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Medical Position Paper

Global Standard for the Composition of Infant Formula: Recommendations of an ESPGHAN Coordinated International Expert Group

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ABSTRACT
The Codex Alimentarius Commission of the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) develops food standards, guidelines and related texts for protecting consumer health and ensuring fair trade practices globally. The major part of the world's population lives in more than 160 countries that are members of the Codex Alimentarius. The Codex Standard on Infant Formula was adopted in 1981 based on scientific knowledge available in the 1970s and is currently being revised. As part of this process, the Codex Committee on Nutrition and Foods for Special Dietary Uses asked the ESPGHAN Committee on Nutrition to initiate a consultation process with the international scientific community to provide a proposal on nutrient levels in infant formulae, based on scientific analysis and taking into account existing scientific reports on the subject. ESPGHAN accepted the request and, in collaboration with its sister societies in the Federation of International Societies on Pediatric Gastroenterology, Hepatology and Nutrition, invited highly qualified experts in the area of infant nutrition to form an International Expert Group (IEG) to review the issues raised. The group arrived at recommendations on the compositional requirements for a global infant formula standard which are reported here. ***JPGN 41:584–599, 2005.*** **Key Words:** Bottle feeding—Food standards—Infant food—Infant formula—Infant nutrition—Nutritional requirements. © 2005 Lippincott Williams & Wilkins

BACKGROUND OF THE ESPGHAN COORDINATED INTERNATIONAL EXPERT GROUP CONSULTATION

The Codex Alimentarius Commission was created in 1963 by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) to develop food standards, guidelines and related texts such as codes of practice under

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the Joint FAO/WHO Food Standards Program (www.codexalimentarius.net). The main purposes of this program are protecting the health of consumers and ensuring fair trade practices in the food trade, and promoting coordination of all food standards work undertaken by international governmental and nongovernmental organizations. The major part of the world's population lives in more than 160 countries that are members of the Codex Alimentarius. The Codex Alimentarius has developed a large number of standards in the area of food quality and safety, which are of paramount importance for the protection of public health and fair trade on all continents.

Codex Standard 72 on Infant Formula (1) was adopted in 1981 and is based on scientific knowledge as available in the 1970s. In view of the progress in the scientific understanding of nutritional needs of infants and in the methods of formula production, the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) agreed to develop a revision of this standard with a part A defining the requirements of infant formulae (intended to meet the normal nutritional requirements of infants) and a part B defining the requirements of foods for special medical purposes for infants (FSMP; intended for infant patients with special dietary needs due to diseases). An Electronic Working Group (EWG) was charged to seek agreement on the essential composition of infant formula, but due to time constraints and other factors could not finish its task.

Therefore, CCNFSDU decided in November 2004 to request additional advice from an international group of scientific experts in the area of infant nutrition. CCNFSDU asked the Committee on Nutrition of ESPGHAN (The European Society for Pediatric Gastroenterology, Hepatology and Nutrition), which is a member of the EWG, to coordinate this exercise. ESPGHAN was asked to initiate a consultation process with the international scientific community to provide proposals on nutrient levels in infant formulae, based on scientific analysis and taking into account existing scientific reports on the subject. It was requested that the scientific advice for possible solutions should be provided in a clearly stated, transparent and comprehensible manner. This paper is expected by CCNFSDU to facilitate the process of decision taking at the following 27th session of this Codex Committee in November 2005.

ESPGHAN accepted the request and, in collaboration with its sister societies in the global Federation of International Societies on Pediatric Gastroenterology, Hepatology and Nutrition (FISPGHAN), invited highly qualified experts in the area of infant nutrition to form an International Expert Group (IEG) to review the issues raised. Criteria for participation in the IEG included expertise in pediatric nutrition research and active contributions to international scientific societies or advisory bodies dealing with pediatric nutrition issues. In order to ensure that experts were in a position to provide objective and disinterested scientific advice, all participating experts submitted a written declaration of personal and nonpersonal (institutional) interests. These were reviewed and approved both by the chair of the IEG (BK) and the chair of the CCNFSDU EWG (HP) as a prerequisite for accepting the participation of the respective experts.

The IEG members were provided with background material, including a summary of the status of the CCNFSDU draft standard on infant formula provided by the EWG chair in January 2005. The IEG members reviewed the proposals taking into account the available scientific evidence, including the recent reviews performed by the Life Science Research Office (LSRO) of the American Societies of Nutritional Sciences (2) and the Scientific Committee on Food of the European Commission (SCF) (3). IEG members submitted written comments, and a meeting was held from 26–29 April 2005 at Tutzing (near Munich), Germany to thoroughly discuss all issues. At this meeting, unanimous agreement was reached on each compositional recommendation made in this report. However, after the meeting one IEG member raised concerns with respect to the recommended minimum iron level, because of a recommendation for a higher minimum iron level by the national academy of pediatrics in the member's country, and withdrew the support for this value. All other IEG members maintained their decision in favor of this recommendation. This final report was written, circulated to all IEG members, approved and submitted to the CCNFSDU and its EWG in June 2005.

GENERAL CONSIDERATIONS

The IEG discussed some general considerations as the basis of its deliberations. The IEG recognizes the multiple benefits of breast feeding for child health (4) and strongly supports breast feeding as the ideal form of infant feeding which should be actively promoted, protected and supported. Infant formulae are intended to serve as a substitute for breast milk in infants who cannot be fed at the breast, or should not receive breast milk, or for whom breast milk is not available (5). The composition of infant formulae should serve to meet the particular nutritional requirements and to promote normal growth and development of the infants for whom they are intended.

Data on the composition of human milk of healthy, well-nourished women can provide some guidance for the composition of infant formulae, but gross compositional similarity is not an adequate determinant or indicator of the safety and nutritional adequacy of infant formulae. Human milk composition shows remarkable variation. Moreover, there are considerable differences in the bioavailability and metabolic effects of similar contents of many specific nutrients in human milk and formula, respectively. Therefore, the adequacy of infant formula composition should be determined by a comparison of

its effects on physiological (e.g. growth patterns), biochemical (e.g. plasma markers) and functional (e.g. immune responses) outcomes in infants fed formulae with those found in populations of healthy, exclusively breast-fed infants.

The IEG concludes that infant formulae should only contain components in such amounts that serve a nutritional purpose or provide another benefit. The inclusion of unnecessary components, or unnecessary amounts of components, may put a burden on metabolic and other physiologic functions of the infant. Those components taken in the diet, which are not utilized or stored by the body, have to be excreted, often as solutes in the urine. Since water available to form urine is limited and the infant's ability to concentrate urine is not fully developed during the first months of life, the need to excrete any additional solutes will reduce the margin of safety, especially under conditions of stress, such as fever, diarrhea or during weight loss.

Minimum and maximum values of nutrient contents in infant formulae are suggested with the goal to provide safe and nutritionally adequate infant formula products that meet the nutritional requirements of healthy babies. The IEG considered that such minimum and maximum values should be based, where available, on adequate scientific data on infant requirements and the absence of adverse effects. In the absence of an adequate scientific evaluation, minimum and maximum values should at least be based on an established history of apparently safe use. The establishment of minimum and maximum values also should take into account, where possible, other factors such as bioavailability and losses during processing and shelf life. Minimum and maximum values refer to total nutrient contents of infant formulae as prepared ready for consumption according to the instructions of the manufacturer.

