codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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Agenda Item 4 (a) **CX/NFSDU 06/28/4-Add.4**
October 2006

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON NUTRITION AND FOODS FOR SPECIAL DIETARY USES
Twenty-eighth Session

PROPOSALS OF THE WORKING GROUP ON SECTION 3: ESSENTIAL COMPOSITION AND QUALITY FACTORS

- Comments on Section 3 -

Comments from:
ARGENTINA
GUATEMALA
KENYA - 1 -
KENYA - 2 -
UNITED STATES OF AMERICA
VIET NAM

ISDI - International Special Dietary Foods Industries

ARGENTINA

3. ESSENTIAL COMPOSITION AND QUALITY FACTORS
3.2 Optional [or non-mandatory] ingredients
3.2.3
As regards the level of nucleotides contained in the table, Argentina has a conservative approach, and, taking into account the views of the ESPGHAN coordinated international expert group, it agrees with keeping total [added] nucleotides at 5mg/100 Kcal between brackets. Argentina also suggests that the Expert Group assess the latest and most recent work addressing this issue, where total added nucleotides are higher and would also be included in human milk levels (5-12) mg/100Kcal.

GUATEMALA

Comments by Guatemala				Justification
Document in English		Document in Spanish		
Page	Text	Página	Texto	
3 3.1.3	To eliminate parenthesis from (100 kJ), leave the sentence as follows: ... 100 kcal or 100 kJ	3 3.1.3	Eliminar paréntesis de (100 kilojulios) y dejar la frase como sigue: …como 100 kcal ó 100 kilojulios …	Prevents confusion caused by the brackets, which might be considered to be a conversion.
4 a) Protein Note [3)]	The difference between the use of caw milk protein non hydrolyzed, hydrolyzed and partially hydrolyzed must be maintained.	4 a) Proteínas Note [3)]	Se considera que debe mantenerse la diferencia entre la utilización entre la proteína de la leche de vaca no hidrolizada y la proteína hidrolizada o parcialmente hidrolizada.	This corresponds to the biological availability of the protein. It is also important to avoid confusion between different products for different uses. The position of the United States of America Department of Agriculture is supported.
4 3.1.4	To remove the paragraph between square brackets	4 3.1.4	Eliminar el párrafo que se encuentra entre corchetes.	The reference to amino acids occurs in Annex 1 which is included in the standard.
4, b) lipids (note [5)])	We support a maximum value of 3% for content of trans fatty acids of total fatty acids.	4, inciso b) lípidos (nota [5)])	Apoyamos un valor máximo del 3% para ácidos grasos trans del contenido total de ácidos grasos.	This is based upon the direct relation between this type of lipids and coronary heart disease, non-transmissible chronic diseases (obesity, hypertension, diabetes), intolerances and other disease risks.
5 c) carbohydrates	To specify measuring unit [g] in carbohydrates	5 inciso c) carbohidratos	Especificar la unidad de medida [g] en carbohidratos	The measuring unit is not specified as in the rest of the document.
NA	NA	5, inciso c) carbohidratos, (nota [6)]) (5 c) carbohidrates, note[6])	Corregir la traducción del párrafo entre corchetes, eliminar lactosa y colocar fructosa. Debe quedar: [..., así como la adición de fructosa, ...] (Correct the translation of the paragraph in square brackets replacing lactosa por fructosa, so that it reads: …)	In the English text, the reference in the square brackets is to fructose.

5 c) carbohydrates (note [6)])	To remove the square brackets and supports the paragraph.	5 inciso c) carbohidratos (nota [6)])	Eliminar corchetes y dejar el párrafo.	Because of the relation between the use of these carbohydrates and the predisposition to non-transmissible chronic diseases.
NA	NA	5 inciso c) carbohidratos (nota [6)]) (5 c) carbohidrates, note[6])	Cambiar la traducción de deberá a debería. Debe quedar: [...debería evitarse particularmente...] (Replace the word "deberá" by "debería" so that it reads: ...)	The English version says "should", not "must", and the correct translation is "debería".

Comments by Guatemala				Justification
Document in English		Document in Spanish		
Page	Text		Texto	
8 e) Minerals and Trace Elements Iron	To maintain both tables making a clear difference between Iron from animal source and from vegetable source. We support the note 13). We require to have a Max/Guidance upper level of 1.8 mg and 3.0 mg/100kcal respectively) instead of a maximum level.	8 e) Minerales y oligoelementos Hierro	Se propone mantener las dos tablas diferenciando el hierro de origen animal y vegetal. Apoyamos la nota de página 13 del inciso e). Sin embargo, solicitamos que se coloque un nivel superior de referencia (1.8 mg y 3.0 mg / 100 Kcal respectivamente) en lugar de un nivel máximo.	As developing countries are suffering from iron deficiency, it is important to ensure that these products contain adequate levels of this micronutrient in order to supplement iron deficiencies in accordance with the different nutritional requirements of all countries.
12 3.2.3	To eliminate parenthesis from (100 kJ), leave the sentence as follows: ... 100 kcal or 100 kJ	12 3.2.3	Eliminar paréntesis de (100 kilojulios) y dejar la frase como sigue: …por 100 kcal ó 100 kilojulios …	Prevents confusion caused by the brackets, which might be considered to be a conversion.
12 Total nucleotides	To eliminate the word [added] and to modify the total of nucleotides in infant formulas to 16 mg/100 kcal	12 Total de nucleótidos	En el cuadro que incluye la información de nucleótidos se solicita eliminar la palabra [añadidos] y modificar el total de nucleótidos en fórmulas infantiles a 16 mg/100 kcal.	This decision was taken subsequent to the technical review provided by ISDI, FDA and the report prepared by the Cochrane Office in Mexico.
NA	NA	Todo el documento (Throughout the document)	Modificar la traducción “formulas for Special Medical Purposes” de “Preparados para usos medicinales especiales” a “Fórmulas con propósitos médicos especiales” (Modify the translation of “formulas for Special Medical Purposes” from “Preparados para usos medicinales especiales” into “Fórmulas con propósitos médicos especiales”.)	We think that this wording is much clearer and avoids confusion.
NA	NA	4 (3.1.4)	Eliminar al final 1]. Que está duplicado. (Delete 1] at the end as it appears in duplicate)	It does not appear in the English text.
NA	NA	8 Vitamina C	Corregir la unidad de medida a (mg) (Correct the measuring unit into (mg)	In the English document it says (mg) while in the Spanish document it says (ug).

