As noted in section 6, Martek submitted a GRAS notification for its ARA Single-Cell Oil from *M. alpina* and FDA completed a favorable review. The safety of Martek's ARA Single-Cell Oil is established by the favorable review of the relevant safety data by FDA. In addition, see Appendix 7 for ARA Single-Cell Oil MSDS.

A number of studies have demonstrated safe use of Martek ARA Single-Cell Oils, and confirm that the source organism is nontoxic, further supporting the safety of ARA Single-Cell Oil (Appendix 9). Clinical trials involving over 3,000 term and preterm infants have been conducted using Martek's ARA Single-Cell Oil with excellent tolerability and safety (Appendix 9).

**10. Comprehensive research reviews and research bibliographies, including reviews and bibliographies which present contrasting positions.**

See Appendix 9 (Research Bibliography).

**11. A "Petition Justification Statement" which provides justification for inclusion of a non-organically produced nonagricultural substance onto the National List.**

The nutritional need for the primary ingredient in ARA Single-Cell Oil, ARA, is set forth in other sections of this petition, particularly Appendix 8.

Martek believes that ARA Single-Cell Oil is eligible under either category of allowed materials for handling under 7 C.F.R. § 205.605. ARA Single-Cell Oil may be classified under either 7 C.F.R. § 205.605 (a) or (b), and additionally may fall under an existing category of approved material, such as "microorganisms" or "nutrient vitamins and minerals" if the boundaries of that category are clarified.

ARA Single-Cell Oil is used to increase the ARA content of infant formulas and growing-up milks. As discussed in this petition, a review of the available data demonstrates the importance of

including ARA in the diets of infants and toddlers. ARA is vital for healthy functioning of the brain and eyes and is recognized as particularly important in the diet of infants and toddlers. Based on consumer demand for products that provide these benefits, food developers and manufacturers recognize the need to provide products containing ARA. Recent research from MamboTrack (2010) indicates that eight in 10 natural and organic consumers regularly read ingredient labels for health and nutrition content and express interest in purchasing functional foods with additional health, nutrition and dietary benefits.

Perhaps most notably, virtually all US infant formula products (both organic and non-organic) now contain ARA (and DHA) because of the well-established importance of ARA (and DHA) intake to support infant development and growth. ARA is naturally found in breast milk and is important for optimal infant brain and eye development and function. Although human milk represents the optimal form of infant nutrition, those parents who need or choose formula should have access to the most nutritionally optimal formula available. If ARA Single-Cell Oil is not added to the National List, organic infant formulas will be nutritionally inferior to conventional infant formulas and will not be able to maintain a competitive position in the market.

Martek is unaware of a commercially available, certified organic, source of ARA Single-Cell Oil, or any other form of ARA currently approved for use in infant formulas sold in the U.S. To Martek's knowledge, no infant formula products containing ARA from non-microbial sources, such as egg phospholipid, have been approved by FDA for use in infant formulas through the GRAS notification process.

ARA Single-Cell Oil in organic and conventional infant formulas is the only FDA-accepted source of ARA for infants of women that are unwilling or unable to continue breastfeeding through the first six months of life, and is the only substantial source of ARA for these infants from seven to twelve months of age. Novel sources of ARA, such as Martek's ARA Single-Cell Oil, have been recognized by expert bodies world-wide as a means of meeting important dietary intake guidelines.

**12. Commercial Confidential Information Statement describing information that is considered to be confidential business or commercial information.**

The analytical results contained in Appendix 4 are considered Confidential Business Information (CBI) that should not be disclosed. The information in Appendix 4 is considered a trade secret because it identifies the nature of the analytical procedures that we perform on the ARA Single-Cell Oil. We have invested considerable time and resources ascertaining the testing that should be performed on the ARA Single-Cell Oil. NOP has recognized that quality control test and data are examples of CBI. The analytical test data are (1) commercially valuable in that we have devoted considerable time and resources identifying the analytical procedures that should be performed on our ARA Single-Cell Oil and would be placed at a competitive disadvantage if this information is released, (2) the analytical tests described in Appendix 4 continue to be used in our business, and (3) these data and test results are maintained in secrecy.

Consistent with the guidance provided by NOP, we are providing a copy of the petition, labeled "CBI Copy" in the upper right hand corner that identifies each page that contains CBI. We have bracketed the CBI information in the text and included "CBI" in the right hand margin next to the bracketed text. We also are providing a separate copy in which we have deleted the CBI. Each page with deleted CBI contains the statement, "CBI-Deleted," in the upper right hand corner and "CBI-Deleted" appears in the right hand margin next to the deleted text.

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## APPENDIX 1

## APPENDIX 1



United States  
Department of  
Agriculture

Agricultural  
Marketing  
Service

STOP 0268 - Room 4008-S  
1400 Independence Avenue, SW.  
Washington, D.C. 20250-0268

Date: November 3, 2006

To: Paul Amador  
Compliance Officer  
Compliance and Analysis

From: Mark A. Bradley  
Associate Deputy Administrator  
National Organic Program *Mark Bradley*

Subject: NOP Complaint, PBM Nutritionals, LLC, Parent's Choice Infant Formula

This memorandum supersedes all earlier National Organic Program (NOP) correspondence on the PBM Nutritionals, LLC, Parent's Choice Infant Formula compliance case NOP-041-06.

Accessory nutrients, that are non-agricultural, are allowed in the production of products to be sold, labeled, or represented as organic under the NOP; provided, they are used in full compliance with Food and Drug Administration (FDA) rules and regulations. Non-agricultural accessory nutrients are covered under Section 205.605(b) *Synthetics allowed*, of the NOP National List (nutrient vitamins and minerals). Agricultural accessory nutrients must be organically produced unless listed as commercially unavailable in section 205.606 of the National List.

Section 205.605(b) "Nutrient vitamins and minerals, in accordance with 21 CFR 104.20, Nutritional Quality Guidelines For Foods" originates from the October 31, 1995, nutrient supplementation recommendation of the National Organic Standards Board (copy attached).

Nutrients allowed under section 205.605(b) are not limited to the nutrients listed in section 104.20(d)(3), because section 104.20(f) provides that nutrients may be added to foods as permitted or required by applicable regulations established elsewhere by FDA; for example, 21 CFR Part 107 Infant Formula.

The complaint that resulted in the opening of this case questioned use of the nutrients docosahexaenoic acid (DHA) and arachidonic acid (ARA) in an organic infant formula. The resulting investigation led to questions concerning the use of the nutrients nucleotides and taurine. FDA permits the use of all four in infant formulas. Accordingly, provided the nutrients in question are used in full compliance with FDA rules and regulations, they would comply with the NOP National List as currently written.

Please transmit this interpretation to Quality Assurance International and request that they inform PBM Nutritionals.

Attachment

## **APPENDIX 2**

## APPENDIX 2

# National Organic Standards Board

**NOSB**

NOSB Administrative  
Information

National List Recommendations -- 1995

NOSB Meetings

NATIONAL ORGANIC STANDARDS BOARD  
FINAL RECOMMENDATION ADDENDUM NUMBER 13  
THE USE OF NUTRIENT SUPPLEMENTATION IN ORGANIC  
FOODS

NOSB  
Recommendations

Executive Committee  
Conference Call  
Summaries

Date adopted: October 31 1995  
Location: Austin Texas

What's New?

Introduction:

NOSB Archives

The Committee has debated the issue of the inclusion of synthetic vitamins, minerals, and/or accessory nutrients in organic foods. Although it is generally considered that foods themselves are the best source of nutrients, in some cases, State regulations mandate the inclusion of vitamins and/or minerals to fortify foods. An example of this is enriched white flour pasta in which some States mandate the inclusion of thiamin, riboflavin, niacin, and iron.

Home

The Committee also believes that recommendation by independent professional associations may also be taken into consideration. An example of this is infant cereals in which fortification of iron is highly recommended by the American Dietetic Association and various associations dealing with pediatric care and nutrition as a baby's stored iron supply from before birth runs out after the birth weight doubles.

In the recommendation listed below, the term "accessory nutrients" means nutrients not specifically classified as a vitamin or mineral but found to promote optimal health. Examples include omega-3 fatty acids, inositol, choline, carnitine, and taurine. Without this inclusion we believe we may be limiting ourselves given future nutritional discoveries. It is also a term used frequently throughout the food and supplement industries.

Recommendation:

Upon implementation of the National Organic Program, the use of synthetic vitamins, minerals, and/or accessory nutrients in products labeled as organic must be limited to that which is required by regulation or recommended for enrichment and fortification by independent professional associations.

## APPENDIX 3

## APPENDIX 3



1400 Independence Avenue, SW.  
Room 2646-S, STOP 0268  
Washington, DC 20250-0201

April 26, 2010

### ACTION MEMORANDUM FOR THE CHAIRMAN OF THE NATIONAL ORGANIC STANDARDS BOARD

FROM: Miles McEvoy  
Deputy Administrator  
National Organic Program

A handwritten signature in black ink, appearing to read "Miles McEvoy", written over a large, empty oval shape.

SUBJECT: Scope of Nutrient Vitamins and Minerals in Organic Food

#### ISSUE:

The National Organic Program (NOP) requests that the National Organic Standards Board (NOSB) reevaluate their recommendation for nutrient vitamins and minerals, currently codified in 7 CFR §205.605(b), in the sunset 2012 process and define the scope of permitted vitamins, minerals and nutrients. This evaluation is requested due to a clarification of scope of the current annotation for nutrient vitamins and minerals which references the Food and Drug Administration (FDA) fortification policy in 21 CFR §104.20.

#### DISCUSSION:

In November 1995, the NOSB voted to permit nutrient vitamins and minerals in organic food. Two technical advisory panel (TAP) reviews were conducted prior to the meeting. The TAP review for "nutrient minerals" covered calcium, phosphorus, magnesium, sulfur, copper, iodine, iron, manganese and zinc; the TAP review for "nutrient vitamins" included vitamins A, D, E, K, C, B6, B12, folic acid, thiamin (B1), riboflavin (B2) and biotin. There was not a TAP review of substances identified as "accessory nutrients."

According to the record of the NOSB October 31 – November 4, 1995 meeting, the Board adopted a final recommendation titled *The Use of Nutrient Supplementation in Organic Foods*.<sup>1</sup>

This addendum includes reference to accessory nutrients, stating:

In the recommendation listed below, the term accessory nutrients means nutrients not specifically classified as a vitamin or mineral but found to promote optimal health. Examples include omega-3 fatty acids, inositol, choline, carnitine, [sic] and taurine. Without this inclusion, we believe we may be limiting ourselves given future nutritional discoveries. It is also a term used frequently throughout the food and supplement industries.

<sup>1</sup> Final Recommendation Addendum Number 13 available at <http://www.ams.usda.gov/AMSv1.0/getfile?dDocName=stelprdc5058973>

ACTION MEMORANDUM FOR THE CHAIRMAN OF THE NOSB

Page 2

**NOSB Recommendation:**

Upon implementation of the National Organic Program, the use of synthetic vitamins, minerals, and/or accessory nutrients in products labeled as organic must be limited to that which is required by regulation or recommended for enrichment and fortification by independent professional associations.

Following the adoption of the above addendum, the NOSB vote on the listing of nutrient vitamins and minerals was recorded as follows:

**Nutrient Vitamins and Minerals** - Determined to be synthetic; Vote - Unanimous. The NOSB's decision is to allow this material for use in organic food processing; Vote: 10 aye / 4 opposed. Annotation: Accepted for use in organic foods for enrichment or fortification when required by regulation or recommended by an independent professional organization.<sup>2</sup>

The recommendation voted upon for nutrient vitamins and minerals did not include the term "accessory nutrients." The NOP proposed rule, published on March 13, 2000 (65 FR 13512), did not include the NOSB annotations "when required by regulation" or "when recommended by an independent professional organization." The NOP final rule, as published on December 21, 2000 (65 FR 80548), retained the reference to 21 CFR §104.20, and did not incorporate the term "accessory nutrients:"

§205.605(b) *Synthetics allowed:*

Nutrient vitamins and minerals, in accordance with 21 CFR §104.20, Nutritional Quality Guidelines for Food. \*

In 2006 the NOP received a complaint that substances such as arachidonic acid (ARA), docosahexaenoic acid (DHA), sterols, and taurine<sup>3</sup> were being added to infant formula and other organically labeled products. In a 2007 letter, the NOP clarified that DHA, ARA and other nutrients are allowed in organic foods because "[n]utrients allowed under section 205.605(b) are not limited to the nutrients listed in section 104.20(d)(3), because section 104.20(f) provided that nutrients may be added to foods as permitted or required by applicable regulations established elsewhere by FDA. Thus, for example, ARA and DHA are covered under section 205.605(b) of the National List because the FDA permits their use as nutrients that are GRAS."<sup>4</sup>

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<sup>2</sup> FINAL MINUTES OF THE NATIONAL ORGANIC STANDARDS BOARD FULL BOARD MEETING AUSTIN, TEXAS, OCTOBER 31 - NOVEMBER 4, 1995

<sup>3</sup> ARA and DHA are omega-6 and omega-3 fatty acids, respectively; phytosterols are a type of organic compound naturally occurring in plants; taurine is an organic acid.

<sup>4</sup> Letter from USDA AMS Compliance to complainant, April 3, 2007.

## ACTION MEMORANDUM FOR THE CHAIRMAN OF THE NOSB

Page 3

### **FDA Clarification**

The FDA fortification policy is established in 21 CFR §104.20. Section 104.20(d)(3) permits the following nutrients for fortification in accordance with its policy: protein, calcium, iron, thiamin, riboflavin, niacin, folate, biotin, pantothenic acid, phosphorus, magnesium, zinc, iodine, copper, potassium, and vitamins A, C, D, E, B<sub>6</sub>, and B<sub>12</sub>.

The NOP met with FDA staff from the Office of Nutrition, Labeling and Dietary Supplements for clarification of the scope of 21 CFR §104.20. The FDA explained that “nutrients” as referenced in 21 CFR §104.20(f) are intended to pertain only to those nutrients listed in §104.20(d)(3) and as specified in the standards of identity (21 CFR Parts 130-169) for a food or class of foods. The standards of identity for enriched cereal-flours and related products, for example, require fortification at specified levels with thiamin, riboflavin, niacin, iron and folic acid (21 CFR §137). The FDA noted that some foods have separate requirements and are not subject to 21 CFR §104.20, such as infant formula which is subject to comply with the nutrition requirements at 21 CFR §107.100.