While the IEG bases its conclusions on a considered review of the evidence available at this time, it recognizes that future scientific progress will necessitate revisiting and updating the compositional standards for infant formulae. The IEG considers it an obligation for Codex Alimentarius to review, on a regular basis, the adequacy of its compositional standards for infant foods.

The IEG recommends that the addition of new ingredients to infant formulae, or of established ingredients in newly determined amounts beyond the existing standards on formula composition, should be made possible if the safety, benefits and suitability for nutritional use by infants have been established by generally accepted scientific data. Given the accumulating evidence that the composition of the diet of infants has a major impact on short and long term child health and development, the IEG finds it imperative that the scientific evidence to support modifications of infant formulae beyond the established standards must always be overseen and evaluated by independent scientific bodies before the acceptance of the introduction of such products to the market.

RECOMMENDATIONS FOR INFANT FORMULA COMPOSITION

Infant formula is a product based on milk of cows or other animals and/or other ingredients which have been proven to be suitable for infant feeding. The nutritional safety and adequacy of infant formula should be scientifically demonstrated to support normal growth and development of infants.

Infant formula prepared ready for consumption in accordance with instructions of the manufacturer shall contain per 100 ml not less than 60 kcal (250 kJ) and not more than 70 kcal (295 kJ) of energy, and it shall contain per 100 kcal the nutrients, with minimum and maximum levels where applicable, as listed in Table 1.

In addition to the compositional requirements listed in Table 1, other ingredients may be added to ensure that the formulation is suitable as the sole source of nutrition for the infant, or to provide other benefits that are similar to outcomes of populations of breastfed babies (Table 2). The IEG takes the view that the mere presence of a substance in human milk by itself does not justify its addition to formula, but that a benefit of the addition should be shown.

The suitability for the particular nutritional uses of infants and the safety of additional compounds added at the chosen levels shall be scientifically demonstrated. The formula shall contain sufficient amounts of these substances that have been demonstrated to achieve the intended effect. The IEG concludes that only limited orientation can be deducted from levels of components in human milk in view of possible differences in bioavailability and the fact that substances other than components found in human milk may need to be used to achieve the desired effects in infants.

COMMENTS

The available scientific information on infant nutrient needs and evaluation of infant formula composition has recently been reviewed (2,3). Therefore, no attempt is made to review here the totality of the available information; rather, our comments focus on issues where different views have arisen in the past.

Proteins from the milk of animals other than cows or from various plant sources are considered potentially suitable for use in infant formulae. However, the suitability and safety should be adequately evaluated and documented for each protein source to be used. At this time the IEG does not recommend to refer to specific animal protein sources other than cows' milk in the text of the standard. As of today, most of the evidence published in the international literature that includes conclusive studies in human infants is limited to the evaluation of cows' milk or soy protein based infant formulae.

TABLE 1. *Proposed compositional requirements of infant formula*

Component	Unit	Minimum	Maximum
Energy	kcal/100 ml	60	70
Proteins			
Cows' milk protein	g/100 kcal	1.8*	3
Soy protein isolates	g/100 kcal	2.25	3
Hydrolyzed cows' milk protein	g/100 kcal	1.8†	3
Lipids			
Total fat	g/100 kcal	4.4	6.0
Linoleic acid	g/100 kcal	0.3	1.2
α-linolenic acid	mg/100 kcal	50	NS
Ratio linoleic/α-linolenic acids		5:1	15:1
Lauric + myristic acids	% of fat	NS	20
Trans fatty acids	% of fat	NS	3
Erucic acid	% of fat	NS	1
Carbohydrates			
Total carbohydrates‡	g/100 kcal	9.0	14.0
Vitamins			
Vitamin A	μg RE/100 kcal§	60	180
Vitamin D_3	μg/100 kcal	1	2.5
Vitamin E	mg α-TE/100 kcal‖	0.5¶	5
Vitamin K	μg/100 kcal	4	25
Thiamin	μg/100 kcal	60	300
Riboflavin	μg/100 kcal	80	400
Niacin#	μg/100 kcal	300	1500
Vitamin B_6	μg/100 kcal	35	175
Vitamin B_{12}	μg/100 kcal	0.1	0.5
Pantothenic acid	μg/100 kcal	400	2000
Folic acid	μg/100 kcal	10	50
Vitamin C	mg/100 kcal	8	30
Biotin	μg/100 kcal	1.5	7.5
Minerals and trace elements			
Iron (formula based on cows' milk protein and protein hydrolysate)	mg/100 kcal	0.3**	1.3
Iron (formula based on soy protein isolate)	mg/100 kcal	0.45	2.0
Calcium	mg/100 kcal	50	140
Phosphorus (formula based on cows' milk protein and protein hydrolysate)	mg/100 kcal	25	90
Phosphorus (formula based on soy protein isolate)	mg/100 kcal	30	100
Ratio calcium/phosphorus	mg/mg	1:1	2:1
Magnesium	mg/100 kcal	5	15
Sodium	mg/100 kcal	20	60
Chloride	mg/100 kcal	50	160
Potassium	mg/100 kcal	60	160
Manganese	μg/100 kcal	1	50
Fluoride	μg/100 kcal	NS	60
Iodine	μg/100 kcal	10	50
Selenium	μg/100 kcal	1	9
Copper	μg/100 kcal	35	80
Zinc	mg/100 kcal	0.5	1.5
Other substances			
Choline	mg/100 kcal	7	50
Myo-inositol	mg/100 kcal	4	40
L-carnitine	mg/100 kcal	1.2	NS

*The determination of the protein content of formulae based on non-hydrolyzed cows' milk protein with a protein content between 1.8 and 2.0 g/100 kcal should be based on measurement of true protein ([total N minus NPN] × 6.25) (31).

†Formula based on hydrolyzed milk protein with a protein content less than 2.25 g/100 kcal should be clinically tested.

‡Sucrose (saccharose) and fructose should not be added to infant formula.

§1 μg RE (retinol equivalent) = 1 μg all-trans retinol = 3.33 IU vitamin A. Retinol contents shall be provided by preformed retinol, while any contents of carotenoids should not be included in the calculation and declaration of vitamin A activity.

‖1 mg α-TE (α-tocopherol equivalent) = 1 mg d-α-tocopherol.

¶Vitamin E content shall be at least 0.5 mg α-TE per g PUFA, using the following factors of equivalence to adapt the minimal vitamin E content to the number of fatty acid double bonds in the formula: 0.5 mg α-TE/g linoleic acid (18:2n-6); 0.75 mg α-TE/g α-linolenic acid (18:3n-3); 1.0 mg α-TE/g arachidonic acid (20:4n-6); 1.25 mg α-TE/g eicosapentaenoic acid (20:5n-3); 1.5 mg α-TE/g docosahexaenoic acid (22:6n-3).

