LSRO

Summary and Comparison of Recommendations For Nutrient Contents of Low-Birth-Weight Infant Formulas

Catherine J. Klein, PhD., R.D.
and
William C. Heird, M.D.

Life Sciences Research Office
9650 Rockville Pike
Bethesda, Maryland 20814
(301) 634-7030

Summary and Comparison of Recommendations for Nutrient Contents of Low-Birth-Weight Infant Formulas

Catherine J. Klein, PhD., R.D. Life Sciences Research Office, Bethesda, MD
and
William C. Heird, M.D., USDA/ARS Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine, Houston, TX

Correspondence to:
William C. Heird, M.D.
Children's Nutrition Research Center
Department of Pediatrics
Baylor College of Medicine
1100 Bates Street
Houston, TX 77030
Ph: 713-798-7177; Fax: 713-798-7187
e-mail: wheird@bcm.tmc.edu

ABSTRACT

Objective: This article summarizes the recommendations for nutrient contents of infant formulas intended for preterm and low–birth–weight (LBW) infants determined by the Life Sciences Research Office (LSRO) for the U.S. Food and Drug Administration (FDA) and compares these with recent recommendations for the nutrient contents of term infant formulas, with recommendations of other organizations for the nutrient intakes of LBW infants, and with the nutrient contents of available LBW infant formulas.

Methodology: In this summary article we list recommendations of the American Academy of Pediatrics (AAP), the Canadian Paediatric Society (CPS) and a consensus group for nutrient intakes of LBW infants and the nutrient contents of LBW formulas in Table form for ease of comparison. The full LSRO report[a] includes considerable description of the process as well as the rationale for the recommended minimum and maximum contents of energy, 45 additional nutrients, and four nutrient-nutrient ratios for LBW infant formulas. Further research to define the nutrient requirements of LBW infants is identified.

Results: Evidence is sufficient to support recommendations for most nutrients in LBW infant formulas. However, LSRO did not find compelling information to specify a required minimum concentration of fluoride or of several fatty acids (*e.g.,* docosahexaenoic acid, eicosahexaenoic acid) nor minimum or maximum recommendations for nucleotides, oligosaccharides, chromium or molybdenum. The composition standards for energy and many other nutrients in LBW infant formulas proposed by LSRO, AAP, CPS and a consensus group are different from those for term infant formulas. The recommended minimum content of protein (and specific amino acids), folic acid, vitamin C, several minerals, and fat soluble vitamins for LBW infant formulas is substantially higher than the content of these nutrients recommended for term infant formulas. This comparison is particularly striking for phosphorus, iron, zinc, and vitamin A; the recommended minimum content of these nutrients for LBW infant formulas exceeds the respective maximum contents recommended for term infant formulas. Currently available U.S. LBW formulas meet LSRO recommendations for the nutrients listed on the product labels.

Conclusions: Despite a few differences among recommendations by various organizations for nutrient contents of LBW infant formulas, all recommendations reflect that scientific knowledge warrants establishing distinct standards for the nutrient content of LBW infant formulas. Moreover, LBW infant formulas meeting the nutrient contents recommended by LSRO are in use in the United States. However, continued research is needed to confirm the accuracy of current recommendations for virtually all nutrients in LBW infant formulas.

[a] Life Sciences Research Office (2001) Nutrient Requirements for Preterm Infant Formulas. (Klein, CJ, ed.) Bethesda MD: Life Sciences Research Office. Full report available at: www.LSRO.org.

The U.S. Food and Drug Administration (FDA) is responsible for ensuring the safety and nutritional quality of infant formulas (1). Currently, specific regulations for term infant formulas are codified in the Code of Federal Regulations but formulas intended for premature and/or low–birth–weight (LBW) infants and infants having other unusual medical and dietary problems are regulated as "exempt infant formulas."[b] This, in essence, means that the contents of various nutrients can deviate from specified contents for term infant formulas in order to meet the nutrient needs of specific groups of infants (*e.g.*, LBW infants with certain inborn errors of metabolism).

To obtain guidance concerning whether formulas for LBW infants should continue to be so regulated or regulated similarly to term infant formulas (*i.e.*, meet accepted minimum/maximum contents of all nutrients) FDA contracted the Life Sciences Research Office (LSRO) of the American Society for Nutritional Sciences[c] to review the medical and scientific literature regarding the nutrient needs of LBW infants and the composition of formulas intended for these infants. The fundamental question addressed in this review was whether there was sufficient scientific evidence to warrant different nutrient requirements for LBW *vs.* term infant formulas.

This article summarizes the recommendations made to FDA published by LSRO in 2002 (2), and compares LSRO recommendations for the nutrient content of LBW infant formulas with earlier LSRO recommendations for the nutrient content of formulas intended for normal term infants (3;4). In addition, the range of nutrient intakes possible from formulas that meet LSRO recommendations are compared with the nutrient intakes recommended for LBW infants by other organizations (5-7). Furthermore, LSRO recommendations for LBW infant formulas are compared to the nutrient content of LBW infant formulas currently available in the United States (8-10). Finally, key areas of further research to better elucidate the nutrient requirements of LBW infants and to better define optimal minimum and maximum nutrient contents of formulas intended for these infants are identified.

LSRO RECOMMENDATIONS FOR THE NUTRIENT CONTENT OF LOW–BIRTH–WEIGHT INFANT FORMULAS

LSRO reviewed scientific studies pertaining to the nutrient needs of LBW infants. To evaluate the information gathered and to respond to the questions posed by FDA, LSRO convened an *ad hoc* panel of scientists and physicians with expertise in relevant disciplines (the Expert Panel). Additional information and expertise were obtained from other scientists recommended as consultants by members of the Expert Panel (Appendix A) and from public input at two open meetings. LSRO considered the materials, information, and opinions from all of these sources in reaching recommendations. The final report (2) was drafted and edited by LSRO in consultation with the Expert Panel. LSRO, its staff and their advisors, and the Expert Panel are referred to collectively as "LSRO" in the remainder of this paper.

