Appendix G

Additional Concerns

Question 4. Is the nutritional quality of the food maintained with the substance? [§205.600 b.3]

The HC Recommendation answers "Yes" to this question, with no basis for making this determination. What happens to the absorption of naturally-occurring beneficial fatty acids in grass-fed cow's milk when DHA is added? Nutrients can compete for absorption in the body, and the question of whether naturally-occurring beneficial fatty acids like CLA are absorbed as well by the body when DHA has been added, was not answered in the TR, nor was it considered by the Handling Committee in answering this question.

Handing Committee Recommendation, Category 1, Question 10: Is there any harmful effect on human health?

The HC Recommendation disregards studies, cited in the TR, showing adverse effects from consuming high levels of DHA. The HC justifies this disregard because the studies were done with fish oil, not algal oil. However, earlier in the same question's answer, the HC uses data from a chart containing more than 10 countries' nutritional guidelines, which recommend omega-3 fatty acids in the diet. These national dietary guidelines do not recommend algal oil, but base their recommendation for omega-3s and DHA in the diet on studies done with fish and fish oil. **It is extremely biased of the Handling Committee to accept data showing the benefits of DHA, based on studies of fish oil, but disregard questions of safety, on the basis that the studies were done with fish oil.**

It is also important to note that both the species and strain of algae and fungus used by Martek to manufacture its oils have never before been part of the human diet, and safety concerns exist.

No post-market surveillance has been conducted

The Food and Drug Administration requested that infant formula manufacturers conduct "rigorous post-market surveillance" to ensure the safety of Martek's novel algal oils in infant formula. **Such post-market surveillance and additional safety studies has never been conducted and shared with the FDA**.

We also question how Martek can claim that its oils have a history of safe consumption when the company has failed to conduct post-market surveillance and failed to track the safety of its oils.

Reports to the FDA indicate gastrointestinal reactions in infants

Reports submitted to the FDA by parents and health care professionals indicate that some infants experience gastrointestinal reactions to Martek's DHA algal and/or ARA fungal oil in formula.

At this point, since nearly all infant formula contains Martek's oils, it is nearly impossible for parents to discover, on their own, that Martek's oils may be to blame for their infant's gastrointestinal symptoms. We continue to receive reports from parents whose infants' symptoms disappear when switched to formula without Martek's oils.

GRAS status with the FDA is not a guarantee of safety
According to the Government Accountability Office, which conducted an investigation of the FDA's GRAS (Generally Recognized As Safe) system, published in February 2010, "FDA's oversight process does not help ensure the safety of all new GRAS determinations."

Long term effects of consuming formula with Martek's oils
Results from a long-term clinical trial (Kennedy et al, 2010) were that "Girls born preterm and randomized to long-chain polyunsaturated fatty acid-supplemented formula showed increased weight, adiposity and blood pressure at 9–11 years, which might have adverse consequences for later health."

Source of the substrate used to ferment the microorganisms
The Technical Report states that one of the substances used to ferment the algae is "glucose" and "ethanol," but does not specify its source. If the glucose and ethanol is derived from corn (likely), does Martek ensure that non-GMO corn is used? Since it would be a great added expense, and there is no claim that they use organic or identity preserved non-GMO corn, this seems unlikely.

Sent email 6-21

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

JUN 05 2009

FOIA Request 2009-3310
Ms Charlotte Vallacys
Farm and Food Policy Analyst
The Cornucopia Institute
P.O. Box 126
Cornucopia, Wisconsin 54827

In response to your request dated April 23, 2009 for access to any records or reports of post-market surveillance and scientific studies monitoring or evaluating the safety of DHASCO and ARASCO (DHA and ARA) in infant formula.

__X__ We have no responsive information in our files. FDA has never received any reports or studies regarding post-market surveillance or scientific studies monitoring or evaluating the safety of DHASCO and ARASCO (DHA and ARA) in infant formula.