#Niacin refers to preformed niacin.

**In populations where infants are at risk of iron deficiency, iron contents higher than the minimum level of 0.3 mg/100 kcal may be appropriate and recommended at a national level.

NS, not specified.

TABLE 2. *Proposed levels of optional ingredients, if added*

Optional ingredients	Unit	Minimum	Maximum
Taurine	mg/100 kcal	0	12
Total added nucleotides	mg/100 kcal	0	5
Cytidine 5′-monophosphate (CMP)	mg/100 kcal	0	1.75
Uridine 5′-monophosphate (UMP)	mg/100 kcal	0	1.5
Adenosine 5′-monophosphate (AMP)	mg/100 kcal	0	1.5
Guanosine 5′-monophosphate (GMP)	mg/100 kcal	0	0.5
Inosine 5′-monophosphate (IMP)	mg/100 kcal	0	1.00
Phospholipids	mg/100 kcal	0	300
Docosahexaenoic acid*	% of fat	0	0.5

*If docosahexaenoic acid (22:6n-3) is added to infant formula, arachidonic acid (20:4n-6) contents should reach at least the same concentration as DHA. The content of eicosapentaenoic acid (20:5n-3) should not exceed the content of docosahexaenoic acid.

The IEG discussed whether one should always provide a label declaration on energy density per unit of powder, or of nutrient content per g powder or per unit of formula as ready for consumption. While it was appreciated that national authorities may choose to request additional label information, no necessity was seen to introduce a general requirement. In this report nutrient contents of infant formulae are generally given per unit of energy (here per 100 kcal), which is physiologically meaningful.

Energy Density

Studies with current methodology have revealed an average energy density of human milk of about 650 kcal/L (6,7), which is some 5–10% less than previously assumed (8). Also, total energy expenditure of infants was found to be lower than previously assumed. A milk energy density markedly higher than typically found in human milk may increase total energy intake and lead to a higher than desirable weight gain. A high weight gain in healthy infants has been associated with an increased risk of later obesity (9,10). The IEG proposes an energy density of infant formulae in the range of 60–70 kcal/100 ml, which is appropriate to support physiological rates of weight gain in healthy infants.

Proteins

Sources of Proteins

Minimum and maximum values are provided for cows' milk proteins, soy protein isolates, and hydrolyzed cows' milk proteins because published data are available for these protein sources that allow the delineation of such minimum and maximum values (2,3). The suitability for use in infant formulae of other proteins sources and their adequate minimum and maximum amounts should be documented on a case-by-case basis. With the information available to the IEG from the published and internationally accessible scientific literature, no recommendations can be made at this time for minimum and maximum amounts of other protein sources.

Nitrogen Conversion Factor

The definition of minimum and maximum values for protein contents requires a prior agreement on the method of calculation of protein, which is usually based on a measurement of nitrogen content multiplied by a conversion factor. Different food proteins contain differing amounts of nitrogen, however, FAO/WHO use a factor of 6.25 for all their reports on protein requirement and quality, based on a 16% (by weight) nitrogen content of mixed protein. For unmodified cows' milk protein a nitrogen conversion factor of 6.38 (i.e. 15.7% nitrogen by weight of total protein) has been determined in the 19th century (11) and is widely used in Codex Standards on milk proteins, both whey and casein, until today. The IEG has no objection to the use of a nitrogen conversion factor of 6.38 for unmodified cows' milk protein and whole cows' milk in general food products, but it also has no objection to the default use of a nitrogen conversion factor of 6.25 in the Codex Alimentarius Guidelines on Nutrition Labeling (12). However, when considering the choice of a nitrogen conversion factor for infant formula protein it is important to appreciate the rather different nitrogen conversion factors of various proteins and protein fractions in bovine milk (Table 3) (13).

Proteins derived from cows' milk used in current infant formulae are usually modified, e.g. enriched in whey protein fractions and other nitrogen containing components with lower N conversion factors than caseins

TABLE 3. *Milk contents and nitrogen conversion factors for isolated bovine milk proteins (without carbohydrate), and for protein fractions**

Bovine milk proteins and protein fractions	Content in milk (g/L)	N conversion factor
α_{s1}-Casein	10.0	6.36
α_{s2}-Casein	2.6	6.29
β-Casein	9.3	6.37
κ-Casein	3.3	6.12
γ-Casein	0.8	6.34
α-Lactalbumin	1.2	6.25
Bovine serum albumin	0.4	6.07
Immunoglobulin	0.8	6.00
Proteose-peptone 5, 8F, 8S	0.5	6.54
Proteose-peptone 3	0.3	5.89
Lactoferrin	0.1	5.88
Milk fat globule membrane	0.4	6.60
Whole milk	33.0	6.31
Acid casein		6.33
Paracasein		6.31
Acid whey		6.21
Rennet whey		6.28

*Adapted from 71.

(Table 3). Variations of nonprotein nitrogen (NPN) contents in infant formulae depending on the methods of production result in further marked changes of the nitrogen conversion factor. Therefore, the use of a nitrogen conversion factor of 6.38 for all milk derived protein sources in infant formulae is not justified. While it would be theoretically conceivable that an individual nitrogen conversion factor might be determined for each product, based on an analysis of its contents of total nitrogen, amino acids and nonprotein nitrogen, this is not feasible in practice. Therefore, it is recommended to use the following calculation for all types of infant formula:

protein content of infant formulae (g) = nitrogen (g) × 6.25

It is emphasized here that the recommendations made by the IEG on formula protein contents are based on this nitrogen conversion factor and cannot be used without adaptation if other nitrogen conversion factors are applied.

Nonprotein Nitrogen

It has been proposed that a maximum level of nonprotein nitrogen (NPN) contents in infant formulae should be set (3), because the proportional content of metabolizable amino acids is usually expected to decrease with a higher percentage of total nitrogen comprised by NPN. In human milk some 20–25% of total nitrogen is contributed by nonprotein nitrogen (NPN), of which up to 50% may be metabolically used (14,15). NPN contents in infant formulae, which tend to be used to a lesser extent by the recipient infants, may account for up to 20% of total nitrogen in formulae based on nonhydrolyzed cows' milk proteins, while relatively high NPN contents may be found in some whey fractions separated by ion-exchange, electrodialysis or ultrafiltration, and up to 25% or more in infant formulae based on soy protein isolates that are partially hydrolyzed for technological reasons, or in infant formulae based on cows' milk protein hydrolysates (2,3,16,17). The IEG discussed this question extensively and acknowledges that the definition of protein quality by a maximum content of NPN has some limitations. For example, the addition of some whey based fractions and other nitrogen containing compounds may increase the biologic value of the formula along with increasing NPN content. Furthermore, the same maximum value for NPN content cannot be applied to formulae based on intact milk proteins as well as formulae based on hydrolyzed milk proteins or soy protein isolates, because the latter two types of formulae contain a larger portion of nitrogen as NPN. The IEG also concluded that the setting of a minimal amount of total nitrogen and of dietary indispensable amino acids (cf. Table 4), along with the general requirement that infant formula should serve to promote normal infant growth and development, would generally suffice to assure an adequate nitrogen intake. Therefore, the IEG concludes that there is no general necessity to limit the maximum NPN content in infant formulae, provided that the other requirements recommended in this report are fulfilled.