In summary, 21 CFR §104.20(f) does not apply to the use of substances such as ARA, DHA, taurine, or sterols that have been added to products such as infant formula, milk, pet food, or energy bars as nutrients.

### **NOSB CONSIDERATION:**

The NOP is requesting that the NOSB reevaluate their recommendation for nutrient vitamins and minerals during the 2012 sunset process, and provide specific recommendations regarding the scope of permitted vitamins, mineral and nutrients in organic food products.

The NOP requests that NOSB consider the following:

- Are the “nutrient vitamins and minerals” specified within 21 CFR §104.20 aligned with the 1995 NOSB recommendation? If not, are there substances that should be prohibited or additional substances that should be allowed?

### **SUMMARY**

In conclusion, the NOP acknowledges that its previous interpretation of 21 CFR 104.20 was incorrect. The NOP recognizes that many certifiers and certified operations have made decisions based on the NOP’s incorrect interpretation of the FDA guidelines.

In the future, the NOP will not be making policy decisions in letters. All policy decisions will be made through the federal register and in compliance with Executive Order 12866. Transparency is a core principle for the NOP, AMS and the USDA administration. We are committed to an open public process. All NOP guidance will be published through the federal register with public comment.

ACTION MEMORANDUM FOR THE CHAIRMAN OF THE NOSB

Page 4

In regards to nutrient vitamins and minerals, the NOP plans to publish draft guidance later this year that will align with the FDA interpretation of 21 CFR 104.20. The draft guidance will provide a transition time for businesses to reformulate products to comply with the regulations as per the FDA guidelines. There will be a 60 day comment period for the draft guidance. Final guidance will be published after consideration of the comments received.

The NOP also notes that companies or interest groups may petition to add substances to the National List during this transition period. Specifically the pet food industry may want to consider petitioning to add substances to the National List in order to meet the nutritional requirements for pets.

**CBI DELETED**

**APPENDIX 4**  
**NON-CBI COPY**

## APPENDIX 5

## APPENDIX 5

### Regulatory Approvals and Market Data for ARA Single-Cell Oil

#### *Australia and New Zealand*

In 2003, the Australia New Zealand Food Authority (ANZFA) approved the use of ARA Single-Cell Oil when used as novel food ingredient in infant formulas for ARA enrichment.

#### *Canada*

In 2002, in response to a novel food application from Martek, Health Canada notified Martek Biosciences Corporation that it had no objections to the use of ARA Single-Cell Oil for use in infant formulas.

#### *China*

ARA Single-Cell Oil (*M. alpina*) is approved as a food additive and has been used as an ingredient in infant formulas and formula milk powders since 2000.

#### *European Union*

ARA Single-Cell Oil is considered to have been consumed in the community “to a significant degree” prior to May 15, 1997. As such, it is not considered a novel food or novel food ingredient and is permitted for use in infant formulas, foods and beverages, and dietary supplements.

#### *France*

In 1996 the Ministry of Health approved the use of Martek’s ARASCO® in infant formulas.

#### *Netherlands*

In 1995 the Ministry of Health independently evaluated and approved Martek’s ARASCO® as safe for use in infant formula.

In addition to regulatory evaluations, Martek’s ARA Single-Cell Oil has an extensive worldwide history of use in both preterm and term infants. Martek’s DHA Algal Oil (see separate petition for listing DHA Algal Oil on the National List) and ARA Single-Cell Oil have been added to conventional infant formulas since 1994 and organic certified infant formulas since 2006.

Sales of products in the United States known to contain Martek’s ARA Single-Cell Oil and DHA Algal Oil account for 96.5% of all sales in the baby formula category (IRI, 2009). The remaining 3.5% of sales are made up of private label sales (2.9%), which are not tracked at the SKU level, and toddler milks, discontinued products and specialty medical formulas (0.6%). According to the largest manufacturer of private label infant formulas in the U.S., substantially all private label infant formulas in the U.S. now contain Martek’s ARA Single-Cell Oil and DHA Algal Oil. Therefore, effectively 100% of the infant formula sold in the United States contains Martek’s DHA and ARA.

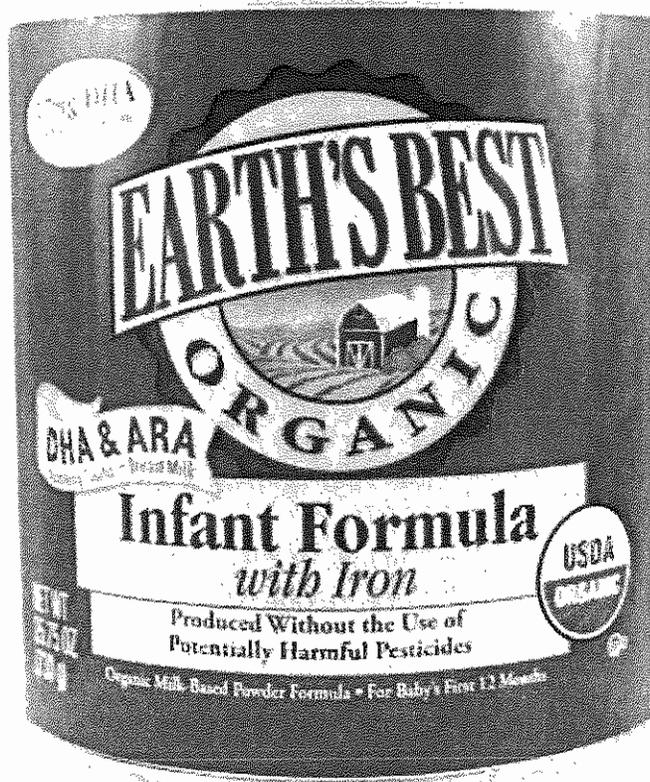
Organic infant formulas containing Martek’s ARA Single-Cell Oil and DHA Algal Oil account for 0.2% of IRI’s total baby formula category. One other organic product, Baby’s Only Organic, is intended for toddlers (one year of age and older) and does not contain DHA and ARA, but it is included in the baby formula category and accounts for 0.004% of total category sales (IRI, 2009). In fact, Baby’s Only recommends parents supplement their baby’s diet with a DHA & ARA fatty acid supplement, derived

from non-vegan, allergenic egg phospholipid, to ensure babies receive the proper amount of DHA & ARA in their diet.

Infant formula products containing Martek's DHA and ARA are commercially available in over 70 countries, including major markets such as:

United States	Canada	Mexico
Brazil	United Kingdom	France
Germany	Italy	Spain
Russia	Poland	Greece
Turkey	Egypt	Saudi Arabia
South Africa	China	Indonesia
Philippines	South Korea	Vietnam
Australia	New Zealand	

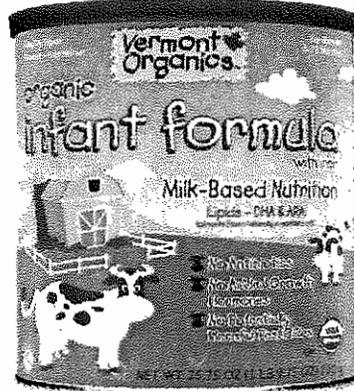
## APPENDIX 6





## Vermont Organics Formulas

### Milk Organic Formula



Milk-Based Nutrition

Certified Organic Infant Formula

Lipids DHA and ARA

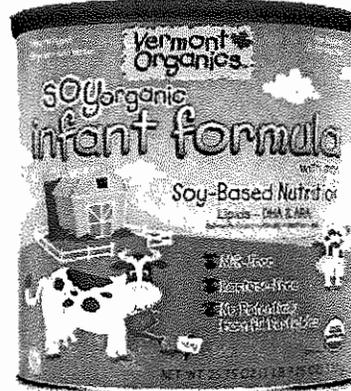
No Potentially Harmful Pesticides

No Added Growth Hormones

No Antibiotics

Gluten-Free

### Soy Organic Formula



Soy-Based Nutrition

Certified Organic Infant Formula

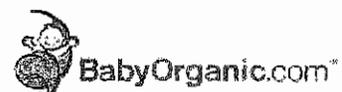
Lipids DHA and ARA

No Potentially Harmful Pesticides

Lactose-Free

Milk-Free

Gluten-Free



## APPENDIX 7



# MATERIAL SAFETY DATA SHEET

Date Issued: 01/27/2010  
MSDS No: O-20002  
Date Revised: 04/15/2010  
Revision No: 2

**ARASCO®**

## 1. PRODUCT AND COMPANY IDENTIFICATION

**PRODUCT NAME:** ARASCO®  
**PRODUCT CODE:** 30480-00, 40400-00, 40401-XX series

### MANUFACTURER

Martek Biosciences Corporation  
6480 Dobbin Road  
Columbia MD 21045  
**Telephone:** (843) 382-6221  
**Fax:** (843) 382-6056

### 24 HR. EMERGENCY TELEPHONE NUMBERS

**CHEMTREC:** US Transport (800) 424-9300,  
International Transport (703) 527-3887

## 2. HAZARDS IDENTIFICATION

### POTENTIAL HEALTH EFFECTS

**EYES:** Mildly irritating to the eyes.

**SKIN:** May cause slight irritation.

**INGESTION:** Not considered hazardous; large amounts may irritate digestive tract.

**INHALATION:** Hazard is negligible unless heated to produce vapor or mist, which may cause irritation to mucous membranes and other symptoms.

**PHYSICAL HAZARDS:** Combustible with heat.

## 3. COMPOSITION / INFORMATION ON INGREDIENTS

Chemical Name	Wt. %	CAS
ARA Fungal Oil	70 - 99	N/A
High Oleic Sunflower Oil	< 1 - 30	N/A
Proprietary Emulsifiers, Antioxidants, and Flavorings	< 0.1	N/A

## 4. FIRST AID MEASURES

**EYES:** Hold eyelids apart and flush eyes with plenty of water for at least 15 minutes.

**SKIN:** Wash with soap and water.

**INGESTION:** If ingested in large quantities and discomfort occurs, contact a physician.

**INHALATION:** Remove to fresh air. Contact a physician if symptoms persist.

## 5. FIRE FIGHTING MEASURES

**FLASHPOINT AND METHOD:** > 232°C (450°F) Pensky-Martens CC

**EXTINGUISHING MEDIA:** Dry chemical or CO2

**FIRE FIGHTING EQUIPMENT:** Firefighters should wear full fire-fighting turn out gear. Firefighters and others exposed to decomposition products should wear self-contained breathing apparatus.

**HAZARDOUS DECOMPOSITION PRODUCTS:** Carbon dioxide, carbon monoxide

## 6. ACCIDENTAL RELEASE MEASURES

**SMALL SPILL:** Absorb small spills or remaining material from large spills with an inert material. Flush residual spill area with soap and water.

**LARGE SPILL:** Contain large spills with dike of absorbent or impervious materials such as earth or clay.

**HANDLING PRECAUTIONS:** Spills of this material are very slippery. Porous material wetted with this product may undergo spontaneous combustion. Monitor closely until material can be disposed of properly.

**SPECIAL PROTECTIVE EQUIPMENT:** Use personal protective equipment recommended in Section 8.

## 7. HANDLING AND STORAGE

**HANDLING:** Handle in accordance with good industrial hygiene and safety practices.

**STORAGE:** Due to sensitivity to heat, frozen storage is recommended.

## 8. EXPOSURE CONTROLS / PERSONAL PROTECTION

**ENGINEERING CONTROLS:** If needed, ventilate area of use.

### PERSONAL PROTECTIVE EQUIPMENT

**EYES AND FACE:** Wear safety glasses with side shields or chemical goggles.

**SKIN:** Wear gloves, protective shoes, long-sleeved shirt, long pants, and a head covering.

**COMMENTS:** No occupational exposure limits are known.

## 9. PHYSICAL AND CHEMICAL PROPERTIES

**PHYSICAL STATE:** Liquid

**ODOR:** Musty

**APPEARANCE:** Free flowing, yellow liquid oil

**pH:** Not Applicable

**FLASHPOINT AND METHOD:** > 232°C (450°F) Pensky-Martens CC

**SOLUBILITY IN WATER:** Insoluble

**SPECIFIC GRAVITY:** 0.90

**COMMENTS:** Partly miscible with acetone, chloroform, hexane, and methanol.

**10. STABILITY AND REACTIVITY**

**STABILITY:** Stable under normal conditions.

**CONDITIONS TO AVOID:** Protect from heat.

**HAZARDOUS DECOMPOSITION PRODUCTS:** Carbon dioxide and carbon monoxide

**INCOMPATIBLE MATERIALS:** Oxidizing agents

**11. TOXICOLOGICAL INFORMATION**

**COMMENTS:** Not yet Determined

**12. ECOLOGICAL INFORMATION**

**GENERAL COMMENTS:** This material is readily biodegradable.

**13. DISPOSAL CONSIDERATIONS**

**DISPOSAL METHOD:** Dispose of in accordance with local, state, and federal regulations.

**14. TRANSPORT INFORMATION**

**DOT (DEPARTMENT OF TRANSPORTATION)**

**OTHER SHIPPING INFORMATION:** This product is not hazardous under the applicable DOT regulations.

**15. REGULATORY INFORMATION**

**UNITED STATES**

**TSCA (TOXIC SUBSTANCE CONTROL ACT)**

**TSCA REGULATORY:** Not Applicable

**FIFRA (FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT):** Not Applicable

**16. OTHER INFORMATION**

**REVISION SUMMARY:** Revision #: 2 This MSDS replaces the April 02, 2010 MSDS. Any changes in information are as follows: In Section 1 MSDS Product Code

**MANUFACTURER SUPPLEMENTAL NOTES:** To request additional MSDS's, please email [msds@martek.com](mailto:msds@martek.com).

**ADDITIONAL MSDS INFORMATION: Legend:** N/A = Not applicable

**GENERAL STATEMENTS:** To the best of our current knowledge, information contained herein is accurate and complete. However, nothing contained herein shall be construed to imply any warranty or guarantee.

**COMMENTS:** Do not use ingredient information and/or ingredient percentages in this MSDS as a product specification. For product specification information refer to a Product Specification Sheet and/or a Certificate of Analysis. These can be obtained from your Martek contact.

## APPENDIX 8

## APPENDIX 8

### The Role of ARA Single-Cell Oil in Human Health and Recommendations of Expert Organizations

#### Overview

ARA is a long-chain omega-6 fatty acid that accumulates in neural tissue. Fifty percent of the omega-6 fatty acids in the brain are ARA and 60% of retinal omega-6 fatty acids are ARA. Haggerty et al. (1997) have reported that the normal human placenta demonstrates selectivity among LCPUFA for uptake and transfer to the fetus in the following order DHA → ALA → LA → ARA, but that the addition of ARA to the maternal diet quickly shifts this order to DHA → ARA → ALA → LA, confirming the importance of both ARA and DHA for fetal development.