____ Certain material has been deleted from the records furnished to you because of preliminary review of the records indicated that the deleted information is not required to be publicly disclosed and that disclosure is not appropriate. FDA has taken this approach to facilitate the process of responding to you. If you dispute FDA's preliminary determination and would like FDA to reconsider any particular deletion, please let us know in writing at the following address: Food and Drug Administration, Freedom of Information Staff, HFI-35, 5600 Fishers Lane, Rockville, MD 20857 within thirty days from date of this letter. If we do not receive a response in that time period we will consider the matter closed. If you do not request further consideration and the agency then formerly denies your request for any or all the previously with held information, you will have the right top appeal that decision. . Any letter of denial will explain how to make this appeal.

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Sincerely yours,

Hilario R, Duncan
Paralegal Specialist
Executive Operations Staff
Center for Food Safety
and Applied Nutrition

NO Enclosure

CORNUCOPIA
INSTITUTE

Official Adverse Reaction Reports Filed With the Food and Drug Administration

Below is a sample of adverse reaction reports submitted to the FDA—these reports, filed by parents, clearly suggest that some infants cannot tolerate Martek's DHA and ARA oils in formula.

The reports were obtained through a Freedom of Information Act request by The Cornucopia Institute.

These 15 reports are just a sample of the 98 that could confidently be linked to intolerance to the DHA/ARA oils.

Hundreds of reports of adverse reactions to DHA/ARA-supplemented formula have been filed. But in some cases it was not possible to determine that the reported problems were due to bacterial contamination of the formula, lactose intolerance or allergies, or other problems commonly experienced with infant formula. Although a clear link could not be established there is still the potential that DHA/ARA oils are implicated in some of these cases.

The adverse reaction reports filed with FDA represent only the tip of the iceberg, especially since most parents remain unaware that Martek's DHA and ARA oils may be the cause of their infant's problems. Many continue to feed their infants the DHA/ARA-supplemented formula—infants endure months of pain and parents months of anxiety and distress.

A warning label alerting parents to the possibility of adverse reactions caused by the DHA and ARA oils is clearly warranted, since a simple switch to non-DHA/ARA formula has been found to relieve symptoms within 24 hours in some infants.

Report #: 61307

"Her baby was fed this Enfamil Lipil formula for the first 3 weeks of his life and was constantly having gas and diarrhea from it, until he was taken off this formula by his pediatrician after the child was taken to the hospital ER by the parents, while having a severe bout of gas and diarrhea. Child was given regular Enfamil with Iron and has been on it ever since without any problems."

Report #: 61309
"Her child was given the Enfamil Lipil for one month. She developed diarrhea, vomiting and bowel obstruction. She was taken off this formula and put on Similac Advance for 2 weeks, was having some problems with this formula. Was given regular Similac with Iron and doing fine."

Report #: 61311
"Child was given this Enfamil Lipil formula at two different times. Child developed severe diarrhea and constipation for 3 days, every time. When switched to Enfamil with Iron did fine. He is now x months old and doing OK."

Report #: 61670
"Complainant fed newborn baby boy Similac Advance with DHA/ARA. Infant immediately spit formula back up. Complainant attempted to feed baby the product twice and both times infant spit it up. Baby was put on plain Similac with iron and tolerates this formula well."

Report #: 64191
"Healthy term newborn receiving formula supplementation – mother with history of breast reduction surgery – in hospital. Mother reported large amounts of emesis (vomiting) with Lipil, which resolved when switched to "original" Enfamil. Subsequently she was unable to obtain more "original" Enfamil – hospital supply not repleted by formula company. Baby again vomiting today with resumption of Lipil. Hospital staff in process of searching for formula without Formulaid [DHA and ARA] at present."

Report #: 69559
"The Similac Advance made my son constipated and very agitated. He would swing his head back and forth and shake his legs. When he started eating Similac with Iron, he stopped being constipated and would eat normally."

Report #: 69679
"My daughter has been unable to tolerate any formula with DHA and ARA components. Particularly Lipil products by Enfamil. They have caused gastric reflux, gas, fussiness, and colic repeatedly. This includes soy and hypoallergenic formulas as well with DHA and ARA."

Report #: 70337
"Ms. K states that her son has a digestive disorder. As a result, he is unable to tolerate the formulas containing DHA and ARA. He is able to tolerate the Nestle Good Start that does not contain these additives. However, Ms. K states that Nestle told her that they also were going to begin adding DHA and ARA to the formulas. Ms. K believes that formula manufacturers should offer both choices so parents can decide which formula is best for their child."