TABLE 4. *Proposed values for amino acid contents in the human milk reference protein expressed as g/100 g protein and as mg/100 kcal*

Amino acid	g/100 g protein	mg/100 kcal
Cystine	2.1	38
Histidine	2.3	41
Isoleucine	5.1	92
Leucine	9.4	169
Lysine	6.3	114
Methionine	1.4	24
Phenylalanine	4.5	81
Threonine	4.3	77
Tryptophan	1.8	33
Tyrosine	4.2	75
Valine	4.9	99

Infant formula should contain per 100 kcal an available quantity of each of the amino acids listed at least equal to that contained in the reference protein, as shown in this table. For calculation purposes, the concentrations of phenylalanine and tyrosine may be added together if the phenylalanine to tyrosine ratio is in the range of 0.7–1.5 to 1, and the concentrations of methionine and cysteine may be added together if the methionine to cysteine ratio is in the range of 0.7–1.5 to 1.

Amino Acid Contents of Human Milk Protein and Requirements for Amino Acid Contents of Formula Protein

The principal nutritional function of food protein is to meet physiological needs by supplying adequate amounts of dietary indispensable (essential) and of dietary conditionally indispensable (conditionally essential) amino acids, and of total nitrogen. In agreement with LSRO and SCF (2,3), the IEG recommends that evaluation of formula protein composition should use an amino acid score based on human milk protein composition as the reference.

The mean amino acid contents in human milk have been calculated by the LSRO report based on analyses published in the 1980s and 1990s (18–21). However, one of these publications is on transitional milk (21), and only one has analyzed complete 24-hour collections of human milk (18). The Food and Nutrition Board of the Institute of Medicine (22) proposed a modified amino acid pattern of human milk, based on 4 references (18,23–25). The reference unit in the different sources is not the same although expressed as mg amino acid per g protein. For example ''protein'' is the sum of total anhydrous amino acids (18,24) or total nitrogen multiplied by 6.38 (23) or total nitrogen minus NPN multiplied by an unknown factor (25). To avoid this problem it seems advisable to refer the individual amino acid content to the nitrogen content to avoid confusion about the nature of the protein calculation, as suggested by the

SCF (3). The IEG has calculated mean values based on published studies on the amino acid content of human milk, taking into account reports with measurements of the total nitrogen content and/or the calculation method for the protein content, including a reference on a large number of human milk samples published in the Japanese language (26) which had not been considered in the previous reports of LSRO and SCF (2,3) (Table 5). These values are also expressed as content of amino acids in mg/g protein (total nitrogen × 6.25) and as mg amino acids/100 kcal, based on a minimum protein content of 1.8 g/100 kcal (Table 4). These calculated values are very similar to those previously suggested by LSRO and SCF.

Infant formula should contain per 100 kcal an available quantity of the amino acids listed in Table 4 in amounts at least equal to those contained in the reference protein. For calculation purposes, the concentrations of phenylalanine and tyrosine, and of methionine and cysteine, respectively, may be added together if the phenylalanine to tyrosine ratio or the methionine to cysteine ratio, respectively, is in the range of 0.7–1.5:1, which is the usual range of these ratios in both human milk and body protein (27–29). The IEG sees no necessity to set maximum levels of individual amino acid contents in infant formulae if the maximum levels of protein are set as recommended.

Protein Content in Infant Formulae Based on Cows' Milk Protein

The available data suggest that a crude protein content of 1.8 g/100 kcal in infant formula, while higher than the protein supply with breast milk, may be marginal for normal growth in young infants, and thus the amount of amino acids supplied to the infant at such low levels of nitrogen intake appears to be critical (2,3). Therefore, it is recommended that protein contents of formulae with a crude protein content (30) between 1.8 and 2.0 g/100 kcal should be based on measurement of true protein ([total N minus NPN] × 6.25) (31), to guarantee a minimum amount of amino acid nitrogen available for protein synthesis. Protein content of infant formula should not exceed 3 g/100 kcal.

Protein Contents in Infant Formulae Based on Hydrolyzed Cows' Milk Proteins

A variety of different cows' milk protein hydrolysates have been used in infant formulae, which may differ in total content, relative composition and bioavailability of amino acids. While the term ''partial'' has sometimes been used to characterize a less extensive degree of protein hydrolyzation, there are no agreed criteria to strictly define a ''partial hydrolysate''; therefore, the use of this term is not supported. Major differences have been reported for different protein hydrolysate formulae with respect to nitrogen retention and growth in the recipient infants (32,33), which point to a potentially significant variation in the biologic value of different hydrolysates. For optimal utilization the hydrolyzed protein source should have a pattern of indispensable amino comparable to that shown in Table 5. The IEG recommends that infant formulae based on cows' milk protein

TABLE 5. *Amino acid content of human milk from published studies which report measurements of the total nitrogen content and/or the calculation method for the protein content, expressed as mg per gram nitrogen*

	Authors								
	Lönnerdal & Forsum (1985) (72)	Darragh & Moughan (1998) (23)	Bindels & Harzer (1985) (73)	Janas et al. (1987) (19)	Villalpando et al. (1998) (25)		Räihä et al. (2002) mod. Nayman et al. (1979) (74)	Yonekubo et al. (1991) (26)	
					24 hours, pooled @ 4–6 months				
Samples	Pooled bank milk @ 4–16 weeks	Pooled over 20 days @ 10–14 weeks (n = 20)	24 hours, pooled @ 5 weeks (n = 10)	24 h pooled @ 8 weeks (n = 10)	Mexico 40	Houston 40	Pooled bank milk @ >1 month	Milk @ 21 days–2 months	**Mean amino acid content (mg/g nitrogen)**
Arginine	157	200	281	184	168	184	172	223	**196**
Cystine (half)	111	173	108	101	167	134	133	118	**131**
Histidine	111	156	255	112	112	108	122	150	**141**
Isoleucine	242	333	376	306	292	331	300	374	**319**
Leucine	457	598	713	611	528	541	572	667	**586**
Lysine	314	406	522	365	366	408	361	421	**395**
Methionine	78	90	89	73	99	76	83	92	**85**
Phenylalanine	153	243	344	183	440	439	217	240	**282**
Threonine	217	316	344	251	248	242	256	269	**268**
Tryptophan	NA	NA	172	79	112	89	111	122	**114**
Tyrosine	201	241	369	191	292	299	233	249	**259**
Valine	253	327	376	267	286	331	317	364	**315**

NA, not analyzed.

hydrolysates with a content of protein hydrolysate less than 2.25 g/100 kcal should be clinically tested, and such products should only be accepted if the results have been evaluated by an independent scientific body before introduction into the market. The protein content of infant formulae based on cows' milk protein hydrolysates should not be less than 1.8 g/100 kcal and not be greater than 3.0 g/100 kcal.