[b] LBW infants are those who weigh less than 2500 g at birth, regardless of gestational age; this includes most prematurely born or preterm infants (*i.e.*, those born before 36 weeks gestation) as well as intrauterine growth restricted (IUGR) infants.

[c] At the time of the study, LSRO, an independent corporation since January 1, 2001, was an office of the American Society for Nutritional Sciences.

LSRO recognized that various factors including essentiality, stability, history of use, and safety are involved in determination of safe and adequate levels of nutrients for infant formulas. To ensure nutrient adequacy, LSRO considered factors used for recommending the nutrient content of term infant formulas (*e.g.*, feeding studies, metabolic balance studies, factorial estimates of requirements, nutrient interactions) (3) as well as other factors relevant for LBW infants (*i.e.*, intrauterine rates of nutrient accretion, degree of infant organ development, and long-term developmental outcome). Data concerning nutrient adequacy and safety for normal term infants, children, and adults were deemed to be of limited value in arriving at nutrient recommendations for LBW infants. Nevertheless, extrapolations based on body weight, metabolic capacity, and/or nutrient load were considered. Fetal growth curves also were used to estimate amounts of specific nutrients needed to support growth of infants at the 50^{th} percentile of intrauterine standards.

Clinical experience with the use of formulas and fortified human milk for feeding LBW infants was also considered. Because these infants experience better outcomes when fed LBW *vs.* term infant formulas or fortified *vs.* unfortified human milk, LSRO decided that neither term infant formulas nor unfortified human milk are appropriate reference standards for specifying nutrient contents of LBW infant formulas. On the other hand, LSRO endorsed the use of human milk as the preferred source of nutrition for the LBW infant, provided the milk is fortified to ensure its nutritional adequacy (*i.e.*, meets LSRO recommendations).

LSRO sought data related to the lowest and highest levels of nutrients fed to LBW infants without findings of deficiency, undesirable nutrient interactions, or toxicity. For some nutrients, the amounts currently fed were obtained from manufacturers' product brochures, which may underestimate or overestimate actual contents. LSRO did not review data on manufacturing processes or changes in nutrient composition during storage and administration.

The recommended nutrient content of LBW infant formulas is appropriate for all LBW infants under medical supervision during their initial hospitalization and until body weight reaches 3000–3500 g. Typically, LBW infants were discharged from the hospital when their body weight reached 2200–2500 g, but more recently infants of 1800–2200 g are discharged (11).

LSRO recommendations were based on the assumption that the infant, on average, will consume 150 mL/kg·d of formula with an energy density of 810 kcal/L. Hence, the expected average energy intake is 120 kcal/kg·d. Whether LSRO recommendations are appropriate to meet the needs of infants who weigh less than 1000 g at birth is not known because few data concerning the nutritional needs of these infants are available, particularly for those weighing less than 750 g at birth. In its report to FDA, LSRO emphasized that the nutritional goals for individual infants should be determined by the infant's physician on a case–by–case basis according to the infant's gestational age, stage of physiological development, and clinical condition. However, it is likely that formulas containing the recommended nutrient contents will suffice for most infants.

A summary of the LSRO recommendations for the minimum and maximum content of nutrients and nutrient ratios for enteral formulas for LBW infants is shown in Appendix B (2). Please refer to the full report for in-depth discussion of the basis for selection of specific nutrient minimum and maximum limits (2). Although evidence was considered sufficient to support

recommendations for a maximum content of several fatty acids (*e.g.,* docosahexaenoic acid; DHA, eicosahexaenoic acid; EPA) and fluoride, data were considered insufficient to warrant recommending minimum amounts of these substances. Data were also considered insufficient to warrant either minimum or maximum recommendations for content of nucleotides, oligosaccharides, chromium, or molybdenum.

Recommendation of a maximum content of a specific nutrient without a minimum content indicates that, despite the lack of convincing evidence of a requirement for that nutrient, amounts up to the maximum content recommended are likely to be safe based on the history of use, the potential for adverse nutrient interactions, and the absence of evidence of toxicity (2). Failure to recommend either a minimum or a maximum content, of course, indicates that evidence is insufficient to warrant either. LSRO emphasized that periodic reassessments of its recommendations are necessary as new literature becomes available.

COMPARISON OF LSRO RECOMMENDATIONS FOR NUTRIENT CONTENT OF LOW–BIRTH–WEIGHT FORMULAS *VS.* TERM INFANT FORMULAS

The fundamental question addressed by LSRO was whether there was sufficient scientific evidence to warrant nutrient requirements for LBW infant formulas that are different from those for term infant formulas. The nutrient content of human milk served as a guide in establishing recommendations for term infant formulas, in contrast to the process used to reach recommendations for LBW infant formulas (3;4). Additional considerations, important for both term and LBW recommendations, included nutrient interactions, history of use, safety, and toxicity.

The basis for the recommendations for vitamin A content of both LBW and term infant formulas demonstrates some of the differences and similarities in the processes used by LSRO to arrive at minimum and maximum recommendations for the two types of formula. The recommended minimum vitamin A content of LBW infant formulas, 204 μg RE (679 IU)/100 kcal, is based on the observation of Koo and coworkers (12) that LBW infants fed formula containing 102 μg RE/100 kcal had low blood retinol concentrations and the observation of Carlson and coworkers (13) that LBW infants fed formula containing 204 μg RE/100 kcal had "normal" blood retinol concentrations. The recommended maximum content of vitamin A for LBW infant formulas, 380 μg RE (1265 IU)/100 kcal, is based on the observation that an intake of 337 μg RE/100 kcal results in no adverse effects (12) and from consideration of the history of safe use of LBW infant formulas containing 375 μg RE/100 kcal.