KENYA - 1 -

3. ESSENTIAL COMPOSITION AND QUALITY FACTORS eWG conclusion
3.1 Essential Composition
3.1.1 Infant formula is a product based on milk of cows or other acceptable animals or a mixture thereof and/or other ingredients, which have been proven suitable for infant feeding. The nutritional safety and adequacy of infant formula shall be scientifically demonstrated to support growth and development of infants. All ingredients and food additives shall be gluten-free. —NO CONSENSUS Kenya proposes to use the word "acceptable" instead of "culturally"

1 Guidance upper levels are for nutrients without sufficient information for a science-based risk assessment. These levels are values derived on the basis of meeting nutritional requirements of infants and an established history of safe use. They may be adjusted based on relevant scientific or technological progress.-- No consensus Kenya concurs with the statement the way it is.

2) [For the purpose of this standard, the calculation of the protein content should be based on N x 6.25, unless a scientific justification is provided for the use of a different conversion factor for a particular nitrogen source.] The protein levels set in this standard are based on a nitrogen conversion factor of 6.25.-NO CONSENSUS Kenya concurs with the statement

3) [Infant formulae based on non-hydrolysed cows' milk protein containing less than 2 g protein/ 100 kcal and infant formula based on hydrolysed proteincontaining less than 2.25 g protein/ 100 kcal should be clinically evaluated.]-NO CONSENSUS

4) Minimum value applies to cows' milk protein. For infant formula based on non-cows' milk protein other minimum values may need to be applied. For infant formula based on soy protein isolate a minimum value of 2.25 g/100 kcal (0.7 g/100 kJ) applies. Consensus Kenya concurs with the statement

3.1.5 Isolated amino acids may be added to Infant Formula only to improve its nutritional value for infants. Essential and semi-essential amino acids may be added to improve protein quality, only in amounts necessary for that purpose. Only L-forms of amino acids shall be used. No consensus

Linoleic acid (g)

Per 100 kcal		Per 100 kJ	
MIN	MAX	MIN	MAX

0.3 1.2Kenya proposes 1.25g max majority of manufacturers have been using this with no problem with fat imbalance 0.07 0.3*

No consensus on Max

6) Lactose and glucose polymers should be the preferred carbohydrates in formula
based on cows' milk protein and hydrolysed protein. Only precooked and/orgelatinised starches may be added to Infant Formula up to 30% of total carbohydrates or up to 2 g/100 ml.
[Sucrose, unless needed, and the addition of fructose particularly should be avoided in infant formula, because of potential life-threatening symptoms in young infants with unrecognised hereditary fructose intolerance.] No consensus

Kenya proposes that sucrose may be used in case where Lactose and glucose are ot available. Sucrose may be used at minimum level but till to cover ther energy requirements

d) Vitamins
Vitamin A (µg RE7))

Per 100 kcal		Per 100 kJ	
MIN	MAX	MIN	MAX
60	180	14	43

No consensus on Max

7)Calciferol. 1 µg calciferol = 40 IU vitamin D Consensus
Vitamin E (mg a TE9))

Per 100 kcal Per 100 kJ
MIN GUIDANCE UPPER
level
MIN GUIDANCE UPPER
level
0.510) 5 0.1210) * 1.2
CONSENSUS
Vitamin K (µg)
Per 100 kcal Per 100 kJ
Min Guidance upper
level
Min Guidance upper
level
4 25 1 6
No consensus on
GUL
Thiamin (µg)
Per 100 kcal Per 100 kJ
Min Guidance upper
level
MIN GUIDANCE UPPER
level
60 300 14 72
No consensus on
GUL
Riboflavin (µg)
Per 100 kcal Per 100 kJ
Min Guidance upper
level
Min Guidance upper
level
80 400 19 100*
Almost consensus
on GUL of 600
□g/100 kcal
Niacin11) (µg)
Per 100 kcal Per 100 kJ
MIN GUIDANCE UPPER
level
Min Guidance upper
level
300 1500 70* 360*
No consensus on
GUL
11) Niacin refers to preformed niacin Consensus
Vitamin B6 (µg)
Per 100 kcal Per 100 kJ
Min Guidance upper
level
Min Guidance upper
level
35 175 8.5* 45*

CONSENSUS

Vitamin B12 (µg)

PER 100 KCAL PER 100 KJ
MIN GUIDANCE UPPER

level
Min Guidance upper
level
0.1 0.5 0.025 0.12
VII. No consensus on
GUL
Pantothenic acid (µg)
Per 100 kcal Per 100 kJ
Min Guidance upper
level
Min Guidance upper
level
60 300 15 75

No consensus

Vitamin C12) (mg)
Per 100 kcal Per100 kJ
Min Max/[Guidance
upper level
Min Max/Guidance
upper level
10 30 2.5 7*
No consensus on

Max/GUL

12) expressed as ascorbic acid Consensus
Biotin (µg)
Per 100 kcal Per 100 kJ
Min Guidance upper
level
Min Guidance upper
level
1.5 7.5 0.4 1.5

No consensus on

GUL
e) Minerals and Trace Elements
Iron (formula based on cows' milk protein and protein hydrolysate) (mg) No consensus

Per 100 kcal		Per 100 kJ	
MIN	MAX	MIN	MAX
0.313)	1.3	0.0713)	0.3-- No consensus

Iron (formula based on soy protein isolate) (mg) No consensus
Per 100 kcal Per 100 kJ
Min Max Min Max
0.45 2.0 0.1* 0.5 No consensus

Phosphorus (formula based on cows' milk protein and protein hydrolysate) No consensus
(mg)