Protein Contents in Infant Formulae Based on Soy Protein Isolates

A higher minimum protein level is recommended for infant formulae with intact proteins other than intact cows' milk protein, to correct for potentially lesser digestibility and biologic value of the nitrogen content, considering that there is a paucity of data documenting adequacy. Formulae based on soy protein isolates should have a minimum protein content of 2.25 g/100 kcal and a maximum protein content of 3.0 g/100 kcal.

Lipids

Total Fat

The recommended total fat content of 4.4–6.0 g/100 kcal is equivalent to about 40–54% of energy content which is similar to values found typically in human milk (34).

Essential Fatty Acids

A linoleic acid (18:2n-6) content of 300 mg/100 kcal (about 2.7% of energy intake) suffices to cover the minimum linoleic acid requirement. A maximum value for linoleic acid content of 1200 mg/100 kcal is considered necessary because high intakes may induce untoward metabolic effects with respect to lipoprotein metabolism, immune function, eicosanoid balance and oxidative stress.

The omega-3 fatty acid α-linolenic acid (18:3n-3) is considered a dietary indispensable fatty acid and serves as a precursor for the synthesis of docosahexaenoic acid (22:6n-3), whose availability has been related to infant development. However, under certain circumstances high intakes of α-linolenic acid may increase the risk of lipid peroxidation, product rancification, and may adversely affect formula stability. Given the limited knowledge on the activity of in vivo formation of docosahexaenoic acid from the precursor α-linolenic acid and on α-linolenic acid requirements in infancy, a minimum α-linolenic acid (18:3n-3) content of 50 mg/100 kcal (about 0.45% of energy intake) is recommended.

To ascertain a proper balance between linoleic and α-linolenic acids as well as the long-chain polyunsaturated fatty acids (LC-PUFA) and eicosanoids resulting from their metabolism, a linoleic/α-linolenic acid ratio in the range of 5–15 to 1 is recommended. The implementation of this ratio also results in an appropriate limitation of the α-linolenic acid contents to no more than 1/5 of 1200 mg/100 kcal, i.e. 240 mg/100 kcal. Therefore, no further maximum level of α-linolenic acid needs to be set.

Lauric and Myristic Acids

In consideration of the potential negative effects of lauric acid and myristic acid on serum cholesterol and lipoprotein concentrations, the sum of myristic acid and lauric acid should not exceed 20% of total fat contents.

Trans Fatty Acids

Trans fatty acids have no known nutritional benefit for infants, but a number of untoward biologic effects have been attributed to trans fatty acid consumption, such as impairment of microsomal desaturation and chain elongation of essential fatty acids, alterations of lipoprotein metabolism and potential impairment of early growth (35–37). Therefore, prudence dictates the limitation of these substances in infant formulae (2). Considering that the concentration of trans fatty acids in bovine milk fat varies, that formulae may contain as much as 40–50% of the fat as bovine milk fat, and also taking the view that the use of hydrogenated oils in infant and follow-on formulae should be discouraged, the IEG recommends that the contents of trans fatty acids should not exceed 3% of total fat content.

Erucic Acid

While erucic acid has no known nutritional benefit for infants, observations in animals have indicated potential myocardial alterations. The IEG recommends that erucic acid contents acids should not exceed 1% of total fat content.

Carbohydrates

Total Carbohydrates

Carbohydrates are an essential source of energy for the infant. Taking into account the glucose needs of the human brain, the recommended minimum total carbohydrate content of 9.0 g/100 kcal is based on a calculation of glucose needs for obligatory central nervous system oxidation while minimizing the contribution of gluconeogenesis (2,3). The IEG proposes a maximum carbohydrate content of 14.0 g/100 kcal being equivalent to about 56% of energy content.

Lactose

The dominant digestible carbohydrate in human milk is lactose, which provides about 40% of the energy value. Lactose is considered to provide beneficial effects for

gut physiology, including prebiotic effects, softening of stools, and enhancement of water, sodium and calcium absorption. Therefore, the IEG considers it prudent to include lactose in infant formula. However, a specific need of young infants for lactose has not been demonstrated. The possible beneficial effects of lactose on gut physiology, gut microflora, stool consistency, and the absorption of water, sodium and calcium by passive nonsaturable diffusion are not restricted to lactose, but may at least in part be achieved by other components in infant formula. Therefore, no minimum or maximum levels can be set based on available scientific evidence.

Glucose

Glucose is found only in minor amounts in human milk and is considered unsuitable for routine use in infant formula. During heat treatment of formula, glucose may react nonenzymatically with protein and form Maillard products (2). The addition of glucose to infant formula would also lead to a marked increase of osmolality, which is not desirable and may cause untoward effects in the recipient infants; the addition of 1 g glucose per 100 ml formula increases osmolality by 58 mOsm/kg. Therefore, the addition of glucose to infant formulae is not recommended.

Sucrose (saccharose) and Fructose

Feeding of formulae with added fructose or sucrose, a disaccharide containing glucose and fructose, may lead to severe adverse effects including death in young infants affected by hereditary fructose intolerance. Hereditary fructose intolerance (aldolase B or fructose-1-phosphate aldolase deficiency) is a potentially fatal disease with a reported incidence as high as 1:20,000 in some populations. Affected young infants fed fructose or saccharose containing formulae develop hypoglycemia, vomiting, malnutrition, liver cirrhosis and particularly at a young age also sudden death. Given the severe adverse effects of dietary fructose supply in early infancy, the IEG recommends that sucrose and fructose should not be added to infant formulae intended for feeding during the first 4–6 months of life.

Starches

Considering the ability of infants to digest starches and the possible need to include some starch contents in infant formulae for technological reasons, the IEG supports that starches (precooked or gelatinized) may be added to infant formulas up to 30% of total carbohydrates or up to 2 g/100 ml.

Vitamins

Lipid Soluble Vitamins

The lipid-soluble vitamins A, E, D and K are deposited in body fats, such as adipose tissue. High intakes over prolonged periods of time may thus lead to their tissue accumulation and may induce untoward effects. Therefore, both too low and too high intakes should be avoided.

Vitamin A

Considering vitamin A contents in human milk, a presumed higher bioavailability from human milk than infant formula, reference intake values and upper tolerable intake levels, a content of 60–180 μg RE/100 kcal (retinol equivalent, 1 μg RE = 3.33 IU vitamin A = 1 μg all-*trans* retinol) is recommended. Since the relative equivalence of β-carotene and retinol in infants is not known and previously assumed equivalence factors may not be adequate, vitamin A contents in infant formulae should be provided by retinol or retinyl esters, while any contents of carotenoids should not be included in the calculation and declaration of vitamin A activity.

Vitamin D

No conclusive evidence is available to allow a comparative assessment of the biologic activity of dietary vitamin D_3 and vitamin D_2 in infants. Therefore, it is recommended to continue to use vitamin D_3 in infant formulae, rather than vitamin D_2, until such comparative data might become available. In agreement with the considerations discussed by previous expert panels (2,3), a vitamin D_3 content in the range of 1–2.5 μg/100 kcal is recommended.

