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U. S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
December 11, 2001

Agency Response Letter
GRAS Notice No. GRN 000080

Thomas L. Ferguson
Mead Johnson Nutritionals
2400 West Lloyd Expressway
Evansville, IN 47721

Re: GRAS Notice No. GRN 000080

Dear Mr. Ferguson:

The Food and Drug Administration (FDA) is responding to the notice, dated August 3, 2001, that you submitted in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received the notice on August 6, 2001, and designated it as GRAS Notice No. GRN 000080.

The subject of the notice is ARASCO (arachidonic acid-rich single-cell oil) for use in term infant formula. The notice informs FDA of the view of Mead Johnson Nutritionals (Mead Johnson) that ARASCO is GRAS, through scientific procedures, for use as a source of arachidonic acid (ARA) in term infant formula with added DHASCO (docosahexaenoic acid rich single-cell oil) as a source of docosahexaenoic acid (DHA) as described in the first column of Table 1.

The use of ARASCO and DHASCO in term infant formula was also the subject of GRAS Notice No. GRN 000041 submitted by Martek Biosciences Corporation (Martek), the manufacturer of ARASCO and DHASCO. In GRN 000041, Martek concludes that ARASCO and DHASCO are GRAS when added to term infant formulas as described in Table 1. FDA responded to GRN 000041 in a letter dated May 17, 2001, and informed Martek that the agency had no questions at that time regarding Martek's conclusion that ARASCO and DHASCO are GRAS under Martek's intended conditions of use.

GRN 000041 includes a report of a panel of individuals (Martek's GRAS panel) who evaluated the data and information that are the basis for Martek's GRAS determination. Martek's GRAS panel concluded that ARASCO and DHASCO, meeting food grade specifications and produced

according to current Good Manufacturing Practices (cGMP), are GRAS for use in infant formula at levels that are twice as high as the levels proposed by Martek in GRN 000041 (see Table 1).

In its GRAS notice, Mead Johnson includes recommendations made in 1994 by a Joint Expert Consultation of the FAO/WHO (Food and Agriculture Organization/World Health Organization) on the amounts of ARA and DHA that should be added to term infant formula (Ref. 1). The level of ARA that is recommended in the 1994 FAO/WHO consultation report is between the level proposed by Martek in GRN 000041 and the level that Martek's GRAS panel concluded would be GRAS (see Table 1). The level of DHA that is recommended in the 1994 FAO/WHO consultation report is lower than the levels proposed either by Martek or by Martek's GRAS panel.

Table 1
Maximum Levels of Use Proposed for Term Infants by
Mead Johnson, Martek and Martek's GRAS Panel;
Levels of Use Recommended for Term Infants by the 1994 FAO/WHO Consultation

	Levels of Use for Term Infants			
	Mead Johnson GRN 000080*	**Martek GRN 000041***	**Martek's GRAS Panel**	FAO/WHO Consultation
ARA				
Percent of daily fat	0.75	0.5	1.0	0.67
Percent of calories	0.375	0.25	0.5	0.33
mg/kg bw/day	45	30	60	40
DHA				
Percent of daily fat	0.50	0.5	1.0	0.33
Percent of calories	0.25	0.25	0.5	0.17

mg/kg bw/day	30	30	60	20
ARASCO				N/A
Percent of daily fat	1.88	1.25	2.5	
Percent of calories	0.938	0.625	1.25	
mg/kg bw/day	113	75	150	
DHASCO				N/A
Percent of daily fat	1.25	1.25	2.5	
Percent of calories	0.625	0.625	1.25	
mg/kg bw/day	75	75	150	

*The ratio of DHASCO to ARASCO (and DHA to ARA) would range from 1:1 to 1:2

Mead Johnson proposes to use DHASCO at the same level as that proposed by Martek in GRN 000041 and to use ARASCO at a level that would be a 50 percent increase relative to that proposed by Martek in GRN 000041. In support of the higher level of use of ARASCO, Mead Johnson cites portions of GRN 000041 and Martek's GRAS panel report and provides a letter, dated July 11, 2001, from Martek to Mead Johnson.

Mead Johnson cites compilations of human milk composition from published studies listed in Martek's GRAS panel report, in Martek's GRAS notice (GRN 000041), and in Martek's July 11 letter to Mead Johnson. Pooled means (not weighted) and standard deviations for levels of DHA and ARA in human milk across 93 population groups are 0.33 ± 0.21 percent of fatty acids for DHA and 0.53 ± 0.18 percent for ARA. Mead Johnson concludes that its proposed use of ARASCO and DHASCO will provide ARA and DHA at levels that are within the range of natural levels of these fatty acids in human milk.

The July 11 letter from Martek to Mead Johnson informs Mead Johnson that Martek had intended that its GRAS notice for the use of ARASCO and DHASCO in term infant formula cover all such term infant formulas that were being developed in the U.S. The July 11 letter states that Martek "fully supports Mead Johnson's proposed use level."