In contrast, the recommended minimum content of vitamin A for term infant formulas is based on the minimum vitamin A content of human milk (range 29-97 μg RE/100 kcal), which is adequate to support growth of term infants. However, since human milk contains bile salt–simulated lipase that enhances the bioavailability of vitamin A esters but infant formulas do not, the minimum breast milk concentration of 30 μg RE/100 kcal was doubled to set the minimum content of vitamin A for term infant formulas to 60 μg RE (200 IU)/100 kcal. The recommended maximum content of vitamin A for term infant formulas, 150 μg RE (500 IU)/100 kcal, reflects history of use and the 90th percentile of chemical analyses of the vitamin A content of market samples of term infant formulas (570 IU/100 kcal).

LSRO was unaware of data indicating that the minimal content of total fat, linoleic acid, α–linolenic acid, choline, *myo*–inositol, potassium, and several of the B–complex vitamins recommended for LBW infant formulas should differ from that recommended for term infant formulas. However, considering the many differences between hospitalized LBW infants and healthy term infants, it is not surprising that most other recommendations for the nutrient contents of formulas for these two distinct groups of infants differ (Appendix B). The recommended minimum content of protein (and specific amino acids), folic acid, vitamin C, several minerals, and fat soluble vitamins for LBW infant formulas is substantially higher than the content of those nutrients recommended for term infant formulas. This comparison is particularly striking for phosphorus, iron, zinc, and vitamin A; the recommended minimum content of these nutrients for LBW infant formulas exceeds the respective maximum contents recommended for term infant formulas. In contrast, the recommended minimum content of iodine is less than that recommended for term infant formulas reflecting the absence of reports of iodine deficiency in LBW infants fed formulas with the lower amount of iodine.

Minimum and maximum levels of arginine (from protein) and taurine, both of which are considered to be conditionally essential during early development, are recommended for LBW infant formulas, whereas a minimal content of these amino acids is not specified for term infant formulas. Considering the many years of experience in successfully feeding human milk and formula containing lactose to preterm infants and the absence of strong evidence for the elimination of lactose from preterm formula, LSRO recommended a minimum content of lactose for LBW formulas. On the other hand, LSRO was not compelled by the evidence to recommend a minimum level of lactose for term infant formulas (3;4).

A maximum but not a minimum amount of DHA, arachidonic acid, EPA, myristic acid, lauric acid, and medium–chain triglycerides is recommended for LBW infant formulas, whereas neither a maximum nor a minimum amount of either is specified for term infant formulas. Currently, LBW infant formulas contain medium-chain triglycerides whereas standard formulas for healthy term infants do not.

COMPARISON OF RECOMMENDED NUTRIENT INTAKES OF LOW–BIRTH–WEIGHT INFANTS

The LSRO recommendations for the minimum and maximum nutrient contents of LBW infant formulas, expressed as amounts per 100 kcal, are based on the perceived nutrient needs of LBW infants. Hence, the recommendations for minimum and maximum nutrient contents of formulas can be converted to a range of recommended daily nutrient needs assuming that the average energy requirement is 120 kcal/kg·d. The range of recommended intakes determined in this way is shown in Table 1 along with intakes recommended by other groups (2;5-7).

In general, Dietary Reference Intakes of the Food and Nutrition Board/Institute of Medicine apply to healthy full-term infants (14). One exception was the establishment of a Tolerable Upper Intake Level of vitamin E of 21 mg/kg·d for infants with birth weights of 1.5 kg. This level is not recommended for daily intake, but serves as the maximum level of exposure that would pose no harm.

For the most part, the recommended nutrient intakes of LBW infants designated in 2004 by the American Academy of Pediatrics Committee on Nutrition (AAPCON) (5) are similar to their earlier recommendations (15). The recent changes include specific recommendations for carbohydrate and total fat intakes, an increase in the recommended intake of folic acid, a decrease in the recommended intakes of phosphorus and vitamin D, and the elimination of specific recommendations for chloride and magnesium intakes.

Tsang and coworkers (6) recently updated their consensus recommendations (16). The 2005 changes include specific ranges for recommended total carbohydrate and fat intakes, an increase in the recommended intake of protein, vitamin C, and vitamin D, and increases in the maximum for chromium, selenium, iron, zinc, chloride and sodium. These changes for iron and zinc now exceed the maximum intakes suggested by LSRO and other groups.

While there are minimal differences in the macronutrient intakes recommended by the four groups listed in Table 1, the recommended intakes of other nutrients differ considerably. For some nutrients, the difference in recommendations among groups varies by five–fold or more. For example, AAPCON, LSRO, the Canadian Paediatric Society (7), and a consensus group (6) recommend minimum niacin intakes of > 300, 660, 756, and 3600 μg/kg·d, respectively.

Formulas containing the minimum content of trace minerals recommended by LSRO meet AAPCON recommendations for all trace minerals. However, formulas containing the minimum amounts of potassium, vitamin D, and several B-complex vitamins recommended by LSRO provide lower intakes of these nutrients than proposed by other groups. In fact, the vitamin D intakes recommended by Canadian Paediatric Society (7) are higher than provided by formulas containing the maximum content of vitamin D recommended by LSRO. In contrast, LSRO recommendations for minimum zinc and manganese are substantially more than those of all other groups. These differences in recommended trace mineral and vitamin intakes among the four groups undoubtedly reflect the difficulties of studying the needs for these nutrients in any pediatric population, particularly LBW infants.