PER 100 KCAL PER 100 KJ

Min Guidance upper
level
Min Guidance upper

LEVE L25 90 6 22-NO CONSENSUS

PER 100 KCAL PER 100 KJ

Min Guidance upper
level
Min Guidance upper
level
30 100 7 25
VIII. No consensus on
Min
Sodium (mg)
Per 100 kcal Per 100 kJ
Min Guidance upper
level
Min Guidance upper
level
20 60 5 14

CONSENSUS ON

levels
No consensus on
Max/GUL
Potassium (mg)
Per 100 kcal Per 100 kJ
Min Guidance upper
level
Min Guidance upper
level
60 160 14* 38
No consensus on
IX. GUL
Manganese (µg)
Per 100 kcal Per 100 J
Min Guidance upper
level

MIN GUIDANCE UPPER

level
1 50 0.25* 12
No consensus on
GUL

Copper (µg)14)
Per 100 kcal Per 100 kJ

MIN MAX MIN MAX

35 80 8.5 19 No consensus

14) Adjustment may be needed in these levels for infant formula made in regions with a high content of copper in the water supply
Zinc (mg)
Per 100 kcal Per 100 kJ

TAURINE MG

Per 100 kcal Per 100 kJ
12 3* Consensus

No consensus on minimum

Total [added] nucleotides mg
Per 100 kcal Per 100 kJ

5 1.2 No consensus

CYTIDINE 5'-MONOPHOSPHATE (CMP) MG
Per 100 kcal Per 100 kJ No consensus
2.5 0.6

URIDINE 5'-MONOPHOSPHATE (UMP) MG
Per 100 kcal Per 100 kJ
1.75 0.4 No consensus

Adenosine 5'-monophosphate (AMP) mg
Per 100 kcal Per 100 kJ
1.5 0.36 No consensus

GUANOSINE
5'-monophosphate (GMP) mg
PER 100 KCAL PER 100 KJ
0.5 0.12 No consensus

Inosine 5'-monophosphate (IMP) mg
Per 100 kcal Per 100 kJ
1.0 0.24 No consensus

Docosahexaenoic Acid15) (% of fatty acids)
Maximum
0.5 No consensus

15) If docosahexaenoic acid (22:6 n-3) is added to infant formula, arachidonic acid (20:4 n-6) contents should reach at least the same concentration as DHA. The content of eicosapentaenoic acid (20:5 n-3), which is not a desirable constituent
of infant formula but can occur in sources of LC-PUFA, should not exceed the content of docosahexaenoic acid. No consensus

3.5 Purity Requirements
All ingredients shall be clean, of good quality, safe and suitable for ingestion by infants. They shall conform with their characteristic quality requirements, such as colour, flavour and odour. No consensus Kenya propses that the words “clean, good quality and suitable” should be deleted.
The sentence should read as follows:
All ingredients shall be sound and safe for consumption by infants

3.6 Specific Prohibitions
The product and its component shall not have been treated by ionizing irradiation.No consensus

Kenya proposes we should not totally prohibit the treatment ionizing radiation where hazardous

radiation are likely to be used, then max exposure level should be defined.

KENYA - 2 -

3. ESSENTIAL COMPOSITION AND QUALITY FACTORS

Essential Composition

3.1.1 Infant formula is a product based on milk of cows or other culturally acceptable animals or a mixture thereof and/or other ingredients, which have been proven to bee suitable for infant

feeding. The nutritional safety and adequacy of infant formula shall be scientifically demonstrated to support growth and development of infants. All ingredients and food additives shall be gluten-free.

Kenya proposes that the word "culturally" to replace the word "acceptable" and the clause to read as indicated above.

3.1.2 Protein

Protein2) (g)

2) [For the purpose of this standard, the calculation of the protein content should be based on N x 6.25, unless a scientific justification is provided for the use of a different conversion factor for a particular nitrogen source.] The protein levels set in this standard are based on a nitrogen conversion factor of 6.25.

Kenya proposes that the bracket be removed and the statement be retained as it is. This was approved by the CAC during the last meeting in Geneva July 2006.

3.1.3 Kenya concurs with the upper levels guidance given for infant formula prepared ready for consumption

3.1.4 For an equal energy value the formula must contain an available quantity of each essential and semi-essential amino acid at least equal to that contained in the reference protein (breast-milk as defined in Annex 1); nevertheless for calculation purposes, the concentrations of methionine and cysteine and of trosine and phenylalanine may be added together (unless the methionine to cysteine or the phenylalanine to tyrosine ratio are outside the range of 0.7-1.5: 1] or any other scientifically acceptable range.

Kenya proposes to add the word "or any other scientifically acceptable range"

Linoleic acid (g)

Kenya proposes 1.25 max`` majority of manufactures have been using this with no problem with fat imbalance.

6) Lactose and glucose polymers should be the preferred carbohydrates in formula based on cows milk protein and hydrolyses protein. Only precooked and/or gelatinized starches may be added to Infant Formula up to 30% of total carbohydrates or up to 2-g/100 ml. [Sucrose, unless needed and the addition of fructose particularly should be avoided in infant formula, because of potential life-threatening symptoms in young infants with unrecognized hereditary fructose intolerance.]

Kenya proposes that sucrose may be used incase where lactose and glucose are not available.
Sucrose may be used at minimum level but till to cover the energy requirements.

3.2.1 In addition to the compositional requirements listed under 3.1.3, other ingredients may be added in order to provide substances ordinarily found in human milk and 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.

3.5 Purity requirements
All ingredients shall be clean, of good quality, safe and suitable for ingestion by infants. They shall conform to their normal quality requirements, such as colour, flavor and odor. Kenya proposes that the word normal be replaced with "characteristic".

3.6 Specific Prohibitions
Ionizing irradiation shall not have treated the product and its component.

4) Minimum value applies to cows' milk protein. Other minimum values may need to be applied. For infant formula based on soy protein isolate a minimum value of 2.25-g/100 kcal (0.7 g/100kJ) applies. Consensus Kenya supports this statement.