Report #: 73857
"Mother normally used the Similac Alimentum powdered formula with iron and had no problems with her infant son; they could no longer find that formula in the stores and began using the Similac Alimentum with iron and added DHA and ARA. Her son had

diarrhea and was extremely fussy for 9 days. They found some of the formula without the additives DHA and ARA and he returned to normal in one day."

Report #: 75278
"Anytime we put my infant son on formulas containing DHA/ARA, he has frequent and forceful spit ups and is extremely cranky. It makes his reflux a lot worse than it already it."

Report #: 72285
"My son cannot tolerate the new infant formulas with DHA/ARA additives, Similac Advance, Enfamil Lipil, Goodstart with DHA/ARA – every time he has tried a DHA/ARA formula he gets extremely gassy, fussy and has terrible gas pains. He does do better on the Similac Advance, which has less DHA/ARA than the other products. I can't find plain Similac in my local store, as they only carry the DHA/ARA formulas. Why did the FDA allow the formula companies to produce these formulas without long term testing???"

Report #: 75951
"Infant demonstrates marked sensitivity to infant formula containing DHA/ARA. We have tried several formulas and all containing these additives have caused severe gas and distress."

Report #: 76537
"I am 100% sure my son's reflux was exacerbated by – possibly even caused by – the DHA/ARA additives to his infant formula. They may be considered "safe" but that does not mean that all babies tolerate the ingredients and I feel there should be a warning and more research into this possibility. Other relevant history: my son has been drinking Enfamil Prosobee Lipil formula and has had painful problems with reflux since about 2 weeks of age when he started on Enfamil Lipil formula. His GERD (acid reflux) has required multiple doctor visits and medications, formula changes, etc. I recently decided to try a non DHA/ARA formula – Enfamil Prosobee without Lipil – and within one day his reflux completely resolved."

Report #: 76856
"Ms. A believes that her daughter is unable to tolerate the DHA and ARA that is now being added to most infant formulas. Ms. A states that the 3 formulas she initially tried contained these ingredients and her child experienced discomfort with each of them. Ms. A states that her child did not improve until she began using formula without these ingredients."

Report #: 82072
"My son has been having serious problems with formulas that contain DHA/ARA. From the time he was 2 weeks old he was on formula that contained DHA/ARA and from the time he went on this he became extremely gassy and fussy. He would scream at each bottle. Under the doctor's advice we tried him on the hypoallergenic formula and he still had the problems. We were on the verge of putting him on medication for reflux when I decided to try a formula that does not contain DHA/ARA and I now have a new baby. He is content and eating without pain. I completely believe that the DHA/ARA was the cause of my son's problem. I truly believe that the DHA/ARA should be studied more and these issues made more public as I know that I am not alone after talking with other mothers."

February 2010

FOOD SAFETY

FDA Should Strengthen Its Oversight of Food Ingredients Determined to Be Generally Recognized as Safe (GRAS)

GAO Accountability • Integrity • Reliability

Highlights

Highlights of GAO-10-246, a report to congressional requesters

Why GAO Did This Study

The Food and Drug Administration (FDA), which is responsible for ensuring the safety of most of the U.S. food supply, is not required to review substances, such as spices and preservatives, added to food that are generally recognized as safe (GRAS) for their intended use. Currently, companies may determine a substance is GRAS without FDA's approval or knowledge. However, a few substances previously considered GRAS have later been banned; and concerns have been raised about the safety of other GRAS substances, including those containing engineered nanomaterials, materials manufactured at a tiny scale to take advantage of novel properties. GAO was asked to review the extent to which (1) FDA's oversight of new GRAS determinations helps ensure the safety of these substances, (2) FDA ensures the continued safety of current GRAS substances, and (3) FDA's approach to regulating engineered nanomaterials in GRAS substances helps ensure the safety of the food supply. GAO reviewed FDA data on GRAS substances and interviewed a range of stakeholders, among other things.

What GAO Recommends

GAO recommends that FDA take steps to better ensure the safety of GRAS substances, including developing a strategy to require any company that conducts a GRAS determination to provide FDA with basic information about it. FDA generally agreed, while raising concerns about certain aspects of several of the recommendations.