Vitamin E

Infant formula should contain 0.5–5 mg α-TE/100 kcal (α-tocopherol equivalent, 1 mg α-TE = 1 mg d-α-tocopherol), but not less than 0.5 mg/g linoleic acid or equivalent. A maximum intake of 5 mg will more than suffice to protect the proposed maximum contents of polyunsaturated fatty acids in the order of 1.5 g/100 kcal. Since vitamin E requirements have been reported to increase with the number of double bonds contained in the dietary fatty acid supply (38), the following factors of equivalence should be used to adapt the minimal vitamin E content to the formula fatty acid composition: 0.5 mg α-TE/g linoleic acid (18:2n-6), 0.75 mg α-TE/α-linolenic acid (18:3n-3), 1.0 mg α-TE/g arachidonic acid (20:4n-6), 1.25 mg α-TE/g eicosapentaenoic acid (20:5n-3), and 1.5 mg α-TE/g docosahexaenoic acid (22:6n-3).

Vitamin K

Reference intakes in infancy have been set in the order of 4–10 μg/d (3). Vitamin K levels of current infant formulae, usually above 4 μg/100 kcal, provide an effective protection against vitamin K deficiency and the occurrence of bleeding and may provide a certain level of safety even under some conditions of incomplete vitamin K absorption (39). A population wide daily supplement of 25 μg vitamin K_2 is provided to infants in the Netherlands (40) and oral supplementation of infants with several mg vitamin K is given during the first weeks of life in different countries without any indication of untoward effects. No known toxicities are associated with a formula content of 25 μg/100 kcal (2). Infant formula should contain 4–25 μg/100 kcal.

Water Soluble Vitamins

General Considerations on Minimum and Maximum Levels

Minimum levels of each vitamin in formula, when consumed in normal amounts, should ensure that the infant is able to grow and develop normally and not be at risk of developing an inadequate nutritional status. Minimum levels in infant formulae have been derived from reference nutrient intakes for infants per day based on the model of an infant with a weight of 5 kg and a formula consumption of 500 kcal/d. Maximum levels should ensure that the infant is not exposed to the risk of excess. Since water soluble vitamins supplied in amounts that cannot be utilized or stored by the body must to be excreted, excessive intakes will reduce the margin of safety, especially under conditions of stress, such as during fever or diarrhea or especially during weight loss (41). Tolerance will vary amongst individuals, with age and other circumstances. However, once adequate allowance has been made to ensure that the normal requirements have been met, a reasonable margin of safety would not be expected to require an intake in excess of two to five times the requirement, unless there is clear evidence to justify an alternative. Nutrients added for technological reasons would not be expected to be present in amounts greater than five times the requirement, without clear evidence to justify an alternative. The IEG notes that very high intakes of water soluble vitamins exceeding five times the requirements have generally not been subjected to systematic evaluation in infants with respect to their biologic effects and potential interaction with other formula components, and the safety of such high intakes in infancy has generally not been documented. The IEG sees no reason to add to infant formulae excessive amounts of any nutrient that do not serve any nutritional purpose or provide any other benefit, and the effects of which have not been evaluated. Therefore, the contents of water-soluble vitamins in infant formulae generally should not exceed five times the minimum level.

Thiamin (vitamin B_1)

In view of a reference or adequate intake for infants of 200–300 μg/d (42–44), infant formulae should contain 60–300 μg/100 kcal.

Riboflavin (vitamin B_2)

Considering a reference or adequate intake for infants of 300–400 μg/d (42–44), infant formulae should contain 80–400 μg/100 kcal.

Niacin (vitamin B_3)

Given that niacin contents in human milk have been reported in the range of about 164–343 μg/100 kcal (45), infant formulae should contain 300–1500 μg/100 kcal. These niacin contents of infant formulae apply to preformed niacin.

Pantothenic Acid (vitamin B_5)

Taking a reference or adequate intake for infants of 200–400 μg/d into account (42,43), infant formulae should contain 60–300 μg/100 kcal.

Pyridoxine (vitamin B_6)

Considering mature human milk contents of about 10–45 μg/100 kcal) (45), infant formula contents of 35–175 μg/100 kcal are recommended.

Cobalamin (vitamin B_{12})

Considering average human milk contents (45) and a reference intake for infants of 0.3–0.5 μg/d (42), levels in infant formula should be 0.1–0.5 μg/100 kcal.

Folic Acid

In view of an infant reference or adequate intake of 50–65 μg/d (42,44), infant formula should contain 10–50 μg folic acid/100 kcal.

L-ascorbic Acid (vitamin C)

Human milk contains about 4.5–15 mg/100 kcal (2). Infant reference intakes have been set at 20 mg/d (44), 30 mg/d (2) and 40 mg/d (46). A minimum level in infant formula of 10 mg/100 kcal is recommended. High ascorbic acid intakes may induce copper deficiency (47). Therefore, the maximum level in infant formula should be 30 mg/100 kcal.

Biotin

Taking into account reported human milk contents in the range of about 0.75–1.3 μg/100 kcal (45) and the absence of agreed numerical reference intakes for infants, infant formula levels of 1.5–7.5 μg/100 kcal are recommended.

Minerals and Trace Elements

Iron

The IEG reached unanimous consensus on the iron recommendation as outline below, but after the IEG meeting one member (SB) raised concerns regarding these conclusions and supported the previous recommendation by the national academy of pediatrics in the member's country that infant formula should have a minimal iron content of 4 mg/L (about 0.6 mg/100 kcal) (48). In contrast, all the other 15 IEG members maintained their support for the recommendations made below.

In 1981 the Codex Alimentarius infant formula standard set a requirement of a minimum iron content of 1 mg/100 kcal (1). Recent data indicate that lower iron contents can suffice to meet infant iron requirements. During the period when infant formula may be fed exclusively, i.e. before the introduction of complementary foods, infant formulae based on cows' milk protein supplying about 0.25 mg/100 kcal and 0.6 mg/100 kcal resulted in similar iron status and hematology results (49), while previous studies showed no difference for feeding infant formulae with about 0.6 mg and 1.0 mg/100 kcal, respectively (50). Thus, there was no significant difference between infants fed formulae containing 0.25 mg, 0.6 mg and 1.0 mg per 100 kcal, and there were no infants with inadequate iron status in either group.

After the age of 6 months, infant formula is unlikely to be fed exclusively if at all, and the introduction of complementary feeding/Beikost and the stepwise introduction of foods from adult diets are recommended. The IEG addressed the question whether formula feeding together with diets having very low iron contents might induce a risk of developing iron deficiency anemia during this time period. In a study from Chile (51), infants were fed formulae with about 0.34 mg and 1.9 mg/100 kcal, respectively, from 6 to 12 months of age. As these Chilean infants received little additional iron from complementary feeding, this study evaluates whether the lower level of iron fortification would be inadequate in a poor setting. There was no significant difference in prevalence of iron deficiency anemia between groups. Only iron deficiency (ID) with anemia (IDA) has been associated with adverse functional outcomes. Infants fed the formula with the higher level of iron had somewhat higher levels of serum ferritin, greater mean cell volumes and lower erythrocyte protoporphyrin levels. The authors concluded that formulae with relatively small amounts of iron appear to prevent IDA. It is not at all surprising that formula with a higher level of iron fortification results in higher iron status, but this study provides no evidence for 0.34 mg iron/100 kcal being inadequate for preventing iron deficiency anemia in infants during the first six months of life.