Table 1. Nutrient intakes provided by enteral formulas that meet Life Sciences Research Office recommendations compared to nutrient intakes for low–birth–weight infants (1000 g to 2500 g) recommended by other groups.[a]

Nutrient	Potential daily intake from formulas that meet LSRO recommendations (2002)	Recommended Intakes		
		AAPCON (2004)[b]	Consensus group (2005)[c]	Canadian Paediatric Society (1995)[d]
Energy (kcal/kg·d)	100 – 141	120	110 – 130	105 – 135
Protein (g/kg·d)	3.0 – 4.3	3.5 – 4.0	3.4 – 4.2	3.0 – 3.6
Carbohydrate (g/kg·d)	Total: 11.5 – 15.0 Lactose: 4.8 – 15.0	Total: 10 – 14	Total: 7 – 17	Total: 7.5 – 15.5 Lactose: 7.5 – 15.5
Fat (g/kg·d)	Total: 5.3 – 6.8 LA: 0.42 – 1.70 ALA: 0.09 – 0.27 LA/ALA: 6 – 16	Total: 5.4 – 7.2 LA: ≥ 0.48 ALA: – LA/ALA: –	Total: 5.3 – 7.2 LA: 0.60 – 1.44 ALA: – LA/ALA: 5 – 15	Total: 4.5 – 6.8 LA: 0.47 – 0.75 ALA: 0.12 – 0.15 LA/ALA: –
Sodium (mg/kg·d)	46.8 – 75.6	57.6 – 80.4	69 – 115	57.5 – 92.0
Chloride (mg/kg·d)	72 – 192	–	107 – 249	89 – 142
Potassium (mg/kg·d)	72 – 192	78 – 117	78 – 117	98 – 137
Calcium (mg/kg·d)	148 – 222	210	100 – 220	160 – 240
Phosphorus (mg/kg·d)	98 – 131	110	60 – 140	77 – 118
Magnesium (mg/kg·d)	8.2 – 20.4	–	7.9 – 15	4.9 – 9.7
Zinc (µg/kg·d)	1320 – 1800	> 600	1000 – 3000	503 – 804
Manganese (µg/kg·d)	7.6 – 30	> 6	0.7 – 7.5	0.55 – 1.1
Copper (µg/kg·d)	120 – 300	108	120 – 150	102 – 203
Iron (mg/kg·d)	2.0 – 3.6	2.0 – 3.0	2.0 – 4.0	2.0 – 3.0
Iodine (µg/kg·d)	7.2 – 42	6	10 – 60	31.6 – 63
Selenium (µg/kg·d)	2.2 – 6.0	–	1.3 – 4.5	3.2 – 4.7
Chromium (µg/kg·d)	–	–	0.1 – 2.25	0.05 – 0.1

[a]ALA: alpha-linolenic acid; α–TE: alpha-tocopherol equivalents; LA: linoleic acid; AAPCON: American Academy of Pediatrics Committee on Nutrition; LSRO: Life Sciences Research Office; RE: retinol equivalents; USP: United States Pharmacopeia.
[b]AAPCON considers that energy intakes of 105 – 130 kcal/kg·d support adequate growth; iron recommendation is for infants older than one month; conversion from 75 – 225 µg/100 kcal for vitamin A as units are incorrect in 2004 AAPCON report; Table 2.1 of AAPCON report recommends > 1.1 USP units vitamin E/100 kcal; minimum ratio of 15 µg pyridoxine/g protein; folic acid recommendation pertains to infants younger than the equivalent of 40 wk postmenstrual age.
[c]Recommendations are for the growth period after the first week of life. For late hyponatremia, may need sodium up to 160 mg/kg·d per day.
[d]Recommendations are for the growth period after the first week of life. Recommendations for vitamin D are 400 IU/kg·d for Caucasian infants and up to 800 IU/kg·d for Black and Asian infants or for serum hydroxyvitamin D of 10 – 20 ng/mL.

Table 1 continued

Nutrient	Potential daily intake from formulas that meet LSRO recommendations (2002)	Recommended Intakes		
		AAPCON (2004)[b]	Consensus group (2005)[c]	Canadian Paediatric Society (1995)[d]
Molybdenum (μg/kg·d)	–	–	0.3	0.19 – 0.38
Vitamin A (μg RE/kg·d)	245 – 456	90 – 270	210 – 450	200 – 450
Vitamin K (μg/kg·d)	4.8 – 30	4.8	8 – 10	–
Vitamin D (IU/kg·d)	90 – 324	324	150 – 400	400 – 800
Vitamin E (mg α–TE/kg·d)	2.4 – 9.6	≥ 0.84	6 – 12	0.5 – 0.9
Thiamine (μg/kg·d)	36 – 300	> 48	180 – 240	40 – 50
Riboflavin (μg/kg·d)	96 – 744	> 72	250 – 360	360 – 460
Niacin (μg/kg·d)	660 – 6000	> 300	3600 – 4800	756 – 972
Pyridoxine (μg/kg·d)	36 – 300	> 42	150 – 210	45 – 54
Pantothenic Acid (μg/kg·d)	360 – 2280	>360	1200 – 1700	800 – 1300
Vitamin B_{12} (μg/kg·d)	0.096 – 0.84	> 0.18	0.3	0.15 μg/d
Biotin (μg/kg·d)	1.2 – 44.4	> 1.8	3.6 – 6	1.5
Folic Acid (μg/kg·d)	36 – 54	40	25 – 50	50 μg/d
Vitamin C (mg/kg·d)	10 – 45	35 – 42	18 – 24	6 – 10
Taurine (mg/kg·d)	6 – 14.4	–	4.5 – 9.0	–
Inositol (mg/kg·d)	4.8 – 52.8	–	32 – 81	–
Carnitine (mg/kg·d)	2.4 – 7.1	–	~2.9	–
Choline (mg/kg·d)	8.4 – 27.6	–	14.4 – 28	–