View GAO-10-246 or key components.
For more information, contact Lisa Shames at (202) 512-3841 or shamesl@gao.gov.

What GAO Found

FDA's oversight process does not help ensure the safety of all new GRAS determinations. FDA only reviews those GRAS determinations that companies submit to the agency's voluntary notification program—the agency generally does not have information about other GRAS determinations companies have made because companies are not required to inform FDA of them. Furthermore, FDA has not taken certain steps that could help ensure the safety of GRAS determinations, particularly those about which the agency has not been notified. FDA has not issued guidance to companies on how to document their GRAS determinations or monitored companies to ensure that they have conducted GRAS determinations appropriately. Lastly, FDA has yet to issue a final regulation for its 1997 proposed rule that sets forth the framework and criteria for the voluntary notification program, potentially detracting from the program's credibility.

FDA is not systematically ensuring the continued safety of current GRAS substances. While, according to FDA regulations, the GRAS status of a substance must be reconsidered as new scientific information emerges, the agency has not systematically reconsidered GRAS substances since the 1980s. FDA officials said they keep up with new developments in the scientific literature and, on a case-by-case basis, information brought to the agency's attention could prompt them to reconsider the safety of a GRAS substance. However, FDA has largely not responded to concerns about GRAS substances, such as salt and the trans fats in partially hydrogenated vegetable oils, that individuals and consumer groups have raised through 11 citizen petitions submitted to the agency between 2004 and 2008. In fact, FDA has decided on the validity of these concerns in only 1 of 11 cases. In addition, FDA does not know to what extent, or even whether, companies track evolving scientific information about their GRAS substances.

FDA's approach to regulating nanotechnology allows engineered nanomaterials to enter the food supply as GRAS substances without FDA's knowledge. While some uses of engineered nanomaterials have the potential to help ensure food safety, uncertainties remain about how to determine their safety in food. After reviewing the uncertainties associated with the safety of engineered nanomaterials, FDA has decided that it does not need additional authority to regulate products containing such materials. Rather, FDA encourages, but does not require, companies considering using engineered nanomaterials in food to consult with the agency regarding whether such substances might be GRAS. Because GRAS notification is voluntary and companies are not required to identify nanomaterials in their GRAS substances, FDA has no way of knowing the full extent to which engineered nanomaterials have entered the U.S. food supply as part of GRAS substances. In contrast to FDA's approach, all food ingredients that incorporate engineered nanomaterials must be submitted to regulators in Canada and the European Union before they can be marketed.

Archives of DISEASE IN CHILDHOOD

Archives of Disease in Childhood
adc.bmj.com
Arch Dis Child 2010;**95**:588-595 doi:10.1136/adc.2009.167270

Original article

The 10-year follow-up of a randomised trial of long-chain polyunsaturated fatty acid supplementation in preterm infants: effects on growth and blood pressure

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Contributors KK provided the main draft of this article and supervised the project, SR collected and analysed the data, EI, AS and AL provided expert advice on the design and interpretation of data, LW was the local investigator in Glasgow and critically revised the article, MSF was the primary investigator who wrote the original protocol providing the original concept and design. All authors contributed to the drafting and revision of this manuscript.

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Abstract

Objective To test the hypothesis that consumption of infant formulas containing long-chain polyunsaturated fatty acids (LCPUFAs) by preterm infants would favourably influence growth, body composition and blood pressure (BP) at age 10 years.

Methods This was a follow-up study of a preterm cohort (<35 weeks and birth weight <2000 g) randomly assigned to unsupplemented or LCPUFA-supplemented formulas to 9 months post term. The setting was a research clinic at Yorkhill Hospital for Sick Children, Glasgow, UK. A total of 107 children aged 9–11 years who participated in the original randomised controlled trial (45% follow-up) took part. Main outcome measures were: (1) anthropometry, (2) body composition and (3) BP.

Results There were no differences in growth or BP between randomised groups for the whole cohort. However, girls who had received LCPUFA-supplemented formula were heavier (42.20 (SD 9.61) vs 36.94 (9.46) kg, p=0.05), had greater skin fold thicknesses (biceps 10.7 (3.3) vs 8.5 (3.6) mm, p=0.03; suprailiac 16.7 (8.2) vs 12.0 (7.5) mm, p=0.03) and higher BP (mean 82.2 (8.4) vs 78.1 (6.2) mm Hg, p=0.04: systolic 111.4 (10.1) vs 105.9 (9.0) mm Hg, p=0.04: diastolic 64.8 (8.4) vs 61.1 (5.4) mm Hg, p=0.05). Differences in weight SD score (0.85 (95% CI 0.13 to 1.58), p=0.02), Ln sum of skin fold thicknesses (0.27 (0.02 to 0.52), p=0.04) and BP (mean 4.6 mm Hg (0.43 to 8.84), p=0.03; systolic 6.1 (0.45 to 11.7), p=0.04) remained after adjustment for prerandomisation confounders. Differences in BP were not significant following adjustment for current weight.

Conclusions Girls born preterm and randomised to LCPUFA-supplemented formula showed increased weight, adiposity and BP at 9–11 years, which might have adverse consequences for later health. No effects were seen in boys. Long-term follow-up of other LCPUFA supplementation trials is required to further investigate this finding.

Responses to this article

Reply to letters from Dr J Hoffman and Dr A Lapillone

Katherine J Kennedy, Alan Lucas, Mary Fewtrell

ADC published online August 24, 2010

[Full text]

Long-term health consequences of LCPUFA supplementation of preterm girls

James P. Hoffman

ADC published online August 24, 2010

[Full text]

Appendix H

Problems with the Technical Review for Martek's DHA Algal Oil

On page 34 of the NOSB Policy Manual, criteria are listed for a Technical Review to be considered acceptable. The TR for DHA Algal Oil fails the majority of these criteria, including the requirement to be consistent, to be free from opinion and conjecture, to be based on the best available information, and to be thoroughly supported using literature citations.

Failure to Verify Martek's Claims – Hexane

The Policy Manual states that the Technical Review should be based on the best available information. The TR fails this criterion, as it relies solely on the Martek petition for information regarding the environmental effects of the use of n-hexane in manufacturing. Since n-hexane is classified as a hazardous air pollutant by the Environmental Protection Agency, factories using this petrochemical solvent are required to report emission data to the EPA. The EPA, in turn, makes this information publicly available. Rather than rely on the EPA's data to determine whether Martek releases the pollutant n-hexane into the environment, the TR simply repeated Martek's claim that all n-hexane is recycled and reused (TR 418-419, TR 448-449). As a result, HC members were led to believe that no environmental adverse effects exist from the manufacture of Martek's DHA and ARA oils.

EPA data reveals that Martek Biosciences Corporation's factory in South Carolina is among the top 100 emitters of the hazardous air pollutant n-hexane. According to EPA data, 8,500 pounds of n-hexane were released into the environment by Martek Biosciences' factory in 2010.

The answer to Category 1, Question 1, "Are there adverse effects on environment from manufacture, use, or disposal?" should take into account n-hexane emission data from the EPA, from the manufacture of Martek's DHA and ARA oil.

It is unclear why such important data was omitted from the Technical Review, especially since this information is so readily available and easily accessible.

Failure to Identify and Analyze Synthetic Ingredients

In its petition, Martek lists several unapproved synthetic ingredients that are part of its DHA Algal Oil. However, numerous <u>other</u> unapproved synthetic ingredients that are currently added to organic foods as part of Martek's DHA Algal Oil, were not disclosed by Martek in its petition and are not mentioned in the Technical Review.

For example, Happy Bellies organic baby cereal by Nurture, Inc. contains non-organic modified starch, glucose syrup solids, sodium polyphosphate, mannitol, and other synthetic and/or non-organic ingredients as part of Martek's added "algal oil powder."

Since these ingredients were not mentioned in the Martek petition, and are not mentioned in the Technical Review, it is unclear whether the modified starch is derived from GMO corn, whether the mannitol is natural or synthetic, etc.

The TR also did not analyze the appropriateness of the synthetic ingredients that Martek did disclose in its petition, like ascorbyl palmitate.

Failure to Review Excluded Methods in Organics – Genetic Modification

For reasons that are unclear, the TR failed to fact-check Martek's claim that the algae strains are "non-genetically modified." Given that Martek Biosciences Corporation is a biotechnology company engaged in recombinant DNA technology and other genetic modification methods, the TR reviewers should have verified these claims. Interestingly, the TR is completely silent on this topic, failing even to repeat the Martek claim that the algae is "non-GMO."

NOSB members should know the techniques used to obtain the strain of algae, which is important information that should have been included in the TR.

The strain of algae that Martek currently uses to produce one type of its DHA Algal Oils was developed in Monsanto's laboratories through "classical mutagenesis," which entails blasting algal microorganisms with chemicals or radiation to artificially induce genetic mutations, and screening the organisms until one with a favorable genetic mutation – in this case, high DHA production – is identified.

Failure to Question Why Non-organic Sunflower Oil is Used in Martek's Oils

The TR notes, in two places (TR 141 and 263), that Martek adds "high-oleic sunflower oil" to its DHA Algal oil. Neither Martek nor the TR identifies this sunflower oil as being organic.

If it is destined for an organic product, any agricultural product must be organic unless it appears on the National List (sunflower oil does not appear on 205.606).

The TR did not, for example, question whether the sunflower oil used by Martek is hexane-extracted. Information regarding the percentage of non-organic sunflower oil in Martek's "DHA Algal Oil" was also omitted.

The annotation for fish oil on the National List states that it must be "stabilized with organic ingredients or only ingredients on the National List." The TR's failure to

raise the issue that the sunflower oil is not organic, and suggest that it should be organic, reveals either the TR reviewers extreme bias in favor of the Martek petition, or a lack of understanding of organics.

Missing Information Regarding Lack of Benefits

The Handling Committee members were led to believe that "the substance is widely added to food products, including infant formulas, for its healthful benefits. See TR at lines 496-524." With regard to infant formula, the TR fails to mention that the vast majority of clinical trials have found no benefits to infant development. Important meta-analysis studies such as Simmer et al., 2008 and Beyerlein et al., 2010 were omitted. These studies combined data from numerous clinical trials and concluded that no benefits to infant development exist from DHA supplementation.

The Policy Manual states that the TR should be based on the "best available information." In terms of scientific research, meta-analysis studies like Simmer et al. 2008 and Beyerlein et al. 2010 are arguable the first and best sources of information a researcher should consult. Meta-analysis studies analyze data from numerous clinical trials, to reach a conclusion regarding the benefits, or lack thereof, of a certain substance.

The TR therefore also fails the Policy Manual's criterion of being free of opinion and conjecture, since the claim that Martek's algal DHA oil is beneficial for infant development is merely conjecture, not backed by sound science.

Conflicting Data within the Technical Review Regarding Benefits

The Policy Manual states that the TR should be free from conjecture, and information should be based on literature citations. Note this paragraph in the TR, which contains misleading and unreferenced statements by the reviewers that directly contradict the studies they cite. Note that the two first sentences are unreferenced, and contradict the results from the study mentioned in the last sentence, which found no benefits from DHA supplementation.

> "Supplementation with omega-3 fatty acids such as DHA could potentially help prevent or treat neurological disorders associated with memory loss, like Alzheimer's disease. ***UNREFERENCED*** DHA appears to be protective against the development of Alzheimer's disease and other types of dementia. ***UNREFERENCED*** Conversely, cognitive decline has been linked to decreased levels of DHA in the brain (Jump, 2009). It is not currently known whether DHA supplementation could be used to treat Alzheimer's disease, but some laboratory studies in animals have shown evidence to that effect (Jump, 2009). A placebo-controlled trial with 295 patients with Alzheimer's disease found that DHA supplementation (2 grams/day) for 18 months was **not** effective in slowing cognitive decline (Jump, 2009). (TR 508-515)." (Emphasis added)

In other words, one clinical trial is cited, which showed no beneficial effects of DHA supplementation (the study's abstract is included in this packet of information for your convenience). Yet the TR makes several unreferenced statements to mislead NOSB members into believing that DHA supplementation is beneficial.

In addition, the one study that is referenced, which showed that DHA supplementation was not effective in slowing cognitive decline, is not correctly referenced. Not only is the Jump 2009 reference not the primary source, but the Jump 2009 article never mentions this trial.

In another example of contradictory statements in the TR, line 120-121 of the TR states that "The results of several randomized controlled trials of preterm and term infants fed formula enriched with DHA have been mixed. It is unclear from the trials whether DHA-enriched infant formula enhances neurological development or visual acuity in full term or preterm infants (Jump, 2009)."

This conflicts with lines 490-492, which is another unreferenced statement: "Randomized clinical trials found that DHA supplementation in infants was associated with positive effects on visual and cognitive maturation, especially in preterm infants." Again, the TR includes unreferenced conjecture, which directly contradicts referenced statements in other parts of the TR.

Failure to Incorporate a Diversity of Opinions

The Policy Manual, on page 36, also states that a diversity of opinions should be incorporated to minimize the risk of bias. The TR reviewers clearly failed to consult a diversity of experts, and relied most heavily on either Martek itself, or sources provided by Martek.

In the TR, Martek's petition is referenced 16 times, including for information that should have been fact-checked (for example, the Martek claim that all n-hexane is recycled is inconsistent with EPA emissions data showing that 8,400 pounds of n-hexane were released into the air).

Another heavily cited reference is "Kyle," which is cited 15 times. David Kyle is one of the founders of Martek Biosciences Corporation, a previous Vice-President of Martek, and a patent holder for several of the DHA algal oils.

The most heavily cited reference is "Jump 2009." This references a webpage on the Linus Pauling Institute website. The Linus Pauling Institute is part of Oregon State University, and a credible source. However, while this webpage contains valuable information with hundreds of scientific references, it is not a published, peer-reviewed academic article and should not serve as a primary source. In some cases (see line 121), Jump 2009 is referenced for statements that do not appear on the webpage.

Moreover, not only was The Cornucopia Institute never contacted, the sources and materials that our organization has collected and analyzed were not consulted. Consulting The Cornucopia Institute's materials would have guided the TR reviewers to important scientific studies, such as the meta-analysis studies cited previously. While none of Cornucopia's materials are primary sources, our materials would have been a gateway for a better, more unbiased and independent analysis on the part of the TR reviewers.

Contradicting Information – Indicative of an Unqualified Reviewer(s)

While the Policy Manual does not state that the third party reviewer should be well-versed and familiar with the substance under review, the term "expert" implies that the reviewer is expected to have more than just a basic understanding of the subject. Not only is one of the TR reviewers clearly not an expert, this individual lacked even a basic understanding of DHA Algal Oil.

Specifically, it appears that one of the reviewers was unaware that the TR should cover both Schizochytrium sp. oil and C. cohnii oil. In line 303, the TR states that "DHA Algal Oil and DHA are available from two natural sources in addition to C. cohnii: an algal source (DHA Algal Oil) and oily fish and shellfish (DHA). DHA Algal Oil can be obtained from Schizochytrium species, another species of marine algae (Doughman et al., 2007)." This line suggests that the person writing this part of the TR was unaware that Martek's petition for DHA Algal Oil includes oil from Schizochytrium species. In other sections of the TR, the reviewer does appear to understand that the review is for both species of algae (see line 225).

Moreover, in line 306, the TR states that "the extraction process [for Schizochytrium oil] is very similar to that used to extract algal oil from C. cohnii." This is incorrect, and provides another example of one of the reviewer's basic lack of familiarity and understanding of the substances under review. The extraction process for Schizochytrium is in fact quite different from C. cohnii oil. It does not involve a chemical solvent but isopropyl alcohol. This perhaps explains why isopropyl alcohol is never mentioned in the TR.

Cornucopia Questions:

What were the reviewer's qualifications for performing this technical review? In several parts of the TR, the reviewer clearly lacks a basic understanding of the materials under review.

Page 4 of the Policy Manual states that the NOP, during phase 4, will determine if the TR is acceptable. Several of the criteria were not met.

1. The policy manual states that the TR must be "consistent in format, level of detail and tone." This is not the case. The TR was clearly written by at least

two separate individuals, one of whom was unaware that the TR should cover Schizochytrium species oil as well as C. cohnii oil (see line 303-306).

2. The second criterion is that the report must be "technically objective and free from opinions or conjecture." How did the NOP allow this TR to be deemed acceptable when numerous unreferenced and misleading statements (conjecture) are included? See lines 502, 520, 490, and others for unreferenced statements.
3. The fifth criterion was not met: "Is based on the best available information that can be obtained within the designated time frame." In too many cases, the reviewers considered Martek's petition to be the "best available information," and failed to fact-check or perform their own research. The most egregious example is the reviewer's failure to consult EPA emissions data to fact-check whether all n-hexane is indeed "recycled," as Martek claims, or whether any of this hazardous air pollutant is emitted into the air.
4. The criterion that the report be "thoroughly supported using literature citations" is also not met. As noted earlier, numerous unreferenced statements are made throughout the TR, misleading NOSB members into believing that scientific data supports the claims that these materials are beneficial. In addition, for 29 of the TR's statements that are referenced, the reference is a webpage ("Jump 2009" is not a published article, but the following webpage: http://lpi.oregonstate.edu/infocenter/othernuts/omega3fa/index.html). These statements should have been fact-checked, and should list the primary source as the reference, not the Linus Pauling Institute webpage.

The Policy Manual also states that the Handling Committee should do the following: "To incorporate a diversity of opinions and to minimize the risk of bias, a committee should aim to work with a range of technical experts (individuals, or institutions)." It appears that the HC wrote its recommendation based on an inadequate and incomplete TR, written by individuals that are clearly not "experts" on this topic. Were any experts, other than those affiliated with Martek, consulted?

It would have been irresponsible to rely only on Cornucopia's research, but no organization has invested as much in analysis of the available published research and public policy implications as Cornucopia. The Policy Manual states that the third-party expert should consult a wide range of opinions to minimize the risk of bias, and it is clear that this criterion was not met.

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Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial.

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Abstract

CONTEXT: Docosahexaenoic acid (DHA) is the most abundant long-chain polyunsaturated fatty acid in the brain. Epidemiological studies suggest that consumption of DHA is associated with a reduced incidence of Alzheimer disease. Animal studies demonstrate that oral intake of DHA reduces Alzheimer-like brain pathology.

OBJECTIVE: To determine if supplementation with DHA slows cognitive and functional decline in individuals with Alzheimer disease.

DESIGN, SETTING, AND PATIENTS: A randomized, double-blind, placebo-controlled trial of DHA supplementation in individuals with mild to moderate Alzheimer disease (Mini-Mental State Examination scores, 14-26) was conducted between November 2007 and May 2009 at 51 US clinical research sites of the Alzheimer's Disease Cooperative Study.

INTERVENTION: Participants were randomly assigned to algal DHA at a dose of 2 g/d or to identical placebo (60% were assigned to DHA and 40% were assigned to placebo). Duration of treatment was 18 months.

MAIN OUTCOME MEASURES: Change in the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) and change in the Clinical Dementia Rating (CDR) sum of boxes. Rate of brain atrophy was also determined by volumetric magnetic resonance imaging in a subsample of participants (n = 102).

RESULTS: A total of 402 individuals were randomized and a total of 295 participants completed the trial while taking study medication (DHA: 171; placebo: 124). Supplementation with DHA had no beneficial effect on rate of change on ADAS-cog score, which increased by a mean of 7.98 points (95% confidence interval [CI], 6.51-9.45 points) for the DHA group during 18 months vs 8.27 points (95% CI, 6.72-9.82 points) for the placebo group (linear mixed-effects model: P = .41). The CDR sum of boxes score increased by 2.87 points (95% CI, 2.44-3.30 points) for the DHA group during 18 months compared with 2.93 points (95% CI, 2.44-3.42 points) for the placebo group (linear mixed-effects model: P = .68). In the subpopulation of participants (DHA: 53; placebo: 49), the rate of brain atrophy was not affected by treatment with DHA. Individuals in the DHA group had a mean decline in total brain volume of 24.7 cm(3) (95% CI, 21.4-28.0 cm(3)) during 18 months and a 1.32% (95% CI, 1.14%-1.50%) volume decline per year compared with 24.0 cm(3) (95% CI, 20-28 cm(3)) for the placebo group during 18 months and a 1.29% (95% CI, 1.07%-1.51%) volume decline per year (P = .79).

CONCLUSION: Supplementation with DHA compared with placebo did not slow the rate of cognitive and functional decline in patients with mild to moderate Alzheimer disease.

TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00440050.

Comment in

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