DHA/ARA Supplemented Infant Formulas

From: *Abreast of our Times* Winter 2003

NABA continues to receive daily inquiries regarding a number of issues related to the DHA/ARA supplementation of US infant formulas. What follows is a discussion of a few of the questions:

"We've been told that the new fatty acids are just like those in breast milk. Is this true?"
Actually these fatty acids are nothing like what is in breast milk and pose a number of known and unknown risks to the infants who consume them. The DHA is extracted from fermented microalgae (Cryptecodiunium cohnii) and the ARA is extracted from soil fungus (Mortierelle alpina). The breast does not use either of these items to manufacture its fatty acids, and these sources are new to the food chain. Each of the processed oils has its own fatty acid composition, adding a number of fatty acids to formula that already are contained in the plant oils mixed into the base formula. Human fatty acids are structurally different from those manufactured from plant sources. Human fatty acids interact with each other in a special matrix. Just because they perform as they do in human milk does not mean they will perform at all in an artificial construct.

"The formula rep told us that these formulas are FDA approved."
Neither the fatty acids themselves nor the formulas containing them are FDA approved. In the words of the FDA, "The law does not require that FDA approve infant formulas but instead requires companies to provide certain information to FDA before they market new infant formulas. Manufacturers must provide assurances that they are following good manufacturing practices and quality control procedures and that the formula will allow infants to thrive. If such assurances are not provided, FDA will object to the manufacturer's marketing of the formulas; however, **the manufacturer may market the new infant formula over FDA's objection**."
http://www.cfsan.fda.gov/~dms/qa-inf22.html
What the FDA receives is a notification by a manufacturer that its product is generally recognized as safe (GRAS). The FDA can then pose no questions or it can conclude that the notice does not provide sufficient data to determine assurances of safety. In 1999, the FDA determined that Wyeth Nutritionals' GRAS notice for use of these fatty acids did not provide sufficient data to assure safety of their use in infant formula. However, in an interesting turn of events, suddenly in 2001, the FDA raised no questions to Martek Biosciences and Mead Johnson who submitted GRAS notifications with assurances that none of the side effects of these fatty acids were a safety issue. Martek conducted its own GRAS evaluation and concluded that the DHA/ARA sources were GRAS. The FDA did **not** carry out its own investigation. The FDA states that any evaluation that the use of a food ingredient is safe is a time-dependent judgment based on general scientific knowledge and for this reason it expects infant formula manufacturers that use these ingredients to conduct scientific and rigorous post-market surveillance to monitor the babies that consume these products. Thus, the FDA did not pass its own judgment, did not evaluate these ingredients for safety, took the word of the manufacturer that DHA/ARA were safe, and has allowed 4 million babies per year to be the experimental group in a "scientific" study of what happen to babies who consume these products.
http://www.cfsan.fda.gov/~rdb/opa-g007.html
http://www.cfsan.fda.gov/~rdb/opa-g080.html
http://www.cfsan.fda.gov/~rdb/opa-g041.html
Most of the clinical studies of these fatty acid enriched formulas were short-term growth studies on small samples of infants. The FDA states that data that becomes available after the new ingredient enters the market must be considered as a "part of the totality of information about the ingredient," which is why the FDA has asked (not required) the manufacturers to monitor babies who use this formula.
http://www.cfsan.fda.gov/~dms/qa-inf20.html
The babies who consume these formulas remain guinea pigs in an uncontrolled experiment that bypasses informed consent, as parents are unaware that even the FDA will not declare that these ingredients are safe.

"Don't these formulas make babies smarter?"
The FDA states that, "There are no currently available published reports from clinical studies that address whether any long-term beneficial effects exist."
http://www.cfsan.fda.gov/~dms/qa-inf17.html

"The formula rep said that DHA/ARA have been used in infant formula for many years in other countries and there are no problems with them"
"Systematic monitoring efforts are not in place to collect and analyze information on effects of infant formulas containing DHA and ARA in countries where these formulas are in use."
http://www.cfsan.fda.gov/~dms/qa-inf19.html

"Breast milk from US mothers does not have very much DHA/ARA in it, so isn't this is better way for babies to get these nutrients?"

The precise amount of DHA/ARA varies in mother's milk depending on their diet, but accretion into central nervous system tissues is better and always accomplished with nature's version of DHA/ARA. Formulas also contain varying amounts of DHA/ARA as manufacturers do not really know how much to put in.

Formula	DHA/100 calories	ARA/100 calories
Enfamil LIPIL (Mead Johnson)	17mg	34mg
Similac Advance (Ross Products)	8mg	21mg
Parent's Choice (Wyeth)	10.7mg	15.9mg

Since no long-term beneficial effects have been documented, the question remains whether formula-fed babies derive any benefits.