3.1.4 For an equal energy valued the formula must contain an available quantity of each essential and semi-essential amino acid at least equal to that contained in the reference protein (breast-milk as defined in Annex 1); nevertheless for calculation purposes, the concentrations of methionine and cysteine and of tyrosine and phenylalanine may be added together CONSENSUS

[Unless the methionine to cysteine or the phenylalanine6yt to tyrosine ratio are outside the range of 0.7-1

UNITED STATES OF AMERICA

I. GENERAL COMMENTS

ANNEX II: GENERAL PRINCIPLES FOR ESTABLISHING MINIMUM AND MAXIMUM VALUES FOR THE ESSENTIAL COMPOSITION OF INFANT FORMULA

Comment: The Chair of the Electronic Working Group has indicated that it may be necessary to reopen discussion of Annex II because of differences in interpretation of maximum and guidance upper levels (GULs) by individual countries. The Committee reached agreement on the General Principles at the 27th session of CCNFSDU. The United States has proposed added language for footnote 1 to clarify that the purpose of the GULs is to provide guidance to manufacturers and that GULs should not be interpreted as goal values. The added language further explains that when a product type or form has ordinarily contained lower levels than the GULs, manufacturers should not increase levels of nutrients to approach the GULs. In addition, ESPGHAN suggested adding the following sentence to footnote 1[1]: "Nutrient contents in infant formulae should usually not exceed the Upper Guidance Levels unless higher nutrient levels cannot be avoided due to high or variable contents in constituents of infant formulae or due to technological reasons." We propose that this sentence also be added to footnote 1 (with a minor edit to refer to GULs rather than Upper Guidance Levels) to help clarify that GULs are conceptually different from maximum values. We believe that addition of these sentences addresses the issues raised by differences in interpretation by member states and that the discussion of Annex II need not be reopened.

REVISED SECTION 3 PROPOSAL PREPARED BY GERMANY

Comment: We are in agreement with the overall organization of Section 3 except for the formatting of maximum values and GULS in Table 3.1.3 which we address in our specific comments. We are also in agreement with the content of 3.1.1, 3.1.2, 3.3, 3.4, 3.5, and 3.6.

Comment: We continue to believe that maximum values should be set only in cases where data are sufficient to support a science-based risk assessment.

Comment: The United States believes that in the specific case of infant formulas, when sufficient evidence is not available to determine maximum values, GULs for manufacturers may be considered if there is a sufficient basis to identify an established history of apparently safe use. We also believe that GULs need not be established for every nutrient, unless consensus can be achieved without delaying the completion of this revised standard. However, in all cases, GULs must be clearly differentiated from maximum values that are based on scientific risk assessment. It is our understanding that the concept of and approach for setting GULs is appropriate only in the case of infant formulas because of the unique nutritional needs and vulnerability of infants and the unique status of infant formula in providing the sole source of nutrition; the concept and approach for setting GULs is not intended to be generalized to other food categories. The approach to setting all values (minimum values, maximum values and GULs) must be made transparent and comprehensible.

[1] Report by the Electronic Working Group 2005/2006. Page 68. Received July 31, 2006.

Comment: We are including the following paragraphs to explain the rationale for our recommendations for guidance upper levels (GULs) in infant formulas. It should be kept in mind that the purpose of the GULs is to provide guidance to manufacturers and they should not be interpreted as goal values. Nutrient contents in infant formulas should usually not exceed the GULs unless higher nutrient levels cannot be avoided due to high or variable contents in constituents of infant formulas or due to technological reasons. When a product type or form has ordinarily contained lower levels than the GULs, manufacturers should not increase levels of nutrients to approach the GULs.

Based on the wide variability in ranges of nutrient values in infant formulas, we question whether it is appropriate to apply numbers for cows' milk-based powdered infant formula to other formulas (e.g., liquid cows' milk-based formulas, formulas based on other mammalian milks, or soy-protein based formulas). Because GULs provide information that is not equivalent to maximum values for nutrients in infant formulas established by science-based risk assessment and because of the variability in the data and the factors that contribute to this variability, we also questioned how these values will be used.

Because of these questions, we earlier identified three options for strategies to move forward in further consideration of GUL:

1. GUL may be very specific in coverage: i.e., careful specification of the products the GUL apply to (and those they don't apply to) and the setting of numbers that are specific to the type(s) and forms of products covered
2. GUL may be very general in coverage: i.e., setting numbers high enough to accommodate all types and all forms of infant formulas
3. National legislation may be another option for setting GUL, given that there are substantive differences in regulatory requirements among countries. The role of Codex would be to provide principles for individual countries to set GUL that take into account their markets and their regulations.

The Chair has pointed out that setting GULs in accordance with national legislation may result in difficulties in international trade. Although we continue to think that setting GULS corresponding to national legislation is an option, we agree that the implications of implementing this option should be considered very carefully.
The 2005 International Expert Group (IEG) report proposed maximum values for nutrients in infant formulas based on scientific data where available and on values derived on the basis of meeting the nutritional needs of infants (multiples of the minimum values). As the IEG report did not reflect information on history of apparently safe use, the infant formula industry (specifically ISDI) offered to provide analytical information on the levels of nutrients found in infant formulas at product release to provide a basis for a history of safe use. The ISDI report was sent to the Electronic Working Group for evaluation in March 2006.

The differences between IEG and ISDI values were substantive for a number of vitamins and minerals. To better understand the factors contributing to the differences in values in the ISDI report and the IEG values, the U.S. Delegate requested additional information from the U.S. infant formula industry. Analyses of release values for formulas manufactured and marketed in the U.S. were prepared by the International Formula Council (IFC). The IFC analyses provided information by protein sources (milk and soy) and forms (powders and liquids).

Based on our assessment of the reports from ISDI and IFC, there are several important technical and manufacturing reasons for the variations found in the levels of nutrients in infant formula:

- Form (liquid vs. powder)
- Inherent levels and variability of the nutrients in ingredients
- Nutrient stability over shelf life
- Analytical variability (within and between laboratories)

- Other technical considerations:
  - Effects of packaging, container material, or container size
  - Effects of processing.

No single factor explained the variability that contributes to the differences between IEG and ISDI levels. Taken together, the number of factors affecting variability illustrated the difficulty of establishing upper levels for nutrients that are not based on scientific risk assessment.