Breast milk always contains ARA and the amount is fairly consistent regardless of maternal dietary intake (Table 1). ARA is typically only found in animal products and is often abundant in the diet of adults. Although breast milk and DHA/ARA supplemented formulas are good sources of ARA, the introduction of complementary foods, which are typically low in ARA, adversely impacts the availability of ARA to infants and children greater than 6 months of age (Luukkainen et al., 1996). The current medical position of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN, 2008) indicates that ARA is important in the complementary diet noting that “ARA is the major LCPUFA of the n-6 series and is well represented in the brain”. Recent intake recommendations from the Superior Health Council of Belgium specify 45 – 110 mg ARA/day for children from 12 – 36 months with increasing amounts for children over 3 years of age.

<b>Table 1. Docosahexaenoic acid (DHA) &amp; Arachidonic acid (ARA) Breast milk Levels</b>		
	DHA mean (% total fatty acids)	ARA mean (% total fatty acids)
<b>World wide<sup>1</sup></b>	<b>0.32</b>	<b>0.47</b>
Japan <sup>2</sup>	0.99	0.40
Philippines <sup>2</sup>	0.74	0.39
Chile <sup>2</sup>	0.43	0.42
Spain	0.34±0.03	0.58
China	0.25 <sup>3</sup>	0.49
Mexico <sup>2</sup>	0.26	0.42
UK <sup>2</sup>	0.24	0.36
Australia <sup>2</sup>	0.23	0.38
U.S.	0.21 <sup>4</sup>	0.45
Canada <sup>2</sup>	0.17	0.37

<sup>1</sup>Brenna et al. *Am J Clin Nutr* 2007; 85:1457-64; <sup>2</sup>Yuhas et al. *Lipids* 2006; 41:851-858; <sup>3</sup> Mean calculated from Peng et al., 2007; Yuhas et al., 2006; Xiang et al., 1999; 2005; Dodge et al., 1999; <sup>4</sup>Mean calculated from Yuhas et al., 2006; Bopp et al., 2005; Auestad et al., 2001; Jensen et al., 2000; 2005; Francois et al., 1998; Henderson et al., 1992; Carlson et al., 1986

The frequent practice of early cessation of breastfeeding (prior to 6 months) also limits ARA availability and necessitates the addition of ARA to infant formula to adequately maintain infant tissue ARA to that of an exclusively breastfed infant. Hoffman et al. (2000) studied the influence of human milk vs. formula that met or exceeded the LCPUFA content of study breast milk. Formula with 0.35% DHA only, formula with 0.36% DHA plus 0.72% ARA, or formula with no supplemental LCPUFA was compared to human milk among US term infants during the first 17 weeks of life. At 6 weeks of age, infants fed human milk or DHA and ARA formula exhibited the highest red blood cell levels of ARA. ARA levels were lowest among infants fed formula devoid of LCPUFA and were significantly lower than those fed both LCPUFA formulas. By 17 weeks, however, the consequence of providing DHA without ARA was evident among DHA only fed infants as ARA levels were significantly reduced compared even to those fed formula without DHA. Makrides et al. (1999) also reported significant depressions in plasma phospholipid ARA levels among infants supplemented with DHA only (0.35%) from birth to 4 months as compared to those fed human milk, DHA and ARA formula (0.34% for both), or non-LCPUFA formula. These data support ESPHGAN recommendations (2005) that ARA content should "be at least the same concentration as DHA" when DHA is added to infant formula.

The importance of maintaining a continuous supply of DHA and ARA during the early post-natal period is evident in the results of Birch et al. (2002) who weaned 6 week old infants from exclusive breast-feeding to either a DHA/ARA formula or a formula without LCPUFA. Despite an extended period of early post-natal supplementation of LCPUFA from human milk, formerly breast-fed infants weaned to non-LCPUFA formula exhibited significantly depleted LCPUFA status by 17 weeks of age. Specifically, at 17 weeks, both red blood cell and plasma levels of DHA and ARA were significantly reduced among formerly breast-fed non-LCPUFA infants as compared to those weaned to LCPUFA formula.

Similar observations have been made among healthy US preterm infants fed formula or human milk. Vanderhoof et al. (1999) studied the effects of human milk vs. DHA and ARA formula (0.35% DHA and 0.50% ARA) or non-LCPUFA formula on plasma phospholipid LCPUFA status after 8 weeks of supplementation. In both, phosphatidylcholine (PC) and phosphatidylethanolamine (PE) plasma fractions, ARA declined from enrollment to 48 weeks post-conception age among non-LCPUFA fed infants to almost half birth levels in the PC fraction. PC levels of ARA among human milk and LCPUFA-fed infants declined among on-LCPUFA infant from enrollment but, in contrast to PC, ARA levels among human milk or LCPUFA fed infants increased throughout the course of the study.

Human milk represents the optimal form of infant nutrition and Martek agrees breastfeeding is the best method of feeding infants. However, those parents who need or choose formula should be able to choose the most nutritionally optimal formula available, including organic versions of infant formulas.

### ***Neural Growth & Visual Development***

ARA also plays an important role in infant neural growth and visual development. All infant formula studies demonstrating a benefit of DHA to visual and cognitive development, for example, have included ARA. The contribution of ARA to visual development, ARA Single Cell Oil in particular, is evident in the comparison of infants supplemented with LCPUFA formulas throughout the first year of life. Birch et al. (2005) reported significant visual improvement in response to LCPUFA supplementation throughout the first year of life of healthy term infants from day 5 of age with 0.36% DHA and 0.72% ARA as compared to non-LCPUFA formula. In contrast Makrides et al. (2000), however, failed to find a benefit associated with a similar level of DHA supplementation throughout the first year of life. Interestingly, the ARA level supplemented by Makrides was less than half that supplemented by Birch and co-workers (2005), and

provided as egg phospholipid, suggesting that the source and level of supplemental ARA is important for achieving developmental benefit. Birch et al. (2005) reported that better sweep VEP acuity was associated with higher levels of both DHA and ARA in red blood cell total lipids at 39 and 52 weeks of age.

The importance of continued LCPUFA supplementation throughout the first year of life is perhaps best illustrated by the meta-analysis conducted by Morale and co-workers (2005). These authors found that a longer duration of a dietary supply of LCPUFA, regardless of source, results in better visual acuity at 52 weeks. Infants supplied with supplemental DHA and ARA for 6 months during the first year of life, on average, exhibited 0.1 logMAR values better than non-supplemented infants. Infants who received a supply of LCPUFAs for the entire 52 weeks had visual acuity 0.14 logMAR better than infants who received no LCPUFAs, equivalent to about 1.5 lines better on an eye chart. Mild deficits in visual acuity can contribute to delays in developmental milestones. It has been suggested that delays in the early stage of visual, cognitive, and motor development can have downstream effects on later maturing processes (Neuringer, 2000). In older children, learning difficulties brought on by fatigue and subsequent reduced attention in the classroom can be the result of mild visual impairments. Improving at least one line on an eye chart in visual acuity equates to a meaningful clinical and functional change.

### ***Neural Benefits***

With regard to cognitive function, a recent meta-analysis indicates that plasma phospholipid ARA levels of children and adults with learning disorders are significantly depressed suggesting that suboptimal ARA intake during critical periods of growth may adversely impact brain development (Morse 2009). Birch et al. (2000) supplemented US term infants with either 0.36% DHA and 0.72% ARA or 0.35% DHA alone for the first 4 months of life. Fourteen months following cessation of LCPUFA supplementation, 18 month old children fed DHA and ARA exhibited significantly higher Bayley's PDI scores as compared to non-LCPUFA supplemented children. Children fed DHA and ARA during the first 4 months of life scored 7 points higher than non-LCPUFA supplemented children, while those fed DHA alone only gained a 4 point, non-significant, advantage over non-LCPUFA supplemented children.

The importance of DHA and ARA addition to infant formula, to most closely match breastfed infants, was confirmed 4 years later in a follow-up study of these children (Birch et al., 2007). At 4 years of age, children fed non-LCPUFA formula and formula with DHA alone had poorer verbal IQ scores compared to those fed breast milk or formula containing both DHA and ARA.

In addition to supporting neural development, ARA from either human milk or LCPUFA-enriched infant formula has been reported to support the development and function of the infant immune system (Field, 2005). Due to the critical role of ARA in infant development, numerous health organizations have recommended the inclusion of minimum levels of ARA and DHA in term infant formula (Table 2).

**Table 2. Summary of Expert & Government Recommendations for DHA and ARA Levels in Infant Formulas**

Organization	LCPUFA ( % of total fatty acids)	
	Term Formula DHA/ARA	Preterm Formula DHA/ARA
British Nutrition Foundation 1992	0.4%/0.4%	20mg/kg DHA
FAO/WHO-expert panel 1994	0.35%/0.7%	40mg/kg DHA; 60mg/kg ARA
FAO/WHO-expert panel 2010	0.2-0.36%/0.4-0.6%	
Child Health Foundation, Koletzko 2001	0.2%/≥0.35%	≥0.35% DHA; ≥0.4% ARA
American Dietetic Association and Dietitians of Canada	≥0.2%/≥0.2%	
World Association Of Perinatal Medicine/Early Nutrition Academy/Child Health Foundation, Koletzko 2008	0.2-0.5%/≥0.2%	
Expert panel ISSFAL 2008	0.35%/0.5%	
Codex (2007) Codex Stan 72-198	≤ 0.5%/ ARA required to meet or exceed added DHA	
Health Council of the Netherlands 2001	20 mg/kg DHA	
Commission of the European Communities 2006	≥0.2/ n-6 2% of total fat maximum 0.1% as ARA	
ESPGHAN, Agostini 2009		DHA: 12-30mg/kg/day or 11- 27mg/100kcal ARA: 18-42mg/kg/day or 16-39mg/100kcal. The ratio of AA to DHA should be in the range of 1-2:1 (Wt/Wt) EPA supply should not exceed 30% of DHA supply.
Agence Français de Sécurité Sanitaire des Aliments (AFSSA) 2010	0.32% DHA/0.5% ARA	

## APPENDIX 9

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## Search Strategies

### **Biosis: 106 refs**

ts=((506-32-1) or (arachidonic\* acid\*)) and ((formula\* or milk\*) same (child\* or infant\*)) and (clinical\* or (double blind) or (control\* trial\*))

Timespan=All Years

### **Medline: 88 refs**

ts=((506-32-1) or (arachidonic\* acid\*)) and ((formula\* or milk\*) same (child\* or infant\*)) and (clinical\* or (double blind) or (control\* trial\*))

Timespan=All Years

### **PubMed: 82 refs**

arachidonic acid AND infant formula AND clinical trial AND humans

Timespan=All Years

## APPENDIX 10

## Martek ARASCO® Single-Cell Oil

### General Characteristics

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Description: Nutritional oil derived from *Mortierella alpina*, a rich source of Omega-6 arachidonic acid (ARA).  
Appearance: Yellow liquid oil  
Aroma: Characteristic

Arachidonic Acid (ARA)	min. 380 mg/g
Peroxide Value	max. 5.0 meq/kg
Unsaponifiable Matter	max. 3.5 %

### Ingredients

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Single-Cell Oil; High Oleic Sunflower Oil; Tocopherols and Ascorbyl Palmitate (as antioxidants).

### Product Storage and Stability

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Maximum stability of ARASCO® is achieved by shipping and storing the product frozen in the original, unopened container at minus 20 degrees centigrade until thawed for use. The oil should be protected from exposure to oxygen and elevated temperatures (> 30°C). Shipping and storage under frozen conditions provides stability for ARASCO® for up to three years if product is kept frozen and unopened.

Once a container is thawed and opened, use entire contents immediately. However, if it is not possible to use the entire amount at one time, the remainder may be nitrogen purged and refrozen at minus 20 degrees centigrade.



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## Organic Shoppers Want Functional Foods: Survey

May 20, 2010

Eight in 10 natural and organic consumers regularly read ingredient labels for health and nutrition content and express interest in purchasing functional foods with additional health, nutrition and dietary benefits, with four in 10, or 39 percent “very interested” in these kinds of foods, according to MamboTrack research from Collingswood, N.J.-based Mambo Sprouts Marketing.

Consumers said they’re most interested foods containing organic ingredients (65 percent) and low-sodium grocery products (47 percent), followed by low-fat/cholesterol (39 percent) and vegetarian items (31 percent). Functional food products with added calcium (44 percent), omega-3 (44 percent), antioxidants (43 percent), probiotics/prebiotics (38 percent), and vitamin D (30 percent) were also popular choices.

The study also revealed interest in specific ingredient-free foods, with one in three natural product consumers looking to buy allergen-free foods. Shoppers were most likely to report purchasing gluten-free/wheat-free items (25 percent), followed by dairy-free products (9 percent). Fewer eschewed soy (6 percent) or peanuts (4 percent). Among the gluten-free products, bread (59 percent), cereal (56 percent), chips and snacks (54 percent), and pasta (46 percent) were the most sought after.

Shoppers are turning to such items for a range of reasons. More than four in 10 gluten-free buyers believe these products are healthier for their family (43 percent), while another one in three (34 percent) had a household member with celiac disease or wheat intolerance, or noted that their favorite brands were already free of gluten (36 percent).

Packaging plays a key role in deciding which brands to buy, the research found. Four in 10 (40 percent) recently tried a new brand or switched brands specifically because of more earth-friendly packaging. Two in three purchased products with recyclable packaging or packaging made of recycled materials (66 percent), and 44 percent bought products with compostable/biodegradable packaging. Among the new eco-packaging options with the most appeal among one in two were compostable/biodegradable, reusable and refillable product packaging.

The study was based on the results of the online Mambo Sprouts Marketing Quick Poll, which surveyed 600 MamboTrack health and natural product consumers between April 19 and April 26, 2010.

### Links referenced within this article

#### Find this article at:

[http://www.progressivegrocer.com/progressivegrocer/content\\_display/features/e3i6bdd9c879228ff511a59c01568adbdc](http://www.progressivegrocer.com/progressivegrocer/content_display/features/e3i6bdd9c879228ff511a59c01568adbdc)

# Importance of arachidonic acid in infant health and development

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## INTRODUCTION

The addition of long chain polyunsaturated fatty acids (LCPUFA) to infant formula began over a decade ago. These additions include docosahexaenoic acid (DHA 22:6, n-3) and arachidonic acid (ARA 20:4, n-6). Their inclusion was an important step toward bringing the health and development of formula-fed infants closer to that of their breastfed counterparts. LCPUFA are normal components of cells and are found in particularly high concentrations in nerve cell membranes, including those of the brain and retina (1). Both fatty acids can be formed from shorter chain precursors, but the efficiency of this conversion is highly variable and often inadequate (2-5). Both are rapidly accrued in the central nervous system and retina during the latter part of pregnancy and throughout the first years of life (1, 6). These nutritionally important LCPUFA

## ABSTRACT

*The long chain polyunsaturated fatty acids, arachidonic acid (ARA) and docosahexaenoic acid (DHA), always present in human milk are important additions to infant formula for health and neurological development. The metabolism and functional activity of these two fatty acids are intertwined and their health benefits for infants are best characterized when considered together. ARA is found in all cell membranes with particularly high levels in neural membranes, especially those of the brain. Endogenous synthesis of ARA is not always sufficient to meet the demands of the growing infant. Tissue levels drop rapidly following birth unless dietary ARA is supplied. The combination of ARA with DHA in infant formula shows benefit for growth, neural development and immune function. The safety of omitting ARA from DHA-supplemented formula has not been established. International authoritative bodies recommend adding ARA to DHA-supplemented formula*

arise from two main fatty acid families, the n-3 and n-6 fatty acids. These two families are complex and intertwined both metabolically and functionally. Initially, the fatty acid of interest for infants was DHA and the important function it played in neurological and visual development. However, early research in this area showed that adding DHA alone to formula, particularly for premature infants, carried negative consequences (7-9). These early studies showed that adding DHA and eicosapentaenoic acid (EPA 20:5, n-3) without also adding ARA to infant formula was associated with sub-optimal growth in premature infants. Further research revealed that throughout infancy, blood levels of ARA decrease if formula feeding contains n-3 LCPUFA without ARA (10-13). The initial safety concerns regarding the supplementation of infant formula with n-3 LCPUFA without n-6 ARA caused future studies to focus on inclusion of ARA in any study with supplementation of DHA even though amounts and ratios varied.

## ARACHIDONIC ACID: OVERVIEW DURING INFANCY

### Human Milk Levels

Arachidonic acid is the primary n-6 LCPUFA in human milk (14). While the levels of DHA can vary widely according to maternal intake, ARA remains relatively constant. In fact, ARA appears to be a protected nutrient in human milk, indicating its importance for the developing infant (14). Breastfeeding of infants by well-nourished mothers is always considered the ideal for providing optimal nutrition. Provisions must be made, however, for infants who do not receive human milk. Therefore, formulation of infant feedings should be designed to provide nutrition as close to human milk as possible.

### Blood and Tissue Levels

ARA is a component of all cell membranes, and is found at particularly high levels in neural membranes, including those of the brain. ARA accumulates rapidly in the central nervous system during the last intrauterine trimester, continuing through the first few years of life. This fatty acid not only plays an essential structural role for neural membrane function, but is also metabolically essential for cells as a

precursor and messenger for a variety of biological processes (1).

Infants of all ages appear to have the capability to synthesize ARA. Studies using isotope tracers indicate that both preterm and term infants can synthesize ARA from its shorter chain dietary precursor, linoleic acid (2). This endogenous synthesis appears to be sub-optimal, however, and blood and tissue levels drop rapidly following birth unless dietary sources of preformed ARA are supplied (3, 5, 15). Plasma and red blood cell levels of ARA are significantly lower in infants fed formula lacking ARA than in those who are breastfed. Supplementation of formula with preformed ARA is required to achieve plasma and red blood cell levels that are equivalent to those of the breastfed infant (3, 5, 15, 16).

There may be multiple mechanisms by which tissue ARA concentrations impact infant health and development. ARA is known to be essential for normal growth, neurologic and immune function. It plays a critical role in cell metabolism as a precursor to series-2 eicosanoids and series-3 leukotrienes. Through these or other intermediates, ARA is a key regulator of cell signaling, including synaptic transmission (17-19).

### Importance for Growth

Human milk always contains DHA and ARA and healthy breastfed infants represent the standard for ideal growth. In infant formula, the combination of DHA and ARA is known to be safe in preterm and term infants. The combination also supports normal, but not excessive measures of growth including length, weight, and head circumference. A study in preterm infants which measured growth through the first 18 months of life (corrected age), showed that DHA+ARA-supplemented formula, but not unsupplemented formula, supported growth equal to that of breastfed infants (20). Recent meta-analyses of infant formula studies reinforced the safety of DHA+ARA-supplemented formula for growth in term and preterm infants (11, 21).

ARA is one of many nutrients associated with growth. In 1993, Carlson and others reported a significant correlation between the growth and arachidonic acid status in preterm infants (15). In 2002, Innis reported that the level of ARA in blood of preterm infants was positively correlated

with weight gain prior to hospital discharge and with weight and length at 40, 48, and 57 weeks post-menstrual age (22). Concerns exist regarding the safety of n-3 LCPUFA-supplemented formula not containing ARA due to reports of inadequate growth. Several clinical studies have shown suboptimal growth in preterm infants fed formula containing fish oil with DHA and EPA but no ARA (7-9). While all age groups studied have shown decreases in circulating ARA levels with n-3 LCPUFA supplementation without ARA, preterm infants may be particularly susceptible to growth problems as a result.

In less vulnerable term infants, a meta-analysis of 14 randomized controlled trials failed to find a negative effect of DHA supplementation without ARA on growth (11). However, the study reports that plasma ARA levels decrease by approximately 25% in term infants fed n-3 LCPUFA formula lacking ARA compared to those fed unsupplemented formula. This reduction of plasma ARA in formula-fed term infants may impact processes which are more sensitive to ARA levels than growth, such as immunity and neural development.

Length, weight, and head circumference are the parameters used in the studies mentioned above as determinants of growth. They are standardized and represent the most frequently reported anthropometric measures in children. Bone growth is a less well defined but potentially important aspect of growth that is also affected by LCPUFA, and particularly ARA, intake. In a study by Weiler and others, the investigators reported a positive correlation between cord red blood cell ARA and whole body bone mineral content. There was also a positive correlation of cord red blood cell ARA:EPA (ratio) with lumbar spine bone mineral content. These results suggest that ARA and perhaps the balance of n-3 to n-6 LCPUFA is important for bone growth in infants (23).

#### **Importance for Neurological Development**

Incorporation of ARA and DHA in neural membranes is important for the developing brain. Numerous studies, although not all, show a difference between LCPUFA-supplemented and unsupplemented formula on neurocognitive development (21). These studies show a positive effect of the combination of DHA and ARA intake on neural development through improved scores on visual, mental, and psychomotor tests (20, 24-28). Although few in number, studies that examined the effect of formula supplemented with DHA without ARA show a negative effect on neural

development. In a study by Birch and others, term infants were given test formulas exclusively for the first 17 weeks of life (29). The infants were fed either formula lacking LCPUFA; formula supplemented with DHA only; or formula supplemented with DHA + ARA. Groups were compared to infants who were exclusively breastfed. At 18 months, the authors found a significant increase in scores on the Bayley Mental Development Index (MDI) in infants fed a formula containing DHA + ARA compared to those fed unsupplemented formula. The infants who had been fed DHA-only formula had MDI scores that were greater than control but lower than the DHA + ARA group, although not statistically different from either. Furthermore, the MDI score of infants fed DHA + ARA formula were equivalent to those of breastfed infants. Most important, the benefits of DHA+ARA supplementation continued beyond the initial period of supplementation into childhood. At age 4, children who received formula without LCPUFA as infants had poorer visual acuity and verbal IQ scores than those who received DHA and ARA. In fact, only those children who received DHA + ARA supplemented formula had verbal IQ scores equivalent to those who had been breastfed (25).

In an earlier study by Scott and others, negative findings were associated with a formula supplemented with DHA and EPA from fish (tuna) oil without ARA (30). In that study, infants fed the fish oil formula not containing ARA had significantly lower scores on the Vocabulary Production subscale of the MacArthur Communicative Development Inventories at 14 months compared to infants fed an unsupplemented control formula. The majority of studies examining the effects of LCPUFA on visual and cognitive development utilized formulas supplemented with both ARA and DHA. Many, although not all, showed a benefit of including DHA and ARA in infant formula on visual and neural development. In fact, many now show long-term benefits as the result of including LCPUFA during the early months of life (20, 24, 25, 31). There is, however, very little research available showing long term effects of LCPUFA formula without added ARA.

#### **Importance for Immune Development and Function**

At all ages, a balance of n-3 and n-6 LCPUFA is thought to play a critical role in immune response (32). ARA is an indispensable precursor for the synthesis of eicosanoids, including prostaglandins, thromboxanes, prostacyclins, and leukotrienes. ARA-derived eicosanoids modulate the activity of various immune cells. ARA is required during early

development with high levels of accretion in the thymus, lymphoid and other cells of the immune system. A study in premature infants showed that DHA + ARA supplemented infants have a more mature immune system than non-supplemented infants (33). The authors concluded that it is important not to compromise the immunoregulatory role of ARA during early development.

In two studies by Field and others (34, 35), the authors found that adding DHA and ARA to preterm formula resulted in immune outcomes more similar to and consistent with those of breastfed infants. A separate lab reported a lower incidence of respiratory illness in infants supplemented with LCPUFA as compared to controls (36).

#### **Recommendations for Infant Formula**

Expert groups and authoritative bodies who have evaluated the literature for LCPUFA requirements during infancy recommend the addition of ARA to formula whenever DHA or other LCPUFA are added. They also recommend a balance of n-6 to n-3 fatty acids overall. The International Expert Group representing the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommend that whenever DHA is added to an infant formula, ARA also be added in at least an equal amount (37). The latest version of the Codex Committee on Nutrition and Foods for Special Dietary Uses defines, in its standards for infant formula, the addition of ARA should reach at least the same concentration as DHA when added to infant formula (38). The recently published European Commission Directive on Infant Formula and Follow-on Formula also requires the addition of n-6 LCPUFA (ARA) in at least an equal amount as DHA (39).

#### **SUMMARY**

DHA and ARA are considered conditionally essential nutrients during early life and are related to cognitive, visual and immune development during infancy and throughout childhood. Human milk always contains both DHA and ARA. DHA + ARA-supplemented formula raises plasma and red blood cell concentrations of DHA and ARA in infants to levels comparable to those of breastfed infants. The consequences of supplementation of infant formula with DHA alone include suboptimal growth in preterm infants, and lower neurocognitive scores in term infants and beyond. As a precursor for eicosanoids and cell messengers, ARA plays an important role in immune development. The addition of ARA to

LCPUFA-supplemented formula is recommended by most expert and authoritative bodies in an effort to ensure that commercially available infant formula provides health benefits closer to those of breast milk.

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# Nucleotides in infant nutrition: an update

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## ABSTRACT

Infants are at higher risk for morbidity resulting from infectious diseases, due in part to immaturity of their immune system. Immune modulators in human

milk explain some of the protective effects of mother milk.

One of those is Nucleotides (NT). NT and their related products play key roles in many biological processes.

They play a role in the development, maintenance and function of the gastrointestinal and immune systems. Studies of compromised or normal term and preterm babies, fortified by NT, showed beneficial effect on cellular and humeral immunity and morbidity.

It seems that there is a clinical dose response effect and mainly the disadvantaged infants benefit the most. NT provide scientific evidence to justify their addition to breast milk substitutes.

## INTRODUCTION

Nucleotides (NT) are ubiquitous component in human milk and are crucially important to fundamental cellular metabolism and functions. When the body needs are greater than the amounts of NT synthesized or salvaged, the term semiessential or conditionally essential nutrients can be applied. Rapid growth, certain disease states, low nutrient intake or disturbed endogenous synthesis represent such conditions. Infant formulas are continuously modified as new scientific evidence about nutrient needs of the baby become available. The field of immunonutrition is expanding and NT is only one on the list. In the last years, several infant manufacturers

# Martek's Communiqué

## The Health Benefits of Arachidonic Acid

### Introduction

Arachidonic acid (ARA) and docosahexaenoic acid (DHA) are the primary long chain polyunsaturated fatty acids (LCPUFA) of the omega-6 and omega-3 families, respectively. Both are critical components of cell membranes and play an important role in the development of the central nervous system (J Pediatr Gastroenterol Nutr 2008 Aug;47 Suppl 1:S7-9). Most research has focused on the role of DHA in the developing brain, but ARA is also critical for optimal neurodevelopment and is required during infancy for normal growth and maturation (J Perinat Med 2008;36(1):5-14). ARA accumulates within the brain during pre- and post-natal development, with particularly rapid accretion during the last 10 weeks of gestation (J Perinat Med 2008;36(1):5-14; J Perinat Med 2008;36(2):101-9; J Pediatr Gastroenterol Nutr 2008 Aug;47 Suppl 1:S7-9). In fact, some evidence suggests fetal brain accretion of ARA exceeds that of DHA so that at term, the brain contains more ARA than DHA (J Perinat Med 2007;35 Suppl 1:S28-34).

ARA is produced endogenously from its dietary precursor, linoleic acid (LA). However, pre-natal conversion of LA to ARA appears to be low, so the developing fetus depends upon maternal ARA supply (J Perinat Med 2008;36(1):5-14). After birth, ARA synthesis is insufficient to maintain stable blood and tissue concentrations, so an exogenous supply of ARA is necessary (J Perinat Med 2008;36(1):5-14). ARA and DHA are present naturally in human breast milk (Am J Clin Nutr 2007 Jun;85(6):1457-64). Infants who are not breastfed need supplemental DHA and ARA to match blood levels of these LCPUFA in their breastfed counterparts (J Pediatr Gastroenterol Nutr 2008 Aug;47 Suppl 1:S7-9). Therefore, DHA and ARA have been added to many infant formulas in the United States since 2002.

Results from some early supplementation trials indicate that it's important to add both DHA and ARA to infant formula. Because omega-3 and omega-6 PUFA compete for the same enzymatic pathway, infant formulas supplying DHA, but not ARA, reduce ARA levels in both term and preterm infants (J Perinat Med 2008;36(2):101-9; J Perinat Med 2008;36(1):5-14). According to a meta-analysis of 6 trials, term infants fed formula containing only omega-3 LCPUFA showed plasma ARA reductions of approximately 25% (Am J Clin Nutr 2005 May;81(5):1094-101). Though not all studies agree, these reductions could negatively affect growth, particularly in preterm infants (J Pediatr Gastroenterol Nutr 2005 Nov;41(5):584-99).

Few studies have evaluated the effects on neurological development of formula supplemented with DHA, but not ARA. Birch and colleagues conducted a clinical trial involving 56 infants fed one of 3 treatments for the first 17 weeks of life: control formula, formula with added DHA or formula with added DHA and ARA (Dev Med Child Neurol 2000 Mar;42(3):174-81). At 18 months of age, infants fed the DHA + ARA formula had significantly higher scores on the Bayley Mental Development Index (MDI) than infants fed the control formula. The DHA + ARA group also had MDI scores higher than those fed formula with DHA only, though the differences did not reach statistical significance. In another study, infants fed formula with DHA but not ARA scored worse on some measures of language assessment at 14 months of age than infants fed either human milk or an unsupplemented control formula (Pediatrics 1998 Nov;102(5):E59). However, scores for infants receiving formula supplemented with both DHA and ARA were not significantly different than those for any of the other groups. Results from these studies indicate that both DHA and ARA are required for optimal neurodevelopment.

Supplementation of infant formula with DHA and ARA may also have favorable effects on blood pressure, immunity and bone mass (J Perinat Med 2008;36(1):5-14). ARA is a precursor to eicosanoids, including prostaglandins and leukotrienes, which have extensive biological activities including immune response modulation and bone formation. In one study, infants fed formula with ARA and DHA showed improved immunity, including differences in T-cell counts, compared with infants fed unsupplemented formula (Lipids 2003 Apr;38(4):323-41). Results from another study showed positive associations between umbilical cord red blood cell ARA levels and whole body bone mineral content in healthy infants (Pediatr Res. 2005 Dec;58(6):1254-8).

Based on the reported benefits of LCPUFA, the International Expert Group from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition supports the optional addition of DHA and ARA to infant formula (J Pediatr Gastroenterol Nutr 2005 Nov;41(5):584-99). Other worldwide expert groups, including the Codex Committee on Nutrition and Foods for Special Dietary Uses, and the European Union Commission, recommend that infant formulas contain ARA whenever DHA is added (Codex Alimentarius Commission, 30 October-3 November 2006; Official Journal of the European Union 30.12.2006:L401/1-33). Specifically, DHA levels

should be between 0.2% - 0.5% of fatty acids and ARA levels should at least equal those of added DHA (Koletzko 2008; J Perinat Med. 2008;36(1):5-14).

The following papers, published during 2007 and 2008, confirm that both ARA and DHA are required during infancy for optimal neurodevelopment, and that levels of ARA and DHA higher than those found in breast milk may benefit cognitive development in preterm infants. In addition, higher levels of ARA may reduce mother-to-child HIV transmission through breastfeeding.

## **Pertinent papers from 2007 and 2008**

**Visual acuity and cognitive outcomes at 4 years of age in a double-blind, randomized trial of long-chain polyunsaturated fatty acid-supplemented infant formula.** Birch EE, Garfield S, Castañeda Y, Hughbanks-Wheaton D, Uauy R, Hoffman D. *Early Hum Dev.* 2007 May;83(5):279-284.

In this randomized, double-blind clinical trial, researchers examined the effects of DHA- and DHA+ARA-supplemented infant formula on cognitive and visual outcomes at 4 years of age. Within the first four days of life, 79 infants were randomly assigned to one of three diets: control formula (Enfamil<sup>®</sup> with iron), formula with 0.35% DHA (Martek DHASCO<sup>®</sup>) of total fatty acids, or formula with 0.36% DHA and 0.72% ARA (Martek ARASCO<sup>®</sup>). Infants received assigned diets exclusively through 17 weeks of age. At 4 years of age, 52 infants were available for follow-up testing for visual and cognitive outcomes. Thirty-two additional infants who were breastfed served as a "gold-standard". Dietary supply of LCPUFA significantly improved visual acuity in the right eye ( $p=0.17$ ), but not in the left eye. Children who received control formula or formula with DHA only had significantly lower verbal IQ than those who were breastfed ( $p<0.0004$ ;  $p<0.02$  respectively). However, verbal IQ for children who received formula with both DHA and ARA was not significantly different than that for breastfed infants. These findings confirm that both ARA and DHA are required for optimal cognitive and visual development during infancy and confer benefits similar to breastfeeding.

**Improved cognitive development among preterm infants attributable to early supplementation of human milk with docosahexaenoic acid and arachidonic acid.** Henriksen C, Haugholt K, Lindgren M, Auvåg AK, Rønnestad A, Grønn M, Solberg R, Moen A, Nakstad B, Berge RK, Smith L, Iversen PO, Drevon CA. *Pediatrics.* 2008 Jun;121(6):1137-1145.

Human breast milk represents the gold standard for providing optimal nutrition for the developing infant. However, even breast milk does not supply as much DHA and ARA as the fetus receives in utero, and this has important implications for preterm infants. This randomized, double-blind, placebo-controlled study examined the effects of ARA and DHA supplementation of breast milk on cognitive development in preterm infants. Subjects included 141 very low birth weight infants who received breast milk from either the mother or a donor within the first 2 day of life. One week after birth, the infants were randomized to receive, until an average of 9 weeks of age, one of two study oils added to breast milk: ARA (31 mg/100 ml breast milk) + DHA (32 mg/100 ml breast milk) (Martek

Biosciences); or control oil. The LCPUFA supplementation more than doubled the ARA and DHA content of the breast milk. At 6 months of age, plasma fatty acid concentrations, cognitive development and recognition memory were evaluated in 129 infants who completed the intervention. Plasma ARA concentrations decreased by 24% in the control group compared with only 6% in the ARA + DHA group ( $p=0.015$ ). Infants who received ARA + DHA scored significantly higher on the problem-solving subset of the Ages and Stages Questionnaire ( $p=0.02$ ) and had significantly better recognition memory for the standard image subset of the electrophysiological recordings ( $p=0.01$ ). No significant differences between groups for any of the other cognitive or memory measurements were found. These findings suggest higher levels of ARA and DHA than those found in breast milk may improve cognitive development in preterm infants.

**Long-chain n-6 polyunsaturated fatty acids in breast milk decrease the risk of HIV transmission through breastfeeding.** Villamor E, Koulinska IN, Furtado J, Baylin A, Aboud S, Manji K, Campos H, Fawzi WW. *Am J Clin Nutr.* 2007 Sep;86(3):682-689.

Mother-to-child transmission of HIV infection through breastfeeding accounts for a substantial proportion of infant HIV infections, especially in sub-Saharan Africa. For economic, safety and other reasons, the World Health Organization still recommends that HIV-infected women exclusively breastfeed their infants for up to 6 months. ARA and other fatty acids are essential for proper immune function in infants and may have virucidal activity as well. Therefore, this nested case-control study was undertaken to determine if concentrations of fatty acids in breast milk are associated with the risk of mother-to-child transmission of HIV infection. Cases included 59 women living in Tanzania who transmitted HIV infection to their infants through breast milk. Matched controls consisted of 59 HIV positive Tanzanian women who breastfed their infants but did not transmit HIV infection. Analyses of breast milk fatty acid concentrations showed that higher percentage weight concentrations of ARA, as well as the omega-6 fatty acids 11c,14c-eicosadienoic acid and dihomo- $\gamma$ -linolenic acid and the omega-9 fatty acid gondoic acid were significantly associated with lower risk of mother-to-child HIV transmission. Of all fatty acids analyzed, ARA concentrations showed the most significant differences between cases and controls ( $p=0.001$ ). Higher concentrations of ARA, as well as total omega-3 PUFA and dihomo- $\gamma$ -linolenic acid were also significantly associated with lower cell-free virus shredding in breast milk, a strong predictor of HIV transmission. These findings suggest that higher levels of certain fatty acids in breast milk, especially ARA, are associated with lower mother-to-child HIV transmission.

## **Conclusions and areas for future research**

ARA plays a critical role in infant growth and development. Supplementation of infant formulas with both ARA and DHA is required to match circulating levels of these LCPUFA in breastfed infants. An exogenous supply of ARA in addition to DHA confers visual and cognitive benefits during infancy and may have other beneficial effects, including improved immunity and bone mass. Future research is needed to establish optimum doses of ARA for term and preterm infants, and further evaluate the effects of ARA on growth, immunity, bone mass, and neurodevelopment.

## **Arachidonic Acid is Necessary in Infant Formula Supplemented with Omega-3 Long Chain Polyunsaturated Fatty Acids (LCPUFA)**

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### **Executive Summary**

- Arachidonic acid (ARA) supplementation in combination with DHA is safe for infants. Both ARA and DHA are always found in human milk
- Arachidonic acid (ARA) is required for development of optimal neurological and cognitive function, and immune system development in infants
- The benefits of ARA+DHA supplementation continue beyond the period of supplementation into childhood
- Regulatory, scientific, and other expert groups recommend the addition of ARA in DHA supplemented formula
- Omission of ARA from formula supplemented with long chain omega-3 polyunsaturated fatty acids may pose a risk to normal infant development

### **Recommendations for ARA Supplementation of Infant Formula**

- In formula supplemented with omega-3 long chain polyunsaturated fatty acids, ARA should be added at a minimum level of 0.2% to a maximum level of 1.0% of total fatty acids
- The ratio of ARA to DHA should be in a range of 1:1 to 2:1

### **ARA is required for optimal neurological function, cognitive outcome, and immune system development in the infant.**

**ARA is in all cell membranes, and is found at particularly high levels in neural membranes, particularly those of the brain.**

ARA accumulates rapidly in the central nervous system during the last intrauterine trimester, continuing through the first 2 years of life. ARA not only plays an essential structural role for neural membrane function, but is also metabolically essential for cells as a precursor and messenger for a variety of biological processes.

Martinez M. Tissue levels of polyunsaturated fatty acids during early human development. J Pediatr 1992;120:S129-38.

**Endogenous synthesis of ARA is insufficient to meet the demands of the growing infant. Tissue levels drop rapidly following birth unless dietary ARA is supplied in either human milk or a supplemented infant formula.** Studies using isotope tracers indicate that both preterm and term infants are capable of synthesizing ARA from linoleic acid. However, the rate of conversion is low and the overall amounts synthesized may be less than optimal. Plasma and red blood cell (RBC) levels of ARA are significantly lower in infants fed unsupplemented formula than in those who are breastfed. Supplementation of formula with preformed ARA is required to achieve plasma and RBC levels that are equivalent to those of the breastfed infant.

Carlson SE, Werkman SH, Peeples JM, Cooke RJ, Tolley EA. Arachidonic acid status correlates with first year growth in preterm infants. *Proc Natl Acad Sci U S A* 1993;90:1073-7.

Clandinin MT, Van Aerde JE, Parrott A, Field CJ, Euler AR, Lien EL. Assessment of the efficacious dose of arachidonic and docosahexaenoic acids in preterm infant formulas: fatty acid composition of erythrocyte membrane lipids. *Pediatr Res* 1997;42:819-25.

Crawford MA. The role of essential fatty acids in neural development: implications for perinatal nutrition. *Am J Clin Nutr* 1993;57:703S-709S.

Hoffman DR, Birch EE, Birch DG, Uauy RD. Effects of supplementation with omega 3 long-chain polyunsaturated fatty acids on retinal and cortical development in premature infants. *Am J Clin Nutr* 1993;57:807S-812S.

Innis SM, Foote KD, MacKinnon MJ, King DJ. Plasma and red blood cell fatty acids of low-birth-weight infants fed their mother's expressed breast milk or preterm-infant formula. *Am J Clin Nutr* 1990;51:994-1000.

Kohn G, Sawatzki G, van Biervliet JP, Rosseneu M. Diet and the essential fatty acid status of term infants. *Acta Paediatr Suppl* 1994;402:69-74.

Koletzko B, Schmidt E, Bremer H, Haug M, Harzer G. Effects of dietary long-chain polyunsaturated fatty acids on the essential fatty acid status of premature infants. *Eur J Pediatr* 1989;147:669-675.

Pita ML, Giron MD, Perez-Ayala M, DeLucchi C, Martinez Valverde A, Gil A. Effects of postnatal age and diet on the fatty acid composition of plasma lipid fractions in preterm infants. *Clin Physiol Biochem* 1989;7:238-48.

Salem N, Jr., Wegher B, Mena P, Uauy R. Arachidonic and docosahexaenoic acids are biosynthesized from their 18-carbon precursors in human infants. *Proc Natl Acad Sci U S A* 1996;93:49-54.

**The combination of ARA with DHA supplementation of infant formula is necessary for optimization of mental/neural development.**

Deposition of ARA and DHA is important for the developing brain. In the only study reporting long-term neurocognitive effects of DHA/ARA vs DHA-only supplemented formula, only those infants supplemented with DHA plus ARA showed improved mental development compared to unsupplemented controls (Birch 2000).

Birch EE, Hoffman DR, Uauy R, Birch DG, Prestidge C. Visual acuity and the essentiality of docosahexaenoic acid and arachidonic acid in the diet of term infants. *Pediatr Res* 1998;44:201-9.

Birch EE, Garfield S, Hoffman DR, Uauy R, Birch DG. A randomized controlled trial of early dietary supply of long-chain polyunsaturated fatty acids and mental development in term infants. *Dev Med Child Neurol* 2000;42:174-81.

Clandinin MT, Chappell JE, Leong S, Heim T, Swyer PR, Chance GW. Intrauterine fatty acid accretion rates in human brain: implications for fatty acid requirements. *Early Hum Dev* 1980;4:121-9.

Clandinin MT, Chappell JE, Leong S, Heim T, Swyer PR, Chance GW. Extrauterine fatty acid accretion in infant brain: implications for fatty acid requirements. *Early Hum Dev* 1980;4:131-8.

**The developmental benefits of infant formula supplemented with both ARA and DHA continue well beyond the period of supplementation extending into early childhood.**

Studies also confirm a need for continued dietary sources of DHA in combination with ARA throughout the first year for optimal growth, cognitive, and visual development. No research has shown long term advantages of formula containing DHA without ARA.

Birch EE, Castaneda YS, Wheaton DH, Birch DG, Uauy R, Hoffman DR. Visual maturation of term infants fed long-chain polyunsaturated fatty acid-supplemented or control formula for 12 mo. *Am J Clin Nutr* 2005;81:871-879.

Clandinin MT; Van Aerde J; Merkel K; Harris C; Springer M.A; Hansen, J S; Diersen-Schade D A. Growth and development of preterm infants fed infant formulas containing docosahexaenoic acid and arachidonic acid. *J Pediatr* 2005;146:461-468.

Forsyth JS, Willatts P, Agostoni C, Bissenden J, Casaer P, Boehm G. Long chain polyunsaturated fatty acid supplementation in infant formula and blood pressure in later childhood: follow up of a randomised controlled trial. *BMJ* 2003;326:953.

Hoffman DR, Birch EE, Birch DG, et al. Impact of early dietary intake and blood lipid composition of long-chain polyunsaturated fatty acids on later visual development. *J Pediatr Gastroenterol Nutr* 2000;31:540-53.

Hoffman D, Birch E, Castaneda Y, et al. Visual function in breast-fed term infants weaned to formula with or without long-chain polyunsaturates at 4 to 6 months: a randomized clinical trial. *J Pediatr* 2003;142:669-77.

Morale SE, Hoffman DR, Castaneda YS, Wheaton DH, Burns RA, Birch EE. Duration of long-chain polyunsaturated fatty acids availability in the diet and visual acuity. *Early Hum Dev* 2005;81:197-203.

Uauy R, Hoffman DR, Mena P, Llanos A, Birch EE. Term infant studies of DHA and ARA supplementation on neurodevelopment: results of randomized controlled trials. *J Pediatr* 2003;143:S17-25.

Willatts P, Forsyth JS, DiModugno MK, Varma S, Colvin M. Effect of long-chain polyunsaturated fatty acids in infant formula on problem solving at 10 months of age. *Lancet* 1998;352:688-91.

**ARA plays a pivotal role in the regulation of immune function.**

ARA is an indispensable precursor for the synthesis of eicosanoids, including prostaglandins, thromboxanes, prostacyclins, and leukotrienes. ARA derived eicosanoids modulate the activity of various immune cells. There is a high requirement for ARA during early development with high levels of accretion in the thymus, lymphoid and other cells of the immune system. A study in premature

infants showed that DHA/ARA supplemented infants have a more mature immune system than non-supplemented infants. Harbige et al. (2003) concluded that it is important not to compromise the immunoregulatory role of ARA during early development.

Field CJ, Clandinin MT, Van Aerde JE. Polyunsaturated fatty acids and T-cell function: implications for the neonate. *Lipids* 2001;36:1025-32.

Field C, Thompson C, VanAerde J, Parrot A, Euler A, Lien E, and Clandinin M. The lower proportion of CD45RO+ cells and deficient IL-10 production by formula-fed infants, compared to human-fed, is corrected with supplementation of long chain-polyunsaturated fatty acids. *J Pediatr Gastroenterol Nutr* 2000;31:291-299.

Harbige LS. Fatty acids, the immune response, and autoimmunity: a question of n-6 essentiality and the balance between n-6 and n-3. *Lipids* 2003;38:323-41.

**The safety of omitting ARA from infant DHA-supplemented formula has not been established.** One recent meta-analysis of LCPUFA supplementation in term infants found no growth issues with omission of ARA (Makrides 2005). However, the study analyzed growth as the only outcome over a brief one year follow-up, making conclusions about overall safety questionable. There are no regulatory or learned scientific bodies that accept or recommend supplementation of infant formula with DHA without ARA.

Makrides M, Gibson RA, Udell T, Reid K.; and the International LCPUFA Investigators. LCPUFA supplementation of infant formula does not influence the growth of term infants. *AJCN* 2005;81:1094-1101.

Kuratko C, Arterburn L, Hoffman JP, Nelson EB. Importance of arachidonic acid in long-chain polyunsaturated fatty acid-supplemented infant formula. *Am J Clin Nutr* 2005;82:1353-4; author reply 1354-5.

## **DHA-supplemented Formula Should Contain a Sufficient Amount of ARA**

**ARA is the predominant n-6 LCPUFA consistently found in human milk.** Human milk always contains both DHA and ARA. It is generally accepted that ARA content remains fairly constant, in a range of 0.3 to 0.8% of total fatty acids. However, DHA content varies depending on maternal diet. On average, human milk contains a ratio of ARA to DHA of about 2:1.

Human infants are able to synthesize a small amount of LCPUFA, and must obtain the majority of their LCPUFA intake from external sources, that is, either from human milk or supplemented infant formula. It is widely acknowledged that breastfeeding is the most desirable method of infant feeding. Therefore, commercial formula should be designed to provide nutrient content which allows the functional and physiological status of formula-fed infants to be as close as possible to breastfed infants. Only infants fed formula containing both ARA and DHA have fatty acid levels approximating those of breastfed infants.

Hoffman DR, Birch EE, Castaneda YS, et al. Visual Function in Breast-Fed Term Infants Weaned to Formula With or Without Long-Chain Polyunsaturates at 4 To 6 Months: A Randomized Clinical Trial. *J Pediatrics* 2003;669-677.

Jensen CL, Prager TC, Zou Y, et al. Effects of maternal docosahexaenoic acid supplementation on visual function and growth of breast-fed term infants. *Lipids* 1999;34.

Koletzko B, Thiel I, Abiodun PO. The fatty acid composition of human milk in Europe and Africa. *J Pediatr* 1992;120:S62-70.

Makrides M, Simmer K, Neumann M, Gibson R. Changes in the polyunsaturated fatty acids of breast milk from mothers of full-term infants over 30 wk of lactation. *Am J Clin Nutr* 1995;61:1231-3.

Makrides M, Gibson RA. Long-chain polyunsaturated fatty acid requirements during pregnancy and lactation. *Am J Clin Nutr* 2000;71:307S-11S.

Sala-Vila A, Castellote AI, Rodriguez-Palmero M, Campoy C, Lopez-Sabater MC. Lipid composition in human breast milk from Granada (Spain): changes during lactation. *Nutrition* 2005;21:467-73.

**ARA should be included in combination with DHA in infant formula and the overall ratio of n-3 and n-6 LCPUFAs should be maintained in a physiological range comparable to that found in human milk.**

It is well established that n-6 and n-3 fatty acids compete for positions on membrane phospholipids as well as for cellular enzymes including those involved in eicosanoid synthesis. Therefore, a ratio of 1:1 to 2:1 (ARA to DHA) should be maintained.

Gibson RA, Makrides M, Neumann MA, Simmer K, Mantzioris E, James MJ. Ratios of linoleic acid to alpha-linolenic acid in formulas for term infants. *J Pediatr* 1994;125:S48-55.

Kinsella JE, Broughton KS, Whelan J. Dietary unsaturated fatty acids: interactions and possible needs in relation to eicosanoid synthesis. *J Nutr Biochem* 1990;1:123-41.

**Reduced growth parameters have been reported in clinical trials in preterm infants when supplemented with high levels of n-3 LCPUFA (particularly eicosapentaenoic acid) without a concomitant addition of ARA. Normal growth has consistently been reported among infants receiving ARA and DHA in a ratio of 1:1 to 2:1.**

This ratio is in agreement with levels typically found in human milk and with the recommendations of several worldwide expert groups. Adverse events associated with omega-3 LCPUFA/ARA supplementation are rare. "However, adverse growth effects have been reported in single studies with supplementation of fish oils without concomitant n-6 LC-PUFA supply, particularly at high EPA intakes." (Koletzko, 2005)

Carlson SE, Werkman SH, Tolley EA. Effect of long-chain n-3 fatty acid supplementation on visual acuity and growth of preterm infants with and without bronchopulmonary dysplasia. *Am J Clin Nutr* 1996;63:687-97.

Carlson SE, Cooke RJ, Werkman SH, Tolley EA. First year growth of preterm infants fed standard compared to marine oil n-3 supplemented formula. *Lipids* 1992;27:901-907.

Koletzko B, Decsi T, Demmelmair H. Arachidonic acid supply and metabolism in human infants born at full term. *Lipids* 1996;31:79-83.

Koletzko B, Baker S, Cleghorn G, et al. Global Standard for the Composition of Infant Formula: Recommendations of an ESPGHAN Coordinated International Expert Group. *J Pediatr Gastroenterol Nutr* 2005;41:584-599.

Ryan AS, Montalto MB, Groh-Wargo S, Mimouni, G., et al. Effect of DHA-containing formula on growth of preterm infants to 59 weeks postmenstrual age. *Am J Hum Biol* 1999;11:457-467.

## Authoritative Statements

**Expert recommendations for LCPUFA supplementation of formula for term infants include at least 0.2 – 0.4% of total fatty acids as DHA and 0.35 – 0.7% as ARA.**

These are considered minimum levels required for supplementation, and higher doses may show additional benefits. In fact, an expert panel has determined that DHA and ARA levels up to 1.0% for each fatty acid are Generally Recognized As Safe (GRAS).

Borzelleca JF, Flamm G, German B, Glinsmann W, Kritchevsky D, Bechtel D. Opinion of an expert panel on the generally recognized as safe (GRAS) status of ARA and DHA single cell oils for infants and children. Martek Biosciences Corporation, 1999.

<http://www.cfsan.fda.gov/~rdb/opa-g041.html>

British Nutrition Foundation. *Unsaturated Fatty Acids: Nutritional and Physiological Significance*. London, England: Chapman & Hall, 1992:152-163.

ESPGAN Committee on Nutrition. Comment on the content and composition of lipids in infant formula. *Acta Paediatr Scand* 1991;80:887-96.

FAO/WHO Expert Committee. The role of essential fatty acids in neural development: implications for perinatal nutrition. *Am J Clin Nutr* 1994;57 (suppl):703S-710S.

ISSFAL Board of Directors. Recommendations for the essential fatty acid requirement for infant formula. In: Simopoulos A, Dutra de Oliveire JE, Desai ID, eds. *World Rev Nutr Diet*. Switzerland: Karger, 1994.

Koletzko B, Agostoni C, SE C, et al. Long chain polyunsaturated fatty acids (LC-PUFA) and perinatal development. *Acta Paediatr* 2001;90:460-464.

Simopoulos AP, Leaf A, Salem Jr N. Workshop Statement on the Essentiality of and Recommended Dietary Intakes for Omega-6 and Omega-3 Fatty Acids. *Prostaglandins Leukot Essent Fatty Acids* 2000;63:119-121.

### ESPGHAN - Term Infants

The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (*ESPGHAN*) recently convened an International Expert Group (*IEG*) meeting at the request of the Codex Committee on Nutrition and Foods for Special Dietary Uses. The group published its recommendation on composition requirements for a global infant formula standard (Koletzko et al, 2005). The report recognized that DHA and ARA are the main LCPUFAs in human milk. The DHA content in

human milk is quite variable and reaches high levels in populations with high marine food consumption, accounting for the variable ratio of ARA to DHA in milk.

The IEG noted that at this time, there is not sufficient documentation of the benefits and safety of DHA without the concomitant addition of ARA to infant formula. Until these benefits have been adequately demonstrated, the optional addition of DHA should not exceed 0.5% of total fat intake, and ARA content should be at least the same concentration as DHA.

Koletzko B, Baker S, Cleghorn G, et al. Global Standard for the Composition of Infant Formula: Recommendations of an ESPGHAN Coordinated International Expert Group. *J Pediatr Gastroenterol Nutr* 2005;41:584-599.

### **ESPGHAN - Preterm Infants Post Hospital Discharge**

Infants with an appropriate weight for postconceptional age at discharge should be breast-fed when possible. When formula-fed, such infants should be fed a formula which provides long-chain polyunsaturated fatty acids. Infants discharged with a subnormal weight for postconceptional age are at increased risk of long-term growth failure, and the human milk they consume should be supplemented, for example, with a human milk fortifier to provide an adequate nutrient supply. If formula-fed, such infants should receive special post-discharge formula with high contents of protein, minerals and trace elements as well as a long-chain polyunsaturated fatty acid supply, at least until a postconceptional age of 40 weeks, but possibly until about 52 weeks postconceptional age.

Aggett PF et al. Feeding Preterm Infants After Hospital Discharge: A Commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroent Nutr*. 2006 May;42(5):596-603.

### **Commission of the European Communities - Term Formula and Follow on Formula**

The Commission of the European Communities has adopted a Commission Directive on Infant Formulae and Follow-On Formulae. The directive allows the addition of LCPUFA to formula:

“In that case their content shall not exceed:

- 1% of the total fat content for n-3 LCP, and
- 2% of the total fat content for n-6 LCP (1% of the total fat content for arachidonic acid (20:4 n-6)

The eicosapentaenoic acid (20:5 n-3) content shall not exceed that of docosahexaenoic (22:6 n-3) acid content.

- The docosahexaenoic acid (22:6 n-3) content shall not exceed that of n-6 LCP.”

This requires that omega-6 LCPUFA, ARA, be present in formula containing DHA in (at least) a 1:1 ratio.

The Commission of European Communities, awaiting publication.  
<http://www.food.gov.uk/multimedia/pdfs/sanco22562006rev1.pdf>

### **Codex Committee on Nutrition and Foods for Special Dietary Uses**

In its Report of the 27th Session, the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) updated the draft infant formula standard (CCNFSDU, 2005), which permits the addition of DHA and ARA. It is recommended that DHA does not exceed 0.5% of fatty acids. The draft standard allows for ARA to be included, provided that DHA is added to the infant formula and that ARA contents should reach at least the same concentration as DHA (i.e. at least a 1:1 ratio).

ALINORM 06/29/26. Joint FAO/WHO Food Standards Programme Codex Alimentarius Commission, Report of the 27th Session of the Codex Committee on Nutrition and Foods for Special Dietary Uses. Bonn, Germany 21 - 25 November 2005

### **Literature Reviews**

**Fleith and Clandinin (2005)** conclude that the overall body of literature reviewed in their report indicates that DHA and ARA are important for growth and development of infants. "Thus for preterm infants, we recommend LCPUFA intakes in the range provided by feeding of human milk typical of mothers in Western countries. This range can be achieved by a combination of ARA and DHA, providing an ARA to DHA ratio of approximately 1.5 and a DHA content of as much as 0.4%. Preterm infants may benefit from slightly higher levels of these fatty acids than term infants. ... The addition of LCPUFA in infant formula for term infants, with appropriate regard for quantitative and qualitative qualities, is safe and will enable the formula fed infant to achieve the same blood LCPUFA status as that of the breast-fed infant?"

Fleith, M., and Clandinin, M.T. Dietary PUFA for preterm and term infants: review of clinical studies. *Crit Rev Food Sci Nutr* 2005;45(3) 205-229.

An examination of the subgroup data from the individual studies included in **Makrides et al (2005)** meta-analysis demonstrates no significant difference in measures of infant length and weight between term infants fed LCPUFA supplemented formulas with both ARA and DHA compared to DHA alone. However, in those studies, the authors report a mean reduction in plasma ARA of ~25% compared with control feeding. The developmental consequences of such a reduced ARA level have not been studied.

Makrides, M., Gibson, R.A., Udell T., and Ried, K. Supplementation of infant formula with long-chain polyunsaturated fatty acids does not influence the growth of term infants. *Am J Clin Nutr* 2005; 81(5):1094-1101.

## APPENDIX 11



June 30, 2010

Mr. Miles McEvoy  
Deputy Administrator  
National Organic Program  
Agricultural Marketing Service  
1400 Independence Avenue, SW  
Room 2646-S, STOP 0268  
Washington, DC 20250-0201

Re: Overview of Accessory/Voluntary Nutrients, 5 February, 2010.

Dear Mr. McEvoy:

Martek Biosciences Corporation is a leader in the innovation and development of vegetarian sources of the omega-3 fatty acid *life'sDHA*<sup>™</sup> (docosahexaenoic acid) for use in infant formula, foods, and dietary supplements, and *life'sARA*<sup>™</sup> (arachidonic acid), an omega-6 fatty acid, for use in infant formula and growing-up milks. Martek's products promote health and wellness through every stage of life and have been used in products certified "organic" and "made with organic" since 2006.

Martek has reviewed the draft Technical Advisory Panel (TAP) report entitled "Overview of Accessory/Voluntary Nutrients", dated 5 February 2010, available on the National Organic Program (NOP) website. NOP made this draft TAP report publicly available on 26 April 2010. We commend the TAP on its comprehensive review of the available information on the role of the omega-3 fatty acids DHA and EPA and the omega-6 fatty acid, ARA, in diet and in health. However, we have identified several inaccuracies in the report that we would like to bring to the TAP's attention. This information should be corrected before the TAP finalizes the report. For example, although the TAP report states DHA and ARA have not been authorized for use in European infant formulas, in fact they have indeed been authorized for use in Europe and have been used in some European countries for over a decade.

We request that NOP provide this comment to the TAP so they will have the most current information available when preparing the final report. Martek also would like to take this opportunity to provide additional information on DHA and ARA that we believe the TAP will find valuable as they finalize the report.

**Statement: "Omega-3 Fatty Acids are Not Considered Essential to the Diet"**

In the discussion of accessory nutrients, the draft TAP report states "omega-3 fatty acids are not considered essential to the diet."<sup>1</sup> Two pages later, the draft report notes that at least one omega-3 fatty acid, alpha-linolenic acid or ALA cannot be synthesized by the body and is essential.<sup>2</sup> The draft

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<sup>1</sup> Overview of Accessory/Voluntary Nutrients Pg. 2, Paragraph 1.

<sup>2</sup> Overview of Accessory/Voluntary Nutrients Pgs. 4-5.

report then also summarizes the various studies that have established the importance of providing DHA in the diet, particularly the diets of infants and young children.

The omega-3 fatty acid ALA is an essential nutrient. Recognition of ALA as essential has been confirmed by the U.S. Institute of Medicine (2007)<sup>3</sup> and recently reaffirmed by FAO/WHO experts.<sup>4</sup> ALA is the parent precursor to DHA in the body. The ability of the body to synthesize DHA from ALA may lead to the assumption that DHA is non-essential. However, the inability of ALA to provide sufficient DHA<sup>5</sup> during critical periods of life has led to the recognition by many experts of the essentiality of DHA during pregnancy, nursing, infancy and childhood<sup>5,6,7</sup> and, most recently, for the general population as a whole.<sup>8</sup> Indeed, the draft TAP report recognizes synthesis of DHA by the newborn infant is “limited” and that “LCPUFA status remains diet dependent in infants and young children.”<sup>9</sup> We encourage the TAP to revise the sentence which presently states that “omega-3 fatty acids are not considered essential to the diet.”

The omega-3 example provides an excellent case study of the ambiguities that would be introduced by defining accessory nutrients as “nutrients that are not considered essential nutrients.”<sup>10</sup> Such a definition would place NOP in the unenviable position of trying to determine whether a particular nutrient is or is not essential. Moreover, it would exclude from this category those nutrients that are considered essential, such as the omega-3 ALA. We believe the 1995 Final Board Recommendation (FBR) by the National Organic Standards Board (NOSB)<sup>11</sup> best captured the accessory nutrient definition. The NOSB defined accessory nutrients as “nutrients not specifically classified as a vitamin or mineral but found to promote optimal health.” We encourage the TAP to consider the 1995 definition, which in our view best captures the nature of these nutrients, the importance of including them in the diet, and avoids the ambiguity introduced by trying to determine whether a nutrient is “essential.”

### **Statement: DHA and ARA are not Permitted in Infant Formula in the EU**

The draft report states DHA and ARA are not permitted in infant formula in the EU.<sup>12</sup> Both DHA and ARA are authorized for use in infant formulas in Europe and have been used in various countries in Europe for well over a decade. The chart below identifies the minimum levels of DHA and ARA that have been authorized by regulatory authorities or expert groups in Europe and other countries outside of the United States.

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<sup>3</sup> Institute of Medicine, National Academy of Science. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids (Macronutrients). The National Academy of Sciences Press, Washington DC, Chapter 8. <http://www.nap.edu/openbook.php?isbn=0309085373>

<sup>4</sup> Uauy R and Dangaonr AD, 2009. Fat and fatty acid requirements and recommendations for infants of 0-2 years and children of 2-18 years. *Ann Nutr Metab* 55:76-96.

<sup>5</sup> Brenna JT et al., for the International Society for the Study of Fatty Acids and Lipids, ISSFAL, 2009. Alpha-linolenic acid supplementation and conversion to n-3 long-chain polyunsaturated fatty acids in humans. *Prost, Leuko, Essent Fatty Acids* 80:85-91.

<sup>6</sup> Brenna JT and Lapillonne A, 2009. Background paper on fat and fatty acid requirement during pregnancy and lactation. *Ann Nutr Metab* 55:97-122.

<sup>7</sup> Haggarty P, 2010. Fatty acid supply to the human fetus. *Annu Rev Nutr*, ahead of print.

<sup>8</sup> AFSSA, 2010. Opinion from the French food safety agency (AFSSA) regarding the update of the recommended dietary intake for fatty acids.

<sup>9</sup> Overview of Accessory/Voluntary Nutrients Pg. 5, Paragraph 1.

<sup>10</sup> Overview of Accessory/Voluntary Nutrients Pg. 2, Paragraph 1.

<sup>11</sup> Final Board Recommendation Addendum Number 13, “The Use of Nutrient Supplementation in Organic Foods” (“the FBR”), 1995.

<sup>12</sup> Overview of Accessory/Voluntary Nutrients Pg. 5, Paragraph 3..

Regulatory Body	Long-chain omega-3/DHA Levels	Long-chain omega-6/ARA Levels
<b>Codex</b> <i>Codex Stan 72-1981 Standard for Infant Formula and Formulas for Special Medical Purposes. Rev. 2007</i>	DHA Upper limit 0.5% total fat content EPA should not exceed DHA Minimum level not specified	ARA Upper limit not specified ARA required to meet or exceed added DHA Minimum level not specified
<b>EU Commission</b> <i>Commission Directive 2006/141/EC of 22 December 2006 on infant formulae and follow-on formulae and amending Directive 1999/21/EC</i>	Upper limit 1% of total fat content for n-3 LCP <sup>2</sup> DHA shall not exceed ARA EPA shall not exceed DHA 0.2% minimum for DHA/if LCP nutrition claim is made	Upper limit of 1% of total fat content for ARA Minimum level not specified ARA ≥ DHA
<b>Australia/New Zealand</b> <i>Standard 2.9.1 Infant Formula Products</i>	Upper limit 1% of total fat content for LC omega-3 <sup>3</sup> Total long chain omega 3:long-chain omega-6 ratio that is not less than 1	Upper limit of 1% of total fat content for ARA Total long chain omega 3:long-chain omega-6 ratio that is not less than 1
<b>Indonesian National Agency for Food and Drug Control</b> <i>Regulation of Head of Indonesian National Agency for Drug and Food Control Number HK.00.05.1.52.3920 on Infant Formula and Infant Formula for Special Medical Purposes</i>	0.2% minimum DHA Upper limit 0.5% DHA addition must be accompanied by addition of ARA according to the ratio of 1-2:1 EPA must not exceed DHA	ARA Upper limit not specified

### Statement: DHA and ARA are not Permitted for Use in European Health Claims

The draft TAP report states DHA and ARA are not permitted for use in European health claims referencing children’s development and health.<sup>13</sup> In fact, the European Food Safety Authority (EFSA) has determined that claims referencing children’s development and health, specifically claims regarding the role of DHA in visual development of infants up to 1 year of age, are adequately substantiated.<sup>14</sup> The adoption and addition of the following claim, “DHA contributes to the visual development of infants,” to the approved list of claims designated by EU Regulation 1994/2006 is currently under way.

### Statement: “In Addition to the Potential Danger of Bleeding”

The “Adverse Effects” section of the report contains a quote from Medline Plus that states high intakes of omega-3 fatty acids have been associated with an increased risk of bleeding. The draft report identifies the source of this information as “NIH Medline-DHA.” We could not find a Medline Plus report on DHA, although we did find a Medline Plus monograph with the title, “Omega-3 fatty acids, fish oil, alpha-linolenic acid” that covers the content mentioned in the draft.<sup>15</sup> By identifying the source of the information as a monograph on DHA, the draft TAP report creates the impression the data are limited to only DHA while the monograph covers the category of omega-3 fatty acids. We would recommend identifying the source of the information with the name used by Medline Plus (i.e., “Omega-3 fatty acids, fish oil, alpha-linolenic acid”).

<sup>13</sup> Overview of Accessory/Voluntary Nutrients, Pg. 7, Paragraph 2.

<sup>14</sup> DHA and ARA and visual development, Scientific substantiation of a health claim related to docosahexaenoic acid (DHA) and arachidonic acid (ARA) and visual development pursuant to Article 14 of Regulation (EC) No 1924/2006. Question No EFSA-Q-2008-211. Adopted 22 January 09. The EFSA Journal 941:1-14.

<sup>15</sup> <http://www.nlm.nih.gov/medlineplus/druginfo/natural/patient-fishoil.html>. Accessed 5-11-2010.

The draft TAP report uses this NIH reference to support the observation that consumption of omega-3 fatty acids presents a potential danger from bleeding.<sup>16</sup> The draft TAP report, however, fails to mention the high level of omega-3 fatty acid intake that is associated with an increased risk of bleeding. Competent authorities world-wide, including the U.S. FDA, recognize DHA and EPA intake must exceed three grams before there could be any potential issues with increased bleeding. When establishing the levels of use of various sources of DHA and EPA, FDA placed restrictions on the maximum amount of DHA and EPA that could be formulated into each food category to ensure that total dietary intake of these two omega-3 fatty acids from all sources would not exceed three grams for the 90<sup>th</sup> percentile of consumers of the products.<sup>17</sup> FDA first adopted this approach when issuing the GRAS affirmation regulation for menhaden oil in 1997 and again when adjusting the allowance assigned to various food groups in 2005.<sup>18</sup> The submitters of the GRAS notifications for various other sources of DHA and EPA have maintained the same restrictions. Importantly, the addition of nearly a decade of additional research for safety evaluation did not change FDA's conclusions with regard to the safety of DHA+EPA for the general population or persons treated for various medical conditions.

The level of omega-3 fatty acids associated with increased bleeding times is magnitudes higher than the levels currently added to many foods, with many foods containing between 16 and 50 mg of added DHA and EPA per serving. By failing to provide information on the very high levels of omega-3 fatty acids that have been associated with increased bleeding times and the restrictions in place to ensure foods do not approach those levels, the draft report could be construed as implying there is a potential safety issue with increased bleeding times through the consumption of foods containing added omega-3 fatty acids. The potential confusion could be mitigated by removing the draft TAP report's reference to increased bleeding times or disclosing the very high levels that must be consumed (i.e., greater than 3 grams) and the restrictions in place to ensure foods do not exceed those levels.

Separately, we found confusing the discussion of the various beneficial effects associated with omega-3 fatty acid consumption under the "Adverse Effects" section. A summary of the beneficial effects would seem more appropriate in a section distinct from one dedicated to adverse events. We also found confusing the conclusion that "merely three uses, out of potentially thirty-six, are supported by strong data." It should be noted that there currently appears to be no DHA specific entry, but rather, an omega-3 fatty acid/fish oil entry specifying the thirty six health relationships. Medline Plus uses a grading scale to evaluate the various health benefits that ranges from "A to F." The "A" designation is used to identify strong scientific support and "B" denotes good support. A "C" designation is used when the scientific evidence is "unclear" while "D and F" are reserved in instances when there is "fair" or "strong," respectively, evidence against the use. The appropriate focus seemingly should not be on the total number of purported health benefits associated with omega-3 fatty acid consumption, but the strength of the data that exists for a particular health benefit. We believe the reader of the TAP report would find more beneficial a discussion of those health benefits found by NIH to be associated with "strong" or "good" data rather than focusing on the total number of health effects falling in the A, B, C, D, or F categories.

**Statement: Vegetable Oil (e.g. soybean, safflower, and corn oil) are sources of Omega-6 Fatty Acids such as ARA**

The draft report contains a chart that identifies potential sources of omega-6 fatty acids, such as ARA as soybean, safflower, and corn oil.<sup>19</sup> These vegetable oils supply linoleic acid from which the body can produce ARA. Food containing preformed ARA is limited to eggs, meat, and certain farm raised

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<sup>16</sup> Overview of Accessory/Voluntary Nutrients Pg. 7.

<sup>17</sup> Menhaden oil GRAS, U.S. FDA 1997.

<sup>18</sup> Menhaden oil GRAS amendment, U.S. FDA, 2005

<sup>19</sup> Overview of Accessory/Voluntary Nutrients Pg. 5, Paragraph 3.

fish, with no one dietary source supplying an abundance of ARA<sup>20,21</sup> other than human breast milk.<sup>22</sup> We would recommend revising the chart by eliminating vegetable oils as a source for ARA.

While ARA is sufficient in the diets of most adults, the current medical position of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) indicates that ARA is important in the complementary diet, noting that “ARA is the major LCPUFA of the n-6 series and is well represented in the brain.”<sup>23</sup> Although breast milk and DHA/ARA supplemented formulas are good sources of ARA, the cessation of exclusive breastfeeding and introduction of complementary foods, which are typically low in ARA, adversely impacts the availability of ARA to infants and children greater than 6 months of age.<sup>24</sup> Without adequate ARA from an abundant source such as breast milk, ARA declines in infants fed formula without added ARA. ARA is believed to contribute to neurologic development during this critical period.<sup>25,26</sup>

### Summary of Dietary Reference Intakes

The draft TAP report contains a summary of various articles that have identified the dietary reference intakes that have been recommended by scientific authorities in various countries regarding DHA and EPA intake. Interestingly, since 2006 at least 10 U.S and international authorities have issued DHA and DHA+EPA intake recommendations for infants, children, pregnant and nursing women, adults at risk for heart disease, as well as the general population. The TAP may find the chart below of interest.

World-wide LCPUFA Intake Recommendations and Guidelines		
Women and Children		
Organization	Amount of DHA or DHA+EPA	Reference
Agence Français de Sécurité Sanitaire des Aliments	250 mg DHA/d for pregnant women	AFSSA Opinion Regarding the Update of the Recommended Dietary Intake for Fatty Acids. AFSSA-Hearing n2006-SA-0359. 2010.
	250 mg DHA/day for breastfeeding women	
Agence Français de Sécurité Sanitaire des Aliments	70 mg DHA/d for children 1-3 years	AFSSA Opinion Regarding the Update of the Recommended Dietary Intake for Fatty Acids. AFSSA-Hearing n2006-SA-0359. 2010.
	125 mg DHA/d for children 3-9 years	
	250 mg DHA/day for children 10-18 years	

<sup>20</sup> Brenna JT and Lapillonne A, 2009. Background paper on fat and fatty acid requirement during pregnancy and lactation. *Ann Nutr Metab* 55:97-122.

<sup>21</sup> Calder P, 2007. Invited Commentary: Dietary arachidonic acid: harmful, harmless or helpful? *Br J Nutr* 98:451-453.

<sup>22</sup> Yuhas R, et al. Human milk fatty acid composition from nine countries varies most in DHA. *Lipids* 41:851-858.

<sup>23</sup> ESPGHAN Committee on Nutrition, 2008. Complementary feeding: A commentary by the ESPGHAN Committee on Nutrition. *JPGN* 46:99-110.

<sup>24</sup> Luukkainen P, Salo MK, Visakorpi JK, et al. 1996. Impact of solid food on plasma arachidonic and docosahexaenoic acid status of term infants at 8 months of age. *J Pediatr Gastroenterol Nutr* 23:229-34.

<sup>25</sup> Hoffman et al., 2000. Impact of early dietary intake and blood lipid composition of long-chain polyunsaturated fatty acids on later visual development. *JPGN* 31:540-553.

<sup>26</sup> Makrides et al., 1996. Effect of maternal docosahexaenoic acid (DHA) supplementation on breast milk composition. *EJCN* 50:352-357.

Belgian Superior Health Council	40-175 mg DHA/d for children ages 12-36 months  45-110 mg ARA/d for children ages 12-36 months	Superior Health Council. Recommendations Nutritionnelles Pour La Belgique. CSS No. 8309. Revision 2009.
European Food Safety Authority (EFSA)	250 mg DHA+EPA/d for all women plus an additional  100-200 mg DHA/d for pregnant and nursing women	Draft Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to dietary reference values for fats, including saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids, <i>trans</i> fatty acids, and cholesterol. 2009. <a href="http://www.efsa.europa.eu/en/calls/documents/nda_op_drv_fat_draft_en_released%20for%20consultation.o.pdf">http://www.efsa.europa.eu/en/calls/documents/nda_op_drv_fat_draft_en_released%20for%20consultation.o.pdf</a>
EFSA	100 mg DHA/d for children ages 7-24 months  250 mg DHA+EPA/d for children 2-18 years	Draft Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to dietary reference values for fats, including saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids, <i>trans</i> fatty acids, and cholesterol. 2009. <a href="http://www.efsa.europa.eu/en/calls/documents/nda_op_drv_fat_draft_en_released%20for%20consultation.o.pdf">http://www.efsa.europa.eu/en/calls/documents/nda_op_drv_fat_draft_en_released%20for%20consultation.o.pdf</a>
International Society for the Study of Fats and Lipids	At least 200 mg DHA/d during pregnancy and nursing	ISSFAL Policy Statement 4: Recommendations for intake of polyunsaturated fatty acids by pregnant and lactating women. 2009.
March of Dimes	At least 200 mg DHA/d during pregnancy and nursing	<a href="http://www.marchofdimes.com/pnhec/159_55030.asp">http://www.marchofdimes.com/pnhec/159_55030.asp</a> , 2009.
FAO/WHO Expert Consultation	At least 200 mg DHA/d toward total 300 mg n-3 EPA+DHA for pregnant and nursing women	From the Joint FAO/WHO Expert Consultation on Fats and Fatty Acids in Human Nutrition, November 10-14, 2008. WHO HQ, Geneva.
FAO/WHO Expert Consultation	80-150 mg DHA/d for children 6-24 months	From the Joint FAO/WHO Expert Consultation on Fats and Fatty Acids in Human Nutrition, November 10-14, 2008. WHO HQ, Geneva.
Perinatal Lipid Intake Working Group	At least 200 mg DHA/d during pregnancy and nursing	Koletzko B, Cetin I, and Brenna TJ. Perinatal Lipid Intake Working Group Consensus Statement: <i>Dietary fat intakes for pregnant and lactating women</i> . Brit J Nutr 98:873-7, 2007.
Australia New Zealand National Health and Medical Research Council	Pregnancy 110- 115 mg/day DHA+EPA+DPA n-3  Lactation 140-145 mg/day DHA+EPA+DPA n-3	Nutrient reference values for Australia and New Zealand including recommended dietary intakes. 2005. <a href="http://www.nhmrc.gov.au/publications/synopses/files/n35.pdf">www.nhmrc.gov.au/publications/synopses/files/n35.pdf</a>

### Adult Cardiovascular Health

Agence Française de Sécurité Sanitaire des Aliments	500 mg EPA+DHA for cardiovascular disease risk reduction	AFSSA Opinion Regarding the Update of the Recommended Dietary Intake for Fatty Acids. AFSSA-Hearing n2006-SA-0359. 2010.
European Food Safety Authority	250 mg DHA+EPA/d	Draft Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to dietary reference values for fats, including saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids, <i>trans</i> fatty acids, and cholesterol. 2009. <a href="http://www.efsa.europa.eu/en/calls/documents/nda_op_driv_fat_draft_en_released%20for%20consultation.o.pdf">http://www.efsa.europa.eu/en/calls/documents/nda_op_driv_fat_draft_en_released%20for%20consultation.o.pdf</a>
Heart Foundation of Australia	500 mg DHA+EPA/day for primary prevention of cardiovascular disease; 1000 mg/day for secondary prevention	Position Statement: Fish, fish oils, n-3 polyunsaturated fatty acids and cardiovascular health. 2008. <a href="http://www.heartfoundation.org.au">www.heartfoundation.org.au</a>
American Dietetic Association/ Dietitians of Canada	Fish twice/wk, both oily or 500 mg DHA+EPA/d	Kris-Etherton PM, Innis S; American Dietetic Association; Dietitians of Canada. Position of the American Dietetic Association and Dietitians of Canada: dietary fatty acids. <i>J Am Diet Assoc.</i> 2007;107:1599-611.
ANZ National Health and Medical Research Council	610 mg/d for men; 430 mg/d for women as DHA+EPA+DPA <sub>n3</sub> for chronic disease risk reduction, primarily based on cardio	National Health and Medical Research Council. Nutrient reference values for Australia and New Zealand including recommended dietary intakes. <a href="http://www.nhmrc.gov.au/publications/synopses/files/n35.pdf">www.nhmrc.gov.au/publications/synopses/files/n35.pdf</a>
UK Scientific Advisory Committee on Nutrition	Fish twice/wk, one of which should be oily, minimum intake 450 mg DHA+EPA+DPA n-3/day	Scientific Advisory Committee on Nutrition. Advice on fish consumption. ISBN 0 11 243083. The Stationary Office. London. 2004. <a href="http://www.sacn.gov.uk/pdfs/fics_sacn_advice_fish.pdf">http://www.sacn.gov.uk/pdfs/fics_sacn_advice_fish.pdf</a>
Superior Health Council of Belgium	An almost daily serving of fatty fish of varied species or alternatively, capsules of fatty fish oil (EPA+DHA) to the amount of 1 g per day	Hoge Gezondheidsraad Superior Health Council, Advisory Report, Recommendations and claims made on omega-3 fatty Acids (SHC 7945). 2004. <a href="https://portal.health.fgov.be/pls/portal/docs/PAGE/INTERNET_PG/HOMEPAGE_MENU/ABOUTUS1_MENU/INSTITUTIONSAPPARENTEES1_MENU/HOGEGEZONDHEIDSRAAD1_MENU/ADVIEZENENAANBEVELINGEN1_MENU/ADVIEZENENAANBEVELINGEN1_DPCS/OMEGA-3%20ENGLISH.PDF">https://portal.health.fgov.be/pls/portal/docs/PAGE/INTERNET_PG/HOMEPAGE_MENU/ABOUTUS1_MENU/INSTITUTIONSAPPARENTEES1_MENU/HOGEGEZONDHEIDSRAAD1_MENU/ADVIEZENENAANBEVELINGEN1_MENU/ADVIEZENENAANBEVELINGEN1_DPCS/OMEGA-3%20ENGLISH.PDF</a>
International Society for the Study of Fats and	500 mg DHA+EPA	International Society for the Study of Fats and Lipids (ISSFAL). ISSFAL Policy Statement 3: Recommendations for intake of polyunsaturated fatty

Lipids		acids in healthy adults. 2004. Available from: <a href="http://www.issfal.org.uk/lipid-matters/issfal-policy-statements/issfal-policy-statement-3-2.html">http://www.issfal.org.uk/lipid-matters/issfal-policy-statements/issfal-policy-statement-3-2.html</a>
American Heart Association	2 servings per week of fish for primary prevention; 1 g DHA+EPA per day for secondary prevention; 2-4 g per day for serum triglyceride reduction	American Heart Association Scientific Statement. Kris-Etherton PM, Harris, WS, Appel LJ and for the Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. 2002. 106:2747-2757. <a href="http://circ.ahajournals.org/cgi/content/full/106/21/2747">http://circ.ahajournals.org/cgi/content/full/106/21/2747</a>
<b>Adult General Health</b>		
Agence Français de Sécurité Sanitaire des Aliments	Adult man – 250 mg DHA/day Adult woman- 250 mg DHA/day	AFSSA Opinion Regarding the Update of the Recommended Dietary Intake for Fatty Acids. AFSSA-Hearing n2006-SA-0359. 2010.
Health Council of the Netherlands	450 mg n-3 fatty acids from fish	English translation, Health Council of the Netherlands. Guidelines for a healthy diet 2006. The Hauge: Health Council of the Netherlands, 2006; publication no. 2006/21E. <a href="http://www.gr.nl/pdf.php?ID=1481&amp;p=1">http://www.gr.nl/pdf.php?ID=1481&amp;p=1</a>
U.S. Institute of Medicine	Up to 160 mg DHA+EPA/d	Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids (Macronutrients). The National Academy of Sciences Press, Washington DC, Chapter 8, 2005. <a href="http://www.nap.edu/openbook.php?isbn=0309085373">http://www.nap.edu/openbook.php?isbn=0309085373</a> .

### Statement: Excerpt from Cornucopia Institute

Lastly, the draft TAP report contains an excerpt quoted directly from a report prepared by the Cornucopia Institute. As disclosed in the draft report, Cornucopia is an advocacy group that is strongly against the inclusion of DHA and ARA in infant formula. The draft TAP report contains a four paragraph excerpt that sets forth Cornucopia's basis for concern. The excerpt from the Cornucopia report contains numerous statements that are lacking in scientific support, including, but not limited to, the following:

“processed utilizing a toxic chemical, hexane” [hexane is one of the most commonly used solvents to extract food-grade vegetable oils and is considered safe for this use by FDA; furthermore, not all DHA Algal Oil produced by Martek utilizes hexane];

“these algal and fungal oils provide DHA and ARA in forms that are structurally different from those naturally found in human milk” [the ARA and DHA in the Martek oils are on a triglyceride, which is the same structural form as that found in breast milk]; and

“scientists have conducted numerous studies that show little or no benefit to an infant's development from adding DHASCO and ARASCO to infant formula” [the statement ignores the extensive studies that have demonstrated a benefit and the recommendations from

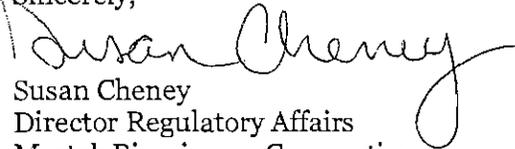
independent experts around the world, summarized in this letter and the draft TAP report, on the importance of including pre-formed DHA and ARA in the diets of infants].

The inclusion of these excerpts in the draft report confers an element of legitimacy to the Cornucopia report that is not supported by an objective review of the underlying data. The Cornucopia excerpt appears in the draft document after excerpts quoted from journal articles that have survived the scrutiny of the peer review process. Martek is concerned the reader could be left with the impression the Cornucopia report is based on the same critical review of the underlying literature and has survived the same rigorous vetting process as the quoted publications authored by Harris et al (2009) and Kris-Etherton et al. (2009). Martek also is concerned that by quoting the Cornucopia report, the TAP could be creating the unintentional impression that it has reviewed the underlying data and believes there is some legitimacy to the positions advanced by Cornucopia.

We question whether it is appropriate for a critical scientific assessment of the underlying literature to include an advocacy piece from either industry or a consumer group. To the extent the TAP considers it appropriate to keep the reference to the Cornucopia report, we believe there should be a qualifying statement making it clear the TAP has not reviewed the underlying data and has not attempted to determine whether there is any scientific support for the statements made in the Cornucopia report.

Martek appreciates the opportunity to provide the National Organic Program information to support the development of an accurate, science-based technical review of accessory nutrients as they relate to DHA and ARA. If you, or any member of your staff, has any questions or would like additional supporting information, do not hesitate to contact us.

Sincerely,



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