"Are there any side effects?"
NABA has received many reports of babies being fed Lipil and experiencing watery, explosive diarrhea. One baby was so severely affected that he was admitted into a NICU for dehydration on day three. Such reactions should be reported to the manufacturer and the FDA as a side effect or adverse event of this formula. This is similar to the selling of olestra (the ingredient in potato chips that prevents a person from absorbing the fat, which caused painful cramping and diarrhea in many adults) that it is a scary comparison. We do not know if babies lose fat, fat soluble vitamins, or any other nutrients through the stool when they consume this formula. As a matter of fact, little is known about any alterations in metabolic parameters, blood chemistry, liver enzymes, etc. Side effects have been reported in animal studies of the DHA and ARA, such as; oily soft stool (steatorrhea) and oily hair coat in rat studies. In four week exposures, rat pups had higher liver weights, in three month exposures they showed elevated serum alkaline phosphatase levels, and undeveloped renal papilla. Fungal food sources have the potential of acting as opportunistic pathogens in immunocompromised individuals. An extensive review of this topic was published in the Journal of Nutrition, November 1998 supplement; Vol 128, Number 11S. It concluded that there was not enough evidence to support the addition of these fatty acids to formula.

Animal studies have shown that when these fatty acids are added to the diet and incorporated into plasma and tissue lipids it increases the susceptibility of membranes to lipid peroxidation and disrupts the antioxidant system. Breast milk is full of antioxidants that protect cells from the damaging effects of oxygen radicals (highly reactive chemicals). These oxygen radicals play a part in provoking diseases such as atherosclerosis, some forms
of cancer, and a host of other diseases and conditions.

Song JH, et al. Polyunsaturated (n-3) fatty acids susceptible to peroxidation are increased in plasma and tissue lipids of rats fed docosahexaenoic acid-containing oils.
J Nutrition 2000; 130:3028-3033)

Song JH, Miyazawa T. Enhanced level of n-3 fatty acid in membrane phospholipids induces lipid peroxidation in rats fed dietary docosahexaenoic acid oil. Atherosclerosis 2001 Mar; 155(1):9-18

Another study has started to question if the large fat supplementation of formula and infant foods is contributing to the obesity epidemic.

Massiera F, et al. Arachidonic acid and prostacyclin signaling promote adipose tissue development: a human health concern? J Lipid Research 2003; 44:271-279

To further complicate this issue, Beech-Nut Nutrition Corp has begun adding DHA to its line of solid baby

foods. Each 4oz "First Advantage" jar contains no less than 60mg of DHA and is marketed for babies 6 months and older. The suggested retail price is $.69, which is $.19-$.24 above the price of a regular jar of baby food. The source of DHA is egg yolks from hens fed a diet with added amounts of DHA. In their U.S. patent 6,149,964 filed May 21, 1998, and issued November 21, 2000, Beech-Nut describes a product that comprises 5% to 25% egg yolk solids which will "provide the daily recommended amount for DHA for infants in only one or two servings." This begs some interesting questions:

- Is there such a thing as too much DHA? If a baby were receiving infant formula with the highest amount of DHA and several jars of DHA-containing baby foods, is there a risk for overdose or adverse effects?
- Since the AAP is likely change its recommendation back to 4-6 months for exclusive breastfeeding as well as imply that solid foods for all babies can be started at 4 months, will this encourage mothers to begin First Advantage foods at four months instead of six?
- How much of a risk for allergy do egg yolks pose?
- Are there any plans for "post-market surveillance" on the babies who consume large amounts of both enriched formulas and enriched baby foods?
- Is there a maximum amount of DHA that young babies should or should not consume?
- Will there be any long-term data gathered on overweight and obesity in the infants fed a combination of these foods?

Is DHA/ARA Profitable?

Martek Biosciences increased its total revenues for the first quarter of 2003 by 244% over the first quarter of 2002. Over 90% of Martek's first quarter revenue was generated by sales of DHA and ARA to Mead Johnson, Wyeth Ayerst, and Abbott Laboratories. With a 15-30% increased cost to the consumer to purchase DHA/ARA enriched formulas, this comes as no surprise.

The Summer/Fall 2002 issue of INFACT Canada's newsletter carried a great tidbit of information from a few years ago when Martek Biosciences was recommended as a strong stock investment: " Infant formula is currently a commodity market, with all products being almost identical and marketers competing intensely to differentiate their product. Even if Formulaid (the name of the DHA/ARA fatty acid combination) has no benefit, we think it would be widely incorporated into formulas as a marketing tool and to allow companies to promote their formula as closest to human milk."

A Bit of Irony

What do the USDA and Martek Biosciences have in common? They share the knowledge of a USDA chemical engineer regarding how to refine and extract DHA from algal sources. Under a confidentiality agreement between USDA's Agricultural Research Service (ARS) and Martek, a refining process was shared by the ARS that allowed Martek to solve their problem of how to successfully segregate and process oil rich in omega-3 fatty acids from the algae. Now the USDA's WIC program can pay the inflated price for the DHA/ARA enriched formulas that they helped to create.

"A link in the chain: from oil refinement to baby formula." Agricultural Research magazine. December 2002 http://ars.usda.gov/is/AR/archive/dec02/oil1202.htm

What Does the Future Hold?