Examination of the IFC analyses by type and form of infant formula revealed that the maximum levels for cow milk protein powder (MP) were closer to the levels recommended by the IEG than maximum levels for other forms and protein source (i.e., soy) for the majority of the nutrients identified in the ISDI report. When MP mean + 2 SD values are compared to the IEG values, there are 3 vitamins (niacin, biotin, and vitamin B12) and 2 minerals (iron and copper) that are notably different. Given the similarity of the IEG proposed maximum values with only the MP mean + 2SD values, the IEG values do not appear to consider history of apparently safe use for all types and forms of infant formula currently marketed worldwide. The IEG proposed maximum values are not consistent with the scope in Section A (1.1) of the standard, which states "This section of the standard applies to infant formula in liquid or powdered form intended for use, where necessary, as a substitute for human milk in meeting the normal nutritional requirements of infants".

The ISDI values for the upper end of the range of means + 2 SD are generally the same or close to the IFC values for infant formulas manufactured and marketed in the U.S. To accommodate the variability contributed by the factors listed above and to be consistent with the principles and the scope of the Infant Formula Standard Section A, we propose that the GULs be set at the upper end of the range of the mean + 2 standard deviations (SD) for each nutrient. GULs set on this basis take into account the sources of variation for all types and forms of infant formulas. Tolerances for analytical variability in products will also need to be taken into account.

Several sources of information support the concept that these values may appropriately be assigned as GULs. For example, in the U.S., growth of infants is routinely monitored in health care settings and surveillance systems are in place to monitor the nutritional status of low-income infants. In addition, the nutrient content of each batch of finished infant formula is analyzed by the manufacturer and products that do not meet the U.S. regulations for nutrient composition are not released into the market. Regular inspections of infant formula plants by FDA include confirmation that infant formula that enters the marketplace meets national specifications for nutrient composition. Finally, there is a mechanism for tracking of complaints by U.S. infant formula manufacturers and FDA inspection of complaint records. Taken together, the information available from these sources supports the concept that the proposed GULs are consistent with a history of apparently safe use.

In cases where the Committee cannot reach agreement on GULs, the Committee could alternatively employ the approach used for the current Infant Formula Standard (CODEX STAN 72-1981 (amended 1983, 1985, 1987, 1997)), i.e., using the designation "N.S." rather than setting a numerical value for all nutrients. Specifically, the current standard identified maximum levels for only five nutrients because there was insufficient evidence to set maximum levels for other nutrients. We also note that, historically, inadequate levels of nutrients rather than high levels appear to have been the source of problems with infant formulas.

II. SPECIFIC COMMENTS ON TABLE 3.1.3

We wish to clarify a point with respect to earlier U.S. comments. The numbers presented by the U.S. Delegate at the 27th Session of the CCNFSDU were identified in ALINORM 06/29/26 as U.S. proposals for GULs for certain nutrients. These values were intended to illustrate that differences existed between the International Expert Group (IEG) values and commercial infant formulas and were not intended as proposed GUL values. The comments submitted in this draft position include our proposals for the GUL values for individual nutrients and the reasons for proposing the particular values.

We continue to believe that Table 3.1.3 should include separate columns for Maximum and Guidance Upper Levels to make it clear that the two types of values are different.

We are submitting the following comments on specific sections of Table 3.1.3.

Footnote 1:

[1] Guidance upper levels (GULs) are for nutrients without sufficient information for a science-based risk assessment. These levels are values derived on the basis of meeting nutritional requirements of infants and an established history of apparently safe use. They may be adjusted based on relevant scientific or technological progress. The purpose of the GULs is to provide guidance to manufacturers and they should not be interpreted as goal values. Nutrient contents in infant formulas should usually not exceed the GULs unless higher nutrient levels cannot be avoided due to high or variable contents in constituents of infant formulas or due to technological reasons. When a product type or form has ordinarily contained lower levels than the GULs, manufacturers should not increase levels of nutrients to approach the GULs.

> Comment: We propose the added text for footnote 1 to clarify and emphasize the purpose and appropriate interpretation of GULs. We believe that addition of this language will alleviate the need to reopen the discussion of Annex II.

a) Protein [2] (g)

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Protein [3,4]	g/100 kcal	1.8	3	
	g/100 kJ	0.45	0.7	

~~[2)] [For the purpose of this standard, the calculation of the protein content should be based on N x 6.25 unless a scientific justification is provided for the use of a different conversion factor for a particular nitrogen source.] The protein levels set in this standard are based on the nitrogen conversion factor of 6.25.~~

Footnote 2:

> [2] The value of 6.38 is established as a specific factor appropriate for conversion of nitrogen to protein for cows milk in Codex milk product standards. In the absence of an established nitrogen conversion factor for a protein source, a factor of 6.25 may used.
> Comment: We propose rewording of footnote 2 as shown above.
>
> Rationale: Upon reviewing the comments from other countries and the Chair's synopsis, we are concerned that there may be differing interpretations on the nitrogen conversion factor (NCF) as currently presented in footnote 2. It is important to keep in mind that the NCF is a factor for calculating the amount (quantity) of protein. The Chair has correctly identified the two issues with regard to the NCF. It is possible to address the Chair's point regarding conversion of nitrogen to protein accretion in infants by using a general factor of 6.25. The nitrogen in a specific protein source to meet that requirement should be converted by a factor specific to that protein source when a specific factor is available.
>
> Our understanding was that specific NCF values should be used when already established for specific ingredients (e.g., 6.38 for milk proteins). Only when a specific NCF has not been established, should the general NCF, 6.25, be used to calculate protein content. Applying the general NCF, 6.25, when specific factors are available is not consistent with scientific principles or other Codex standards. In earlier comments, we proposed the removal of the square brackets when we thought the specific factors would be used as consistent with the other Codex commodity standards. However, given that the current wording may be interpreted differently, we believe the footnote needs to be reworded to remove any ambiguity.