A further consideration addressed was the argument that a low iron bioavailability from formula might justify that the minimum level should be kept higher. It has commonly been assumed that iron absorption from breast milk is much higher (about 5-fold) than from infant formula. However, such data were generated more than two decades ago, and there were several methodological problems with these studies. For example, a commonly cited study by Saarinen et al. (52) used an extrinsic labeling technique that is not valid, and what they called ''formula'' was a homemade product made from cows' milk. In addition, infant formulae have developed during the last two decades and ''current infant formulas have a high iron bioavailability, which is an appealing argument for lowering the level of iron fortification in these products'' (53). Recent studies show that iron absorption from both breast milk and modern infant formulae is about 15–20%; thus, there is no major difference in iron absorption between modern infant formulae and human milk (53–56). Therefore, a breast-fed infant consuming 750 ml of milk will absorb 20% of 0.2–0.3 mg/L = 0.03 – 0.05 mg of iron per day. A formula-fed infant consuming 500 kcal/d would absorb 15–20% of 0.3 mg/100 kcal (proposed minimum for cows' milk based formulae) equal to 0.22 – 0.3 mg of iron per day. Thus, infants fed the proposed minimum level would absorb 4–10 times more iron than breast-fed infants.

The IEG considered potential risks associated with providing too much iron in early life. Prior to the deliberations of LSRO (2) there was little evidence suggesting that too much iron could be detrimental. While both Haschke et al. (57) and Lönnerdal and Hernell (50) had shown lower copper status and copper absorption in infants fed formula with a higher level of iron (1.5 mg/100 kcal and 1 mg/100 kcal, respectively), this had not been associated with any functional outcomes. However, in a recent study on Swedish and Honduran infants (4–9 months of age), Swedish breast-fed infants with adequate iron status, who were given iron supplements, had significantly lower length gain than unsupplemented infants (58). This was not observed for the Honduran cohort as such, but when dividing these infants according to iron status which varied much more in Honduras, infants with adequate iron status given iron supplements had significantly lower length gain. Further, infants with adequate iron status who were given iron had a significantly higher prevalence of diarrhea and a marginally higher prevalence of upper respiratory infections. Thus, in both settings, one affluent and one poor population, providing excess iron caused adverse effects.

While it may be argued that the supplemental iron was given in free form and not in formula, basic studies on

iron homeostasis in infants suggest that there may be reasons for concern, regardless of the form of iron provided. In the Swedish cohort described earlier, iron absorption studies with stable isotopes have been performed (59). Iron absorption at 6 months was identical in infants who had received iron supplements for 2 months and those who had not been supplemented. Thus, at this age there is no homeostatic downregulation of iron absorption as would occur in adults. By 9 months of age, iron absorption was significantly lower in Fe-supplemented infants than in nonsupplemented infants. This shows that regulation of iron absorption is immature at a young age and does not start reaching adult levels until after 9 months of age. This was further supported by the fact that hemoglobin and serum ferritin of infants with adequate iron status increased to the same extent as they did in non-supplemented infants (60), i.e. whatever amounts of iron given will be absorbed and accumulated in the body raising the possibility of iron excess. Whether the adverse effects of excess iron are due to pro-oxidative events caused by Fe, interactions with zinc which may affect insulin like growth factor 1 and thereby growth, or the immune system and be related to infection risks, or other factors cannot be determined with certainty at this time. However, the observed effects warrant caution with respect to supplying iron exceeding requirements. Iron contents higher than 1.3 mg/100 kcal provide no additional benefit, but adverse affects on copper status have been observed (50,57).

A further question addressed was whether a minimum iron content of 0.3 mg/100 kcal would be appropriate for all populations. Various bodies, including the World Health Organization, have made efforts to improve the micronutrient supply of infants with complementary foods globally. In many parts of the world, weaning foods containing meat and iron fortified baby foods with a good bioavailability of iron are commonly used between 6–12 months. Thus, many infants receive quite substantial quantities of iron in their diet, and there may be good reasons to allow formula manufacturers to use a level close to the minimum level. However, in populations where infants are at high risk of iron deficiency, iron contents in infant formula higher than the recommended minimal level seem appropriate.

Phytic acid contained in infant formulae based on soy protein isolates inhibits iron absorption (61), therefore, the minimum and maximum irons level in soy-protein based infant formulae should be about 1.5 times higher than in the cows' milk protein-based formulae. Iron content in infant formulae based on cows' milk protein and its hydrolysates should be in the range of 0.3–1.3 mg/100 kcal, whereas infant formulae based on soy protein isolates should have an iron content of 0.45–2.0 mg/100 kcal. It is emphasized that after the age of about 6 months, other iron containing foods should supplement the iron supplied by formulae. In populations where infants are at high risk of iron deficiency, iron contents in infant formula higher than 0.3 mg/kcal may be appropriate, and national authorities may choose to stipulate iron contents which they consider appropriate.

Calcium

In view of the lower bioavailability of calcium from infant formulae than from cows' milk, and in agreement with previous expert consultations (2,3), a calcium content of 50–140 mg/100 kcal is recommended.

Phosphorus

The bioavailable fraction of total phosphorus contents is about 80% in formulae based on cows' milk proteins and their hydrolysates, and about 70% in soy protein isolate based formulae (2,3). While it is theoretically conceivable to set a level of absorbable phosphorus in infant formulae, the in vivo bioavailability is difficult to determine and no standard method has been established. Therefore, different levels of phosphorus contents in formulae based on cows' milk proteins and their hydrolysates (25–90 mg/100 kcal), and on soy protein isolates (30–100 mg/100 kcal) are recommended.

Calcium-Phosphorus Ratio

In view of possible untoward effects of unbalanced ratios between calcium and phosphorus contents and in line with previous expert consultations (2,3), the calcium-phosphorus-ratio (weight/weight) should not be less than 1:1 and not be greater than 2:1.

Magnesium

Infant formula should contain a minimum similar to human milk contents (about 4.8–5.5 mg/100 kcal) (62), with a range of 5–15 mg/100 kcal.

Sodium, Potassium, Chloride

Infant formula contents similar to those suggested by previous expert consultations (2,3) are recommended: sodium 20–60 mg/100 kcal, potassium 60–160 mg/100 kcal, and chloride 50–160 mg/100 kcal.

Manganese

The recommended minimum level of 1 μg/100 kcal is in the order of human milk concentrations (62). There is no major difference in manganese bioavailability between breast milk and formulae. The maximum content should be 50 μg/100 kcal which is equivalent to that of unsupplemented soy formula, and about 60 times higher than breast milk levels. Higher manganese contents should be avoided, since due to immature manganese excretion in infants they may cause accumulation in tissues including brain and might induce potential

adverse effects, such as neurodevelopmental abnormalities observed in newborn animals (63).

Fluoride

Infants may be exposed to an additional fluoride intake, e.g. from fluoride containing water. The benefit of a high fluoride intake during early infancy is questionable and carries the risk of dental fluorosis. Therefore, maximum levels should be as low as possible and not exceed 60 μg/100 kcal. No minimum level is needed.

Iodine

Considering infant reference nutrient intakes set by different bodies in the range of 35 to 130 μg/d (3) and the range of human milk contents (62), infant formula should contain 10–50 μg/100 kcal.

Selenium

Reported human milk contents vary considerably, with median values in the range of about 0.8 to 3.3 μg/100 kcal (3). Infant reference nutrient intakes set by different bodies range from 5 to 30 μg/d (3). Very high intakes may cause untoward effects (64). Infant formula should contain 1–9 μg/100 kcal.

Copper

Since there is no major difference in bioavailability between human milk and formulae, a minimum level of 35 μg/100 kcal which is similar to breast milk contents is proposed. It appears prudent to limit the concentration of pro-oxidative elements like copper, and a maximum level of 80 μg/100 kcal, about 3 times higher than in human milk, is recommended.

Zinc

Reference nutrient intakes for infants range from 1–5 mg/d. Even though there is a difference in bioavailability between formulae based on cows' milk proteins and on soy protein isolates, respectively, one single minimum value of 0.5 mg/100 kcal is considered sufficient as it will cover the need of zinc also in infants fed soy formula. Since high intakes may interfere with the absorption and metabolism of other micronutrients, a maximum level of 1.5 mg/100 kcal is set.

Other Substances

Choline

In accordance with the conclusions of previous expert reviews (2,3), a minimum choline content of 7 mg/100 kcal is recommended. LSRO and SCF recommended maximum levels of 30 mg/100 kcal based on extrapolation of adult data. Since no major safety concerns exist and no adverse effects of higher choline intakes have been documented in infants, we suggest a maximum level of 50 mg/100 kcal to harmonize the maximum choline content with a proposed maximum phospholipid content of 300 mg/100 kcal (see optional ingredients, below), considering that a major part of added phospholipids may be provided as phosphatidyl choline.

Myo-inositol

The recommendations of previous expert reviews (2,3) for a myo-inositol content of 4–40 mg/100 kcal are supported.

L-carnitine

The recommendations of previous expert reviews (2,3) for a minimum L-carnitine content of 1.2 mg/100 kcal are supported. In contrast to the SCF, LSRO suggested a maximum level of 2 mg/100 kcal based on the upper end of the usual range found in human milk (2). In the absence of indications of any untoward effects of higher L-carnitine intakes in infants, the IEG concluded that no maximum level is needed to be set.

Optional Ingredients

Taurine

In line with previous expert consultations (2,3), the IEG sees no need for mandatory addition of taurine to infant formulae, but recommends the optional addition in amounts up to 12 mg/100 kcal.

Nucleotides

Several publications have reported beneficial effects of the addition of nucleotides to infant formulae (2,3). The IEG did not find sufficient data to support additional benefits from increasing intakes to levels greater than 5 mg/100 kcal, while adverse affects of higher contents such as increased risk of respiratory tract infections have been reported (65). The optional addition of nucleotides at a maximum total content of 5 mg/100 kcal as well as maximal levels of 2.5 mg/100 kcal CMP, 1.75 mg/100 kcal UMP, 1.5 mg/100 kcal AMP, 0.5 mg/100 kcal GMP, and 1.0 mg/100 kcal IMP are recommended.

Phospholipids

Phospholipids such as phosphatidyl choline have key functions in signal transduction affecting important cell functions. In milk and in the intestinal lumen phospholipids contribute to solubilizing lipophilic compounds. Phospholipids may also be added to infant formulae as a source of long-chain polyunsaturated fatty acids. A

maximum concentration of 300 mg/100 kcal (equivalent to about 2 g/L) seems safe with respect to the potential range obtained of triglyceride/phospholipids ratios.

Long-Chain Polyunsaturated Fatty Acids (LC-PUFA)

In view of beneficial effects of the addition of LC-PUFA to infant formulae reported in a number of publications (2,3), their optional addition to infant formulae is supported by the IEG. Docosahexaenoic acid (DHA, 22:6n-3) and arachidonic acid (AA, 20:4n-6) are the main LC-PUFA in human milk, both of which are always present (66). The DHA contents in human milk are quite variable and reach high levels in populations with high marine food consumption, with consecutive marked variation of the DHA to AA ratio in milk (66–68). LC-PUFA of the n-3 series such as DHA and of the n-6 series such as AA, respectively, are metabolic competitors with differential effects for example on eicosanoid metabolism, membrane physiology, and immune function. Eicosapentaenoic acid (EPA, 20:5n-3) is found in only minor concentrations in human milk and infant tissues and is a direct metabolic competitor of AA. A large number of studies in which LC-PUFA were added to infant formulae have not raised major safety concerns and a recent meta-analysis found no indication of adverse effects on growth of the addition of both DHA and AA, and neither were adverse effects reported in analyzing the limited number of studies with addition of only n-3 LC-PUFA (69). However, adverse growth effects have been reported in single studies with supplementation of fish oils without concomitant n-6 LC-PUFA supply, particularly at high EPA intakes (69). It is noted that at this time there is no sufficient documentation of the benefits and safety of the addition of DHA to infant formula at levels $>0.5\%$ of total fat content, or of DHA without concomitant addition of AA. Until the benefits and suitability for particular nutritional uses and the safety of other additions have been adequately demonstrated, the optional addition of DHA should not exceed 0.5% of total fat intake, and AA contents should be at least the same concentration as DHA, whereas the content of EPA in infant formula should not exceed the DHA content.

Carrageenan

The IEG noted that carrageenan is included in the provisional list of accepted food additives for infant formulae of the current draft of the Codex Alimentarius for an infant formula standard. Carrageenan is used as a thickener, stabilizer, and textures in a variety of processed foods. In animals carrageenan can induce inflammatory reactions in the intestine. As a component of a barium enema solution, carrageenan produced allergic reactions (70). Given the lack of adequate information on possible absorption of carrageenan by the immature gut in the young infants and its biologic effects in infancy, it appears inadvisable to use carrageenan in infant formulae intended for feeding young infants, including those in the category of foods for special medical purposes.

GLOSSARY ABBREVIATIONS

CCNFSDU, Codex Committee on Nutrition and Foods for Special Dietary Uses

ESPGHAN, European Society of Pediatric Gastroenterology, Hepatology and Nutrition

EWG, Electronic working group of CCNFSDU

FAO, Food and Agriculture Organization of the United Nations

FISPGHAN, Federation of International Societies of Pediatric Gastroenterology, Hepatology and Nutrition

FSMP, Food for special medical purposes

LSRO, Life Science Research Office, American Society for Nutritional Sciences

ID, Iron deficiency

IDA, Iron deficiency anemia

IEG, ESPGHAN coordinated International Expert Group

NPN, Nonprotein nitrogen

RE, Retinol equivalent

SCF, Scientific Committee for Food of the European Commission

TE, Tocopherol equivalent

WHO, World Health Organization

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