In its notice, Mead Johnson discusses preclinical and clinical studies, conducted using infant formula containing ARASCO and DHASCO, that Martek's GRAS panel reviewed in its report. In addition, Mead Johnson cites two recently published preclinical neonatal piglet studies (Dr. Brenna's study and Dr. Odle's study) as well as new clinical data in support of their GRAS determination. Mead Johnson concludes that these studies, which are discussed below, provide additional support for the safety of DHASCO and ARASCO when added to infant formula at the specified levels.

Dr. Brenna's study (Ref. 2) measured the dose response of DHASCO and ARASCO (1:2 ratio) in piglets fed milk-based formulas with increasing amounts of DHA and ARA. The highest level tested was approximately 5 times Mead Johnson's proposed maximum level of use. Because piglets consume more formula per unit body weight than human infants, the actual intake by the piglets corresponds to 16 times the expected intake by human infants on a body weigh basis. The authors of this study reported no adverse effects. There were no statistically significant differences observed between the groups of piglets (fed different amounts of ARASCO and DHASCO) in body weights or weight gain, absolute or relative organ weights (liver, brain, heart, kidney, spleen and lung), or serum chemistry values. In addition, analysis of liver sections revealed no histopathological changes.

Dr. Odle's study (Refs. 3 and 4) compared effects in piglets fed formulas containing DHA and ARA from two different sources (i.e., Martek's single cell oils (DHASCO and ARASCO) or an egg phospholipid source) with piglets fed formulas without DHA or ARA. The piglets in the DHASCO and ARASCO group were fed formula that provided approximately 1.8 times Mead Johnson's proposed maximum level of ARASCO and 1.3 times Mead Johnson's proposed maximum level of DHASCO. No statistically significant differences were observed between piglets fed the control formula (i.e., formula without either DHA or ARA) and piglets fed formula containing DHASCO and ARASCO with respect to the following parameters: weight gain, concentration of plasma cholesterol, and concentrations of liver enzymes ALT and AST (Ref. 3); and villi width, crypt depth, and gross liver histopathology (Ref. 4). In addition, based on its analysis of Dr. Odle's study, Mead Johnson reports that no statistically significant differences were observed with respect to body weight, weight gain or feed efficiency, plasma concentrations of glucose, urea nitrogen, or alkaline phosphatase, lactase activity in the jejunum or ileum, ileal or rectal apparent dry matter digestibility, spleen or liver weight (absolute or relative to body weight), crude protein or fat composition in liver, or liver histopathology.

The notice also summarizes the results of recently published clinical studies that were designed to evaluate the effects of DHA and ARA on visual and mental development in infants (Refs. 5, 6, 7, and 8). In a series of studies, infants were fed formula containing DHASCO and ARASCO (with DHA at 0.36 percent of total fat and ARA at 0.72 percent of total fat) for their first four months and compared with infants fed formula without DHA or ARA. The authors report no adverse effects that were attributed to the study formula (Refs. 5, 6, and 7). More recently, a

published abstract reports on a study conducted with infants weaned from human milk and fed either ARA and DHA supplemented formula or control formula (i.e., formula without ARA or DHA) until one year of age. The authors did not report any negative effects from the ARA and DHA supplemented formula (Ref. 8).

Based on the information provided by Mead Johnson, as well as other information available to FDA, the agency has no questions at this time regarding Mead Johnson's conclusion that ARASCO is GRAS under the intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of ARASCO. As always, it is the continuing responsibility of Mead Johnson to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

As you know, under section 412 of the Federal Food, Drug, and Cosmetic Act (the FFDCA), a manufacturer of a new infant formula must make a submission to FDA, providing required assurances about the formula, at least 90 days before the formula is marketed. FDA's response to your GRAS notice does not alleviate your responsibility to make the submission required by section 412 for any new infant formula that you manufacture to contain ARASCO and DHASCO under the conditions of use described in your GRAS notice.

As you are aware, in our response to GRN 000041 FDA informed Martek that it is FDA's view that any evaluation that a use of a food ingredient is safe is a time-dependent judgment that is based on general scientific knowledge as well as specific data and information about the ingredient. For this reason, FDA would expect any infant formula manufacturer who lawfully markets infant formula containing ARASCO and DHASCO to monitor, through scientific studies and rigorous post-market surveillance, infants who consume such a formula. Importantly, because the broader scientific community could contribute to this continuing evaluation, and because the use of ARASCO and DHASCO in infant formula would be based on the GRAS provision of the FFDCA, we also would expect that any reports to FDA about such studies would not be considered to be confidential.

In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter, as well as a copy of the information in your notice that conforms to the information in proposed 21 CFR 170.36(c)(1), is available for public review and copying on the homepage of the Office of Food Additive Safety (on the Internet at http://www.cfsan.fda.gov/~lrd/foodadd.html).

Sincerely,
/s/
Alan M. Rulis, Ph.D.
Director
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition

References

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