The use of the 6.38 NCF for milk proteins is supported by other Codex standards. For example, Codex standards using an NCF of 6.38 include whey powders (Codex Standard A15 – 1995 Rev. 1 – 2003), edible casein products (Codex Standard A18 – 1995 – Rev.1 – 2001), evaporated milks (Codex Standard A3 – 1971 Rev. 1 – 1999), and milk powders (Codex Standard A5 – A 10). The Codex Committee on Milk and Milk Products also stated its continued support of the 6.38 NCF at its recent meeting (ALINORM 06/29/11, para 17):

> 17. The Committee had already established the use of 6.38 as the nitrogen conversion factor in all milk product standards adopted by the Commission addressing protein content and this had support in the scientific literature. The Committee reiterated its position that there is a need for a consistent application of the conversion factor used for the calculation of milk protein throughout Codex and the Committee continues to support the nitrogen conversion factor of 6.38 as scientifically justified.

The scientific literature suggests that use of 5.71 as a specific NCF is appropriate for soy protein. However, this specific factor is not applied consistently in Codex standards. For example, the general factor of 6.25 is used as the NCF in CODEX STAN 175-1989, the general standard for soy protein products. This may need to be reexamined by the appropriate Codex committee(s).

[3] [Infant formulae based on non-hydrolyzed cows' milk protein containing less than 2 g protein/100 kcal and infant formula based on partially hydrolyzed protein containing less than 2.25 g protein/100 kcal should be clinically evaluated.]

Comment: We continue to stress the need to distinguish between infant formulas containing proteins that are partially hydrolyzed versus those that contain extensively hydrolyzed proteins. Extensively hydrolyzed infant formulas are formulas for special medical purposes for use in infants who are allergic to cow milk proteins. Extensively hydrolyzed proteins derived from cows' milk contain most of the nitrogen in the form of free amino acids and peptides less than 1500 kDa in size. In contrast to extensively hydrolyzed proteins, partially hydrolyzed proteins can have a median molecular weight of about 1500 kDa; however, a significant portion of the protein or peptides in these formulas can have a molecular weight greater than 1500 kDa. This distribution can contain protein fragments and peptides of 5000 kDa or larger. Formulas based on partially hydrolyzed cows' milk proteins formulas are not for use for the dietary management of infants with cows' milk allergy as any formula with intact cows' milk proteins and large peptides may provoke reactions in infants allergic to cows' milk proteins. Therefore, formulas containing partially hydrolyzed proteins are appropriately included in Part A of the infant formula standard and formulas based on extensively hydrolyzed proteins are appropriately included in Part B.

[4] Minimum values apply to cows' milk protein. For infant formula based on non-cows' milk protein, other minimum values may need to be applied. For infant formula based on soy protein isolate, a minimum value of 2.25 g/100 kcal (0.7 g/100 kJ) applies.

3.1.4 For an equal energy value the formula must contain an available quantity of each essential and semi-essential amino acid at least equal to that contained in the reference protein (breast-milk as defined inn Annex I); nevertheless for calculation purposes, the concentrations of methionine and cysteine and of tyrosine and phenylalanine may be added together. ~~[unless the methionine to cysteine or the phenylalanine to tyrosine ratio are outside the range of 0.7-1.5:1]~~

Editorial Comment: We suggest incorporating this statement as a footnote to the protein section of Table 3.1.3 rather than inserting a separately numbered item into the Table.

Comment: We suggest that the phrase [unless the methionine to cysteine or the phenylalanine to tyrosine ratio are outside the range of 0.7-1.5:1] be deleted.

Rationale: The recommendation of this ratio is based on one study of parenterally fed piglets and a report of a new approach for setting amino acid requirements using measurements of amino acid oxidation, a technique that has not been fully validated and has apparently not been applied to

children younger than 3 years of age. In the case of methionine and cysteine, the ratio inherent to intact cows' milk protein (casein:whey 82:18) is typically around 3:1 and the ratio of these amino acids in casein-dominant formulas is outside the range proposed in 3.1.4. Casein dominant formulas based on intact cows' milk protein at levels greater than or equal to 2 g/100 kcal are known to be nutritionally adequate for infants even though the ratios of methionine to cysteine are outside the proposed range of 0.7–1.5:1. If a ratio for these amino acids is included in the standard, language should be added to indicate that the ratio does not apply to casein dominant formulas based on intact cows' milk protein at levels greater than or equal to 2 g/100 kcal. In cases where the protein content for the formula is less than 2 g/100 kcal, footnote 3 for Table 3.1.3 a includes the provision that infant formulas containing less than 2 g protein/100 kcal . . . should be clinically evaluated. These studies provide a way of evaluating on a case-by-case basis whether there is a need for addition of cysteine to specific infant formulas.

In the case of phenylalanine and tyrosine, the ratio of phenylalanine to tyrosine in whey is 1.09:1 and in casein is 0.85:1. It is clear that any formula based on cows' milk, regardless of the whey to casein ratio, will fall within the range of 0.7:1 to 1.5:1. Thus, there seems to be no reason to include this ratio in the standard.

Comment: The amino acids and values listed in Annex I (Essential and semi-essential amino acids in breast milk) appear to be the same as those listed in the 2003 report of the EC Scientific Committee on Food (SCF) and in the draft revised standard before receipt of the 2005 recommendations from the IEG. Please clarify what list of amino acids and values are now being proposed for the draft revised standard.

Comment: Table 10 in the 2003 EC SCF report and Table 4 of the 2005 IEG report demonstrate the considerable variation of amino acid composition of breast milk and the considerable variation in analytical values obtained with different methods of amino acid analysis. Methods of amino acid analysis have changed over time and data obtained by newer methods may not be directly comparable to data generated by methods used earlier. For example, older methods of analysis overestimated the amount of tryptophan and cystine/cysteine. With the large amount of variation in breast milk and in methodology for determination of amino acids, it is essential to account for this variability in establishing an amino acid pattern of breast milk that provides a scientifically sound basis for evaluation of protein quality in infant formulas. Establishing a reference pattern for the amino acid content of breast milk without accounting for this variability could require addition of amino acids to infant formulas for which there is not evidence of inadequacy of protein quality.