[a]ALA: alpha-linolenic acid; α–TE: alpha-tocopherol equivalents; LA: linoleic acid; AAPCON: American Academy of Pediatrics Committee on Nutrition; LSRO: Life Sciences Research Office; RE: retinol equivalents; USP: United States Pharmacopeia.
[b]AAPCON considers that energy intakes of 105 – 130 kcal/kg·d support adequate growth; iron recommendation is for infants older than one month; conversion from 75 – 225 μg/100 kcal for vitamin A as units are incorrect in 2004 AAPCON report; Table 2.1 of AAPCON report recommends > 1.1 USP units vitamin E/100 kcal; minimum ratio of 15 μg pyridoxine/g protein; folic acid recommendation pertains to infants younger than the equivalent of 40 wk postmenstrual age.
[c]Recommendations are for the growth period after the first week of life. For late hyponatremia, may need sodium up to 160 mg/kg·d per day.
[d]Recommendations are for the growth period after the first week of life. Recommendations for vitamin D are 400 IU/kg·d for Caucasian infants and up to 800 IU/kg·d for Black and Asian infants or for serum hydroxyvitamin D of 10 – 20 ng/mL.

COMPARISON OF LSRO RECOMMENDATIONS FOR THE NUTRIENT CONTENT OF LOW–BIRTH–WEIGHT INFANT FORMULAS WITH CURRENTLY AVAILABLE INFANT FORMULAS

The nutrient contents listed on product labels or in product information brochures of LBW infant formulas currently available in the United States meet LSRO recommendations for most nutrients (Appendix B) (8-10). One exception is arginine, the recommended minimum content of which is not met by some formulas. Formulas designed specifically to restrict iron intake also do not meet the LSRO recommendation for minimum iron content. Although chromium and molybdenum are not listed as individual ingredients on product labels, they may actually be present in formulas as contaminants or as inherent components of the other ingredients (***e.g.***, milk products). It would be helpful if the concentrations of these trace minerals were known. Such data might support a future recommendation for a minimum content of these nutrients based on history of use.

The contents of carnitine, arachidonic acid, fluoride, threonine, and sulfur–containing amino acids in some LBW infant formulas exceed the maximum contents recommended by LSRO. The maximum concentration of carnitine recommended by LSRO, 5.9 mg/100 kcal, is based primarily on history of use. Carnitine concentrations of 5.9-6.0 mg/100 kcal have resulted in no known adverse effect whereas, in short term studies, a carnitine content of 8.1 mg/100 kcal increased ketogenesis (2) and resulted, after 3 months of feeding, in increased urinary excretion of free carnitine (17). One current LBW infant formula contains 6.1 mg of carnitine/100 kcal, which is somewhat above the maximum content recommended by LSRO but well below levels associated with adverse effects.

The recommended maximum content of arachidonic acid (0.6% of total fatty acids) for LBW infant formulas is based on studies of supplementation at this level without evidence of adverse effect. Although one current LBW formula contains 0.67% of total fatty acids as arachidonic acid, this formula's ratio of arachidonic acid to DHA is within the range recommended by LSRO thus helping to guard against imbalances of endogenous eicosanoids synthesized from ω-6 *vs.* ω-3 fatty acids.

The recommended maximum concentration of fluoride for LBW infant formulas (25 μg/100 kcal) is based on a 25-year history of use of ready-to-feed LBW infant formulas made with de–fluoridated water. One current LBW infant formula has an average analyzed fluoride content of 45 μg/100 kcal which results in a somewhat greater fluoride exposure (54 μg/kg·d) than that of older children who drink fluoridated water (50 μg/kg·d).

The analytical value reported by manufacturers for the content of some amino acids varies considerably between brands of LBW infant formulas. These differences are curious because the protein source of both currently available formulas is nonfat milk and whey protein concentrate and both brands have similar total protein concentrations (~ 3 g/100 kcal; Appendix B). One marketed LBW infant formula has an average analytical value of 140 mg of methionine plus cysteine per 100 kcal, which is greater than the recommended maximum of 123 mg/100 kcal, whereas another has an average analytical value of 95 mg/100 kcal. Similarly, one current LBW infant formula has an average analytical value of threonine of 192 mg/100 kcal, which is greater

than the recommended maximum content of 163 mg/100 kcal, whereas another presumably has 159 mg/100 kcal. All current LBW infant formulas have total protein content within the range recommended by LSRO. However, none has protein content approaching the maximum content recommended by LSRO

RESEARCH NEEDED TO FURTHER ELUCIDATE THE NUTRIENT REQUIREMENTS OF LOW–BIRTH–WEIGHT INFANTS

Hay and coworkers (18) identified several key areas of further research concerning the nutrient needs of LBW infants. Areas identified, all of which remain relevant, include but were not limited to:

- Establishing the requirements for amino acids, fatty acids, trace elements, m*yo*–inositol, choline, and nucleotides
- Ascertaining the relationships between nutritional care and protein catabolism, hyperglycemia, growth failure, susceptibility to diseases (*e.g.*, sepsis), and response to treatment (*e.g.*, surgery, dexamethasone)
- Determining the optimal mixture, rate of administration, and rate of delivery of protein (amino acids), carbohydrate, and lipids

As emphasized by Cooke and coworkers (19), standards for growth of LBW infants must be more precise before recommended nutrient needs can be refined. This area of research should address the question of whether a growth rate that matches the intrauterine rate is sufficient for all infants or if a greater rate to compensate for the seemingly inevitable initial weight loss after birth is beneficial. Moreover, it is not known whether an even more accelerated rate of growth (*i.e.*, growth of fat mass) increases risks of detrimental acute and long-term effects.

LSRO identified many of these same research needs as well as others and also recognized some of the many challenges to research in this vulnerable population, such as a scarcity of research funds for badly needed but costly long-term studies. Another critical research need identified by LSRO is to determine the nutrient requirements of infants who weigh < 1000 g at birth, particularly those who weigh < 750 g. Further research is also needed to understand the short term effects of nutrient intake during infancy on neurodevelopment as well as on long term health risks.

SUMMARY

LSRO reviewed the available scientific evidence for defining different requirements for energy density and nutrient content of formulas intended for use by LBW *vs*. term infants. Despite a few differences among recommendations by various organizations for nutrient contents of LBW infant formulas, all recommendations reflect the fact that scientific knowledge warrants establishing distinct standards for the nutrient content of LBW infant formulas. However, LSRO did not find sufficient evidence to support a required minimum concentration of nucleotides, DHA, arachidonic acid, EPA, or fluoride in LBW infant formulas. Therefore, the essentiality of these nutrients for LBW infants was not recognized. Current evidence also was considered

insufficient to warrant a recommendation for a maximum concentration of nucleotides, or for the maximum ratio of vitamin E to polyunsaturated fatty acids. LSRO did not find sufficient evidence to recommend a concentration range for chromium or molybdenum, but others have suggested that setting such a range for molybdenum would be particularly beneficial (18). Currently available U.S. LBW formulas meet LSRO recommendations for the nutrients listed on the product labels. Further research is needed to confirm the continued accuracy of the recommendations for minimum and maximum concentrations of virtually all nutrients in LBW infant formulas. Chemical analyses of currently available infant formulas should be published including the content of total and individual polyunsaturated fatty acids and other individual fatty acids as well as the content of specific amino acids, fluoride, chromium, and molybdenum. These data would aid recommendations based on history of use. Most notable, however, is the need to better define the nutritional requirements of LBW infants, particularly very low and extremely LBW infants and to evaluate feeding practices that may better support more optimal short term and long term growth and development of these vulnerable infants.

REFERENCES

1. U.S. Food and Drug Administration. FDA regulation and critical information on the manufacture and distribution of infant formula. Online 2002. Available at: http://www.cfsan.fda.gov/~dms/inf-regu.html. Accessed March 18, 2004.

2. Klein CJ. Nutrient requirements for preterm infant formulas. J Nutr 2002;132:1395S-577S.

3. Life Sciences Research Office. Assessment of Nutrient Requirements for Infant Formulas. Prepared by the Life Sciences Research Office, 9650 Rockville Pike, Bethesda, MD for the Center for Food Safety and Applied Nutrition, Food and Drug Administration, Department of Health and Human Services, Washington, DC 20204 under Contract No. 223-92-2185. J Nutr 1998;128:2059S-294S.

4. Life Sciences Research Office. Assessment of Nutrient Requirements for Infant Formulas. Prepared by the Life Sciences Research Office, 9650 Rockville Pike, Bethesda, MD for the Center for Food Safety and Applied Nutrition, Food and Drug Administration, Department of Health and Human Services, Washington, DC 20204 under Contract No. 223-92-2185. [Erratum] Histidine was not included in the list of indispensible amino acids, Table 5-1 (p. 2117S). J Nutr 1998;129:1090.

5. American Academy of Pediatrics Committee on Nutrition (AAPCON). Nutritional needs of the preterm infant. In: Kleinman RE, ed. Pediatric Nutrition Handbook. Washington, DC: American Academy of Pediatrics, 2004:23-54.

6. Tsang RC, Lucas A, Uauy R, Zlotkin S. Nutrition of the Preterm Infant. Scientific Basis and Practical Guidelines. 2nd ed. Digital Educational Publishing, Inc., 2005.

7. Canadian Paediatric Society (CPS), Nutrition Committee. Nutrient needs and feeding of premature infants. CMAJ 1995;152:1765-85.

8. Mead Johnson. Enfamil® Premature Lipal®. Online 2004. Available at: http://www.meadjohnson.com/products/hcp-infant/premature.html. Accessed: January 15, 2004.

9. Ross. Similac® Special Care® Advance® with Iron 24. Abbott Laboratories Online 2005. Available at: http://rpdcon40.ross.com/pn/PediatricProducts.NSF/web_Ross.com_XML_PediatricNutrition/57D6C2D590FACECD85256A8000754757?OpenDocument. Accessed: September 29, 2005.

10. Ross. Similac® Special Care® Advance® with Iron 20. Abbott Laboratories Online 2005. Available at: http://rpdcon40.ross.com/pn/PediatricProducts.NSF/web_Ross.com_XML_PediatricNutrition/1847383032E5B6AA85256A800075471B?OpenDocument. Accessed: September 29, 2005.

11. Cruz H, Guzman N, Rosales M et al. Early hospital discharge of preterm very low birth weight infants. J Perinatol 1997;17:29-32.

12. Koo WW, Krug-Wispe S, Succop P, Tsang RC, Neylan M. Effect of different vitamin A intakes on very-low-birth-weight infants. Am J Clin Nutr 1995;62:1216-20.

13. Carlson SE, Peeples JM, Werkman SH, Koo WW. Plasma retinol and retinol binding protein concentrations in premature infants fed preterm formula past hospital discharge. Eur J Clin Nutr 1995;49:134-6.

14. Institute of Medicine. DRI Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington, DC: National Academy Press, 2000.

15. American Academy of Pediatrics Committee on Nutrition (AAPCON). Nutritional needs of low-birth-weight infants. Pediatrics 1985;75:976-86.

16. Tsang RC, Lucas A, Uauy R, Zlotkin S. Nutritional Needs of the Preterm Infant. Scientific Basis and Practical Guidelines. Pawling, NY: Caducceus Medical Publishers, Inc., 1993.

17. Novak M, Monkus EF, Buch M, Silverio J, Clouston OM, Cassady JC. L-carnitine supplementation of a soybean-based formula in early infancy: plasma and urine levels of carnitine and acylcarnitines. J Pediatr Gastroenterol Nutr 1988;7:220-4.

18. Hay WW, Jr., Lucas A, Heird WC et al. Workshop summary: nutrition of the extremely low birth weight infant. Pediatrics 1999;104:1360-8.

19. Cooke RJ. Nutrient requirements in preterm infants. Pediatr Res 2003;53:2.

Appendix A. *Ad Hoc* Expert Panel and Special Consultants.

Expert Panel

Stephanie A. Atkinson, Ph.D.
Department of Pediatrics
McMaster University
Hamilton, Ontario, Canada

Michael K. Georgieff, M.D.
Division of Neonatology
University of Minnesota School of Medicine
Minneapolis, MN

Margit Hamosh, Ph.D.
Department of Pediatrics
Georgetown University School of Medicine
Washington, DC

William C. Heird, M.D.
Department of Pediatrics
Baylor College of Medicine and Children\'s Nutrition Research Center
Houston, TX

C. Lawrence Kien, M.D., Ph.D.
Department of Pediatric
University of Texas Medical Branch
Galveston, TX

David K. Rassin, Ph.D.
Department of Pediatrics
University of Texas Medical Branch
Galveston, TX

Richard J. Schanler, M.D.
Department of Pediatrics/Neonatology
Baylor College of Medicine and Children's Nutrition Research Center
Houston, TX

Special Consultants to the Life Sciences Research Office

K. Michael Hambidge, M.D.
Department of Pediatrics
University of Colorado Health Sciences Center
School of Medicine
Denver, CO

William W. Hay, M.D.
Department of Pediatrics
University of Colorado Health Science Center
Denver, CO

Satish C. Kalhan, M.D.
Center for Metabolism and Nutrition
Case Western Reserve University
School of Medicine
Cleveland, OH

Winston W. Koo, M.D.
Department of Pediatrics
Hutzel Hospital
Wayne State University
Detroit, MI

Nancy F. Krebs, M.D.
Department of Pediatrics
University of Colorado Health Sciences Center
School of Medicine
Denver, CO

Appendix B. Comparison of minimum and maximum nutrient content of low-birth-weight (LBW) and term infant formulas recommended by the Life Sciences Research Office (LSRO) and the nutrient content of infant formulas currently available in the United States

A. MACRONUTRIENTS AND OTHER COMPONENTS				
		LSRO Recommendations		Available LBW Formulas[a]
		LBW	Term	
Energy (kcal/100 mL)	Minimum	67	63	67
	Maximum	94	71	81
Total fat (g/100 kcal)	Minimum	4.4	4.4	5.1
	Maximum	5.7	6.4	5.43
Linoleic acid (LA) (% of total fatty acids)	Minimum	8	8	12.9
	Maximum	25	35	15.9
α-linolenic acid (ALA) (% of total fatty acids)	Minimum	1.75	1.75	1.76
	Maximum	4.0	4.0	1.86
LA: ALA	Minimum	6:1	6:1	7:1
	Maximum	16:1	16:1	9:1
Protein (g/100 kcal)	Minimum	2.5	1.7	3.0
	Maximum	3.6	3.4	3.0
Nucleotides (mg/100 kcal)	Minimum	−	0	4.2
	Maximum	−	16	10.7

A. MACRONUTRIENTS AND OTHER COMPONENTS (cont'd)				
		LSRO Recommendations		Available LBW Formulas[a]
		LBW	Term	
Carnitine (mg/100 kcal)	Minimum	2	1.2	2.4
	Maximum	5.9	2.0	6.1
Choline (mg/100 kcal)	Minimum	7	7	10
	Maximum	23	30	20
Myo-Inositol (mg/100 kcal)	Minimum	4	4	40
	Maximum	44	40	44
Total carbohydrate (g/100 kcal)	Minimum	9.6	9	10.3
	Maximum	12.5	13	11
Lactose (g/100 kcal)	Minimum	4	–	4.4
	Maximum	12.5	–	10.3
Oligosaccharides (g/100 kcal)	Minimum	–	–	*
	Maximum	–	–	*
Docosahexaenoic acid (DHA) (% of total fatty acids)	Minimum	–	–	0.24
	Maximum	0.35	–	0.33
Arachidonic acid (AA) (% of total fatty acids)	Minimum	–	–	0.39
	Maximum	0.6	–	0.67

A. MACRONUTRIENTS AND OTHER COMPONENTS (cont'd)				
		LSRO Recommendations		**Available LBW Formulas**[a]
		LBW	**Term**	
AA:DHA	Minimum	1.5:1	–	1.6:1
	Maximum	2:1	–	2:1
Eicosapentaenoic acid (% of DHA)	Minimum	–	**	0
	Maximum	30	**	*
Myristic acid (% of total fatty acids)	Minimum	–	–	0.2
	Maximum	12	–	3.5
Lauric acid (% of total fatty acids)	Minimum	–	**	0.2
	Maximum	12	**	9.1
Medium-chain triglycerides (% of total fatty acids)	Minimum	–	–	40
	Maximum	50	–	50

B. MINERALS				
		LSRO Recommendations		Available LBW Formulas[a]
		LBW	Term	
Calcium (mg/100 kcal)	Minimum	123	50	165
	Maximum	185	140	180
Phosphorus (mg/100 kcal)	Minimum	82	20	83
	Maximum	109	70	100
Ratio (mass), Calcium:Phosphorus	Minimum	1.7:1	1.1:1	1.8:1
	Maximum	2:1	2:1	2:1
Magnesium (mg/100 kcal)	Minimum	6.8	4	9
	Maximum	17	17	12
Iron (mg/100 kcal)	Minimum	1.7	0.2	1.8
	Maximum	3.0	1.65	1.8
Zinc (mg/100 kcal)	Minimum	1.1	0.4	1.5
	Maximum	1.5	1.0	1.5
Manganese (µg/100 kcal)	Minimum	6.3	1.0	6.3
	Maximum	25	100	12
Copper (µg/100 kcal)	Minimum	100	60	120
	Maximum	250	160	250
Iodine (µg/100 kcal)	Minimum	6	8	6
	Maximum	35	35	25

B. MINERALS (Cont'd)				
		LSRO Recommendations		Available LBW Formulas[a]
		LBW	Term	
Sodium (mg/100 kcal)	Minimum	39	25	43
	Maximum	63	50	58
Potassium (mg/100 kcal)	Minimum	60	60	98
	Maximum	160	160	129
Chloride (mg/100 kcal)	Minimum	60	50	81
	Maximum	160	160	90
Selenium (µg/100 kcal)	Minimum	1.8	1.5	1.8
	Maximum	5.0	5.0	2.8
Fluoride (µg/100 kcal)	Minimum	–	0	*
	Maximum	25	60	45
Chromium (µg/100 kcal)	Minimum	–	–	0.2
	Maximum	–	–	*
Molybdenum (µg/100 kcal)	Minimum	–	–	0.4
	Maximum	–	–	*

C. VITAMINS				
		LSRO Recommendations		Available LBW Formulas[a]
		LBW	Term	
Vitamin A (µg RE/100 kcal)	Minimum	204	60	375
	Maximum	380	150	375
Vitamin D (IU/100 kcal)	Minimum	75	40	150
	Maximum	270	100	240
Vitamin E (mg α-TE/100 kcal)	Minimum	2	0.5	4.0
	Maximum	8	(5 mg α-TE/g PUFA)	6.3
Ratio, Vitamin E (*mg*): PUFA (*g*)	Minimum	>1.5:1	0.5:1	3.9:1
	Maximum	-	5:1	5.6:1
Vitamin K (µg/100 kcal)	Minimum	4	1.0	8
	Maximum	25	25	12
Vitamin B_1 (thiamin) (µg/100 kcal)	Minimum	30	30	200
	Maximum	250	200	250
Vitamin B_2 (riboflavin) (µg/100 kcal)	Minimum	80	80	300
	Maximum	620	300	620

C. VITAMINS (Cont.'d)				
		LSRO Recommendations		Available LBW Formulas[a]
		LBW	Term	
Vitamin B_3 (niacin) (µg/100 kcal)	Minimum	550	550	4000
	Maximum	5000	2000	5000
Vitamin B_6 (pyridoxine) (µg/100 kcal)	Minimum	30	30	150
	Maximum	250	130	250
Vitamin B_{12} (cobalamin) (µg/100 kcal)	Minimum	0.08	0.08	0.25
	Maximum	0.7	0.7	0.55
Folic acid (µg/100 kcal)	Minimum	30	11	37
	Maximum	45	40	40
Pantothenic acid (µg /100 kcal)	Minimum	300	300	1200
	Maximum	1900	1200	1900
Biotin (µg/100 kcal)	Minimum	1.0	1.0	4
	Maximum	37	15	37
Vitamin C (ascorbic acid) (mg/100 kcal)	Minimum	8.3	6	20
	Maximum	37	15	37

D. AMINO ACIDS				
		LSRO Recommendations		Available LBW Formulas[a]
		LBW	Term	
Isoleucine (mg/100 kcal)	Minimum	129	88	174
	Maximum	186	176	182
Leucine (mg/100 kcal)	Minimum	252	171	310
	Maximum	362	342	335
Lysine (mg/100 kcal)	Minimum	182	124	210
	Maximum	263	248	269
Methionine + cysteine (mg/100 kcal)	Minimum	85	58	95
	Maximum	123	116	140
Phenylalanine + tyrosine (mg/100 kcal)	Minimum	196	133	244
	Maximum	282	266	254
Threonine (mg/100 kcal)	Minimum	113	77	159
	Maximum	163	154	192
Tryptophan (mg/100 kcal)	Minimum	38	26	45
	Maximum	55	52	51
Valine (mg/100 kcal)	Minimum	132	90	184
	Maximum	191	180	191

D. AMINO ACIDS (Cont'd)				
		LSRO Recommendations		Available LBW Formulas[a]
		LBW	Term	
Histidine (mg/100 kcal)	Minimum	53	36	59
	Maximum	76	72	70
Arginine (mg/100 kcal)	Minimum	72	**	68
	Maximum	104	**	90
Taurine (mg/100 kcal)	Minimum	5	0	6
	Maximum	12	12	6.9

[a]α–TE: alpha-tocopherol equivalents; PUFA: polyunsaturated fatty acids; RE: retinol equivalents. For some nutrients, values shown represent the range of nutrients reported on product labeling, whereas for other nutrients, values provided by the manufacturers represent analytical amounts. Products: Similac® Special Care® Advance with Iron 20 and Similac® Special Care® Advance with Iron 24 (Ross Products Division, Abbott Laboratories, Columbus, Ohio 43215) (9-10) and iron-fortified Enfamil® Premature LIPIL® 20 kcal/ fl oz. and 24 kcal/ fl oz. mixtures (Mead Johnson & Company, Evansville, IN, 47721) (8).

* indicates no value given on product label or in product information.

** indicates that conclusions do not address this component (3).