- New strains of soil fungus as a source for ARA
- Fractionated dairy proteins such as bovine alpha-lactalbumin added to infant formulas. Ingested alpha-lactalbumin increases the concentration of tryptophan in the body, which increases the brain's serotonin levels, inducing sleep. This could be marketed as the bed-time formula to persuade babies to sleep longer!
- Ross Products Division GRAS application to the FDA for using a combination of tuna oil (DHA) and soil fungus oil (ARA) in formulas for preterm babies, post-discharge preterm babies, and term infants.
- Genetically engineered DHA. In 2001, Martek and the Torrey Mesa Research Institute were working on a project to find and characterize genes from microalgae. Martek would retain the rights to use the genes in microbial production of DHA. Chemical Market Reporter June 11, 2001

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Fatal Infections from Powdered Infant Formula

From: *Abreast of our Times* Summer/Fall 2002

The recent death from meningitis of a hospitalized US preterm infant due to consuming Portagen formula is the latest in a growing number of unfortunate incidents involving powdered infant formulas. Clusters of infections and deaths of neonates fed powdered infant formulas have been reported worldwide since 1961, including the recent death of a full term infant in Belgium and a full term baby in Iceland who suffered permanent neurological sequelae. Central to these outbreaks over the last 40 years is Enterobacter sakazakii, a gram-negative rod-shaped bacterium that causes sepsis, necrotizing enterocolitis (NEC), and meningitis in neonates. Fatality rates can be as high as 50%. Any babies who recover from the brain abscess and ventriculitis caused by the meningitis suffer mental and physical developmental delays. The death of the preterm US baby occurred in April of 2001, but the manufacturer of the product (Mead Johnson) did not recall it until April of 2002. More than 17,000 cans of this formula were in circulation for an entire year. Powdered infant formula products are commonly used in many hospitals, especially the NICU setting, with some hospitals using powdered formula as the principal source of patient feeding. E. sakazakii has also been traced back to the powdered formulas used to fortify human milk feedings. It is a common contaminant of powdered formula, present in as many as half of all powdered formulas tested. Even low levels of contamination that are within internationally accepted limits can lead to development of infection. It is extremely resistant to heat and of great concern is the increasing antibiotic resistance being observed among Enterobacter species.

It is important to realize that powdered infant formula is not sterile and provides an excellent medium for the growth of the bacteria present in the powder. The FDA has become increasingly aware that a substantial percentage of premature neonates in NICUs are being fed non-commercially sterile dry infant formula. Many of these babies are also fed a transition formula for low birth weight babies after discharge that is available in powdered form. Some of the specialty formulas are only available in powdered form. Portagen is used for babies with conditions of decreased ability to metabolize long chain fatty acids. Human milk can be skimmed and fed to these babies. The FDA recommends that powdered infant formulas not be used in neonatal intensive care settings unless there is no alternative available. The Centers for Disease Control and Prevention (CDC), the FDA, and the American Dietetic Association (ADA) have all published guidelines for appropriate formula use, including details on proper preparation, storage, and administration. They stress minimizing "hang time" (the amount of time formula is held at room temperature in the feeding container and accompanying lines during enteral tube feeding) to no more than four hours. "Longer times should be avoided because of the potential for significant microbial growth in reconstituted infant formula."

What is notably absent from any of the guidelines or recommendations is the basic preventive action of breastfeeding or the use of banked human milk. Paying for banked human milk is less expensive than the price tag for disease and the loss of brain function or life.

References

American Dietetic Association. Preparation of formula for infants: guidelines for healthcare facilities. Chicago, IL: 1991

Baker RD. Infant formula safety. Pediatrics 2002; 110:833-835

Biering G, Karlsson S, Clark NC, et al. Three cases of neonatal meningitis caused by Enterbacter sakazakii in powdered milk. J Clin Microbiol 1989; 27:2054-2056

Centers for Disease Control and Prevention. Enterobacter sakazakii infections associated with the use of powdered infant formula – Tennessee, 2001. MMWR 2002;51:297-300

FDA. Recalls and Safety Alerts. Powder product recall. Available at: www.fda.gov/oc/po/firmrecalls/meadjohnsono3_02.html

FDA. Letter to health care professionals. Available at: www.cfsan.fda.gov

Lai KK. Enterobacter sakazakii infection among neonates, infants, children, and adults:

case reports and a review of the literature. Medicine 2001; 80:113-122

Muytjens HL, Roelofs-Willemse H, Jaspar G. Quality of powdered substitutes for breast milk with regard to members of the family Enterbacteriaceae. J Clin Microbiol 1988; 26:743-746

Nazarowec-White M, Farber JM. Thermal resistance of Enterobacter sakazakii in reconstituted dried-infant formula. Lett Appl Microbiol 1997; 24:9-13

Simmons BP, Gelfand MS, Haas M, et al. Enterbacter sakazakii infections in neonates associated with intrinsic contamination of a powdered infant formula. Infect Control Hosp Epidemiol 1989; 10:398-401

Van Acker J,DeSmet F, Muyldermans G, et al. Outbreak of necrotizing entercolitis associated with Enterobacter sakazakii in powdered milk formula. J Clin Microbiol 2001; 39:293-297

Weir E. Powdered infant formula and fatal infection with Enterobacter sakazakii. JAMC 2002; 166:1570