To take the variability in breast milk composition and variability in analytical methods into account, we recommend use of a more comprehensive table such as Table 4 in the IEG report, which lists values that can be linked to specific methods of analysis, rather than a summary table of average values as presently included in Annex I of the draft revised standard. If a more comprehensive table of ranges is used, manufacturers and government agencies can compare their analytical results to values that were obtained by comparable methodology. With the large amount of variation in breast milk and in methodology for determination of amino acids, we remain reluctant to support the adoption of an average amino acid pattern for protein quality evaluation for infant formulas and question whether there are clinical studies to support recommendation of an average amino acid pattern in the infant formula matrix.

3.1.5 Isolated amino acids may be added to infant formula only to improve its nutritional value for infants. Essential and semi-essential amino acids may be added to improve protein quality, only in amounts necessary for that purpose. Only L-forms shall be used.

Editorial Comment: We suggest incorporating this statement as a footnote to the protein section of Table 3.1.3 rather than inserting a separately numbered item into the Table.

b) Lipids

Total fat [5] (g)
Commercially hydrogenated oils and fats shall not be used in infant formulas.
Editorial Comment: We suggest that this statement be incorporated into footnote 5 as shown below.

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Total fat	g/100k cal	4.4	6.0	
	g/100 kJ	1.05	1.4	

[5] Lauric and myristic acids are constituents of fats, but combined should not exceed 20% of [total fatty acids]. The content of trans fatty acids shall not be higher than [3%] of total fatty acids. Trans fatty acids are endogenous components of milk fat. The acceptance of up to [3%] of trans fatty acids is intended to allow for the use of milk fat in infant formulae. The erucic acid content shall be less than 1% of total fatty acids. Commercially hydrogenated oils and fats shall not be used in infant formulas.

Linoleic acid

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Linoleic acid	g/100k cal	0.3	~~1.2~~	1.6
	g/100 kJ	0.07	~~0.3~~	0.38

Comment: We support a GUL for linoleic acid because data are not sufficient for a science-based risk assessment to establish a maximum value for infant formula. The value proposed for the GUL takes into consideration the variability of linoleic acid among product forms (liquids and powders) and inherent variability of linoleic acid in oils used as ingredients in infant formulas.

Linolenic acid

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Linolenic acid	g/100k cal	50	N.S.	
	g/100 kJ	12	N.S.	

Ratio linoleic acid/ α-linolenic acid

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Ratio linoleic/α-linolenic acid		5:1	15:1	
		5:1	15:1	

c) Total carbohydrates[6]

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Total carbohydrates	g/100 kcal	9.0	14.0	
	g/100 kJ	2.2	3.3	

[6] Lactose and glucose polymers should be the preferred carbohydrates in formula based on cows' milk protein and partially hydrolyzed protein. Only precooked and/or gelatinized starches may be added to infant formula up to 30% of total carbohydrates or up to 2g/100 ml. [Sucrose, unless needed, and addition of fructose, as an ingredient, ~~particularly~~ should be avoided in infant formula because of potential life-threatening symptoms in young infants with unrecognized hereditary fructose intolerance.]

Comment: Although we recognize the serious nature hereditary fructose intolerance and the medical need to restrict sources of fructose in infants with this disorder, we are puzzled by the proposed restriction for formulas for healthy infants. Avoiding addition of sucrose to Part A formulas is not supported by scientific evidence of adverse effects of sucrose consumption by healthy, term infants.

Sucrose may be used as an ingredient in infant formulas (e.g., in soy-based infant formulas) when there is a need to limit lactose consumption. If this language is maintained, it is essential to add the phrase "as an ingredient" because ingredients such as corn syrup solids and oligosaccharides, which may be added to some formulas, may contain some monosaccharides.

Comment: We believe the word "partially" should be added to the first sentence to differentiate between infant formulas based on partially and extensively hydrolyzed proteins. Please see detailed comment on footnote 3.

d) Vitamins

Vitamin A (µg RE[7])

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Vitamin A	µg RE/100 kcal	60	~~180~~	225
	µg RE/100 kJ	14	~~43~~	54

[7] Expressed as retinol equivalents (RE). 1µg RE = 3.33 IU vitamin A = 1µg all-trans retinol. 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.

Comment: We support a GUL for vitamin A because data are not sufficient for a science-based risk assessment to establish a maximum value for vitamin A consumed in infant formulas. The United States has a history of safe use with a maximum of 225 µg RE/100 kcal. The GUL proposed value takes into consideration variability of vitamin A among product forms (liquids and powders), losses over shelf life, and a history of apparently safe use.

The lowest chronic intake of vitamin A by infants associated with hypervitaminosis A cited by the EC Scientific Committee on Food (SCF) (2003) is 7200 µg RE/day. This intake corresponds to levels in infant formulas of 1440 µg RE/100 kcal when intake of formula is about 500 ml/day, an intake representative for infants over the first months of life. The maximum level proposed in the draft revised standard is 180 µg RE/100 kcal, but a clear explanation was not provided for how the IEG determined the maximum level for vitamin A and whether the maximum level took into account variability of vitamin A among product forms (liquids and powders), losses over shelf life, and a history of apparently safe use. Incorporation of amounts of vitamin A to ensure compliance with the maximum value of 180 µg RE/100 kcal in the proposed Codex infant formula standard may not provide sufficient vitamin A to meet the nutritional needs of infants.

Vitamin D_3 (µg[8])

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Vitamin D_3	µg/ 100 kcal	1	2.5	
	µg/ 100 kJ	0.25	0.6	

[8] Calciferol. 1µg calciferol = 40 IU vitamin D.

Vitamin E (mg α-TE[9])

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Vitamin E	mg α-TE/100 kcal	0.5 [10]		5
	mg α-TE/100 kJ	0.12		1.2

[9] 1 mg α-TE (alpha tocopherol equivalent) = 1 mg d-α-tocopherol

[10] 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 (18:2 n-6); 0.75 mg α–TE/g linoleic acid (18:3 n-3); 1.0 mg α–TE/g arachidonic acid (20:4 n-6); 1.25 mg α–TE/g eicosapentaenoic acid (20:5 n-3); 1.5 mg α–TE/g docosahexaenoic acid (22:6 n-3).

Comment: The United States supports the proposed GUL for vitamin E and we agree with the content of footnotes 9 and 10.

Vitamin K

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Vitamin K	µg/ 100 kcal	4		~~25~~ 30
	µg/ 100 kJ	1		~~6~~ 7

Comment: We support a GUL for vitamin K because data are not sufficient for a science-based risk assessment to establish a maximum value. The value proposed for the GUL takes into consideration inherent variability of vitamin K in oils used as ingredients in infant formulas, analytical variability for vitamin K measurement, and history of apparently safe use.

Thiamin

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Thiamin	µg/ 100 kcal	60		~~300~~ 340
	µg/ 100 kJ	14		~~72~~ 80

Comment: We support a GUL for thiamin because data are not sufficient for a science-based risk assessment to establish a maximum value for infant formulas. The value proposed for the GUL takes into consideration variability among product forms (liquids and powders), losses over shelf life, and history of apparently safe use.

Riboflavin

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Riboflavin	µg/ 100 kcal	80		~~400~~ 520
	µg/ 100 kJ	19		~~100~~ 120

Comment: We support a GUL for riboflavin because data are not sufficient for a science-based risk assessment to establish a maximum value for infant formulas. The value proposed for the GUL takes into consideration variability among product forms (liquids and powders), inherent variability of riboflavin in milk-derived ingredients used in infant formulas, losses over shelf life, and history of apparently safe use.

Niacin [11](µg)

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Niacin	µg/ 100 kcal	300		~~1500~~ 2600
	µg/ 100 kJ	70		~~360~~ 630

[11]Niacin refers to preformed niacin.

Comment: We support a GUL for niacin because data are not sufficient for a science-based risk assessment to establish a maximum value for infant formulas. The value proposed for the GUL takes into consideration variability among product forms (liquids and powders), losses over shelf life, and history of apparently safe use.

Vitamin B_6

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Vitamin B_6	µg/ 100 kcal	35		175
	µg/ 100 kJ	8.5		45

Comment: The United States supports the proposed GUL for vitamin B_6.

Vitamin B_{12}

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Vitamin B_{12}	µg/100 kcal	0.1		~~0.5~~ 1.4
	µg/ 100 kJ	0.025		~~0.12~~ 0.3

Comment: We support a GUL for vitamin B_{12} because data are not sufficient for a science-based risk assessment to establish a maximum value for infant formulas.

The inherent variability of vitamin B_{12} in milk-derived ingredients used in infant formulas is large and it is possible to exceed the maximum value proposed in the draft revised standard solely from the contribution of the milk-derived ingredients without addition of vitamin B_{12}. Analytic methodology for vitamin B_{12} has a high amount of inter- and intra-laboratory variability. Furthermore, the amounts in infant formula are near the lower limits of detection for vitamin and use of higher levels will more reliably ensure that the analytical method accurately detects the level of vitamin in infant formulas. Loss of vitamin B_{12} occurs throughout shelf-life and incorporation of amounts to ensure compliance with the maximum value proposed in the draft revised standard may not ensure the presence of the amount needed to meet the nutritional needs of infants.

The value of 1.4 µg vitamin B_{12}/100 kcal proposed for the GUL takes into consideration variability among product forms (liquids and powders), inherent variability of vitamin B_{12} in milk-derived ingredients used in infant formulas, analytical issues associated with vitamin B12 measurements, losses over shelf life, and history of apparently safe use. A GUL of 1.4 µg/100 kcal will more reliably ensure that the analytical method accurately detects the level of B_{12} in infant formulas.

Pantothenic acid

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Pantothenic acid	µg/ 100 kcal	~~60~~ 400		~~300~~ 2000
	µg/ 100 kJ	~~15~~ 100		~~75~~ 500

Comment: The United States does not find reason to lower the minimum and GUL to levels below the Adequate Intake for infants (1.7 µg/day or about 340 µg/100 kcal). As proposed by the EC, the U.S. supports a minimum of 400 based on the AI for infants. A GUL of 2000 µg/100 kcal is proposed based on a lack of toxicity of pantothenic acid.

Folic acid

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Folic acid	µg/ 100 kcal	10		50
	µg/ 100 kJ	2.5		12

Comment: We support a GUL for folic acid because there are no data to provide a basis for a science-based risk assessment to establish a maximum value for infant formulas. The United States supports the proposed GUL for folic acid.

Vitamin C[12]

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Vitamin C	mg/ 100 kcal	10		~~30~~ 70
	mg/ 100 kJ	2.5		~~7~~ 17

[12] Expressed as ascorbic acid

Comment: In addition to its role as a nutrient, vitamin C functions as an antioxidant that is critical in protecting other nutrients during processing, storage and use of infant formula. Its role as an antioxidant has become even more important with the addition of long-chain polyunsaturated fatty acids to infant formula. The value proposed for the GUL in the draft revised standard does not take into account the need for higher levels of vitamin C to provide adequate protection against oxidation for other nutrients. Moreover, variability among product forms (liquids and powders), analytical variability for vitamin C measurements, variability due to processing methods, losses over shelf-life, and history of apparently safe use do not appear to be considered. Given that these factors that must be taken into consideration in setting a GUL for vitamin C, it is not prudent to set a GUL of 30 mg/100 kcal. Incorporation of amounts of vitamin C at or below the GUL of 30 mg/100 kcal

proposed in the draft revised standard may not ensure the presence of sufficient vitamin C to meet the nutritional needs of infants.

We support a GUL for vitamin C because data are not sufficient for a science-based risk assessment to establish a maximum value for infant formulas. The value of 70 mg/100 kcal for the GUL takes into consideration its function as a nutrient and as an antioxidant, variability among product forms (liquids and powders), analytical variability for vitamin C measurements, variability due to processing methods, losses over shelf life, and history of apparently safe use.

Biotin

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Biotin	µg/ 100 kcal	1.5		~~7.5~~ 12
	µg/ 100 kJ	0.4		~~1.5~~ 2.9

Comment: We support a GUL for biotin because data are not sufficient for a science-based risk assessment to establish a maximum value for infant formulas. The value proposed for the GUL takes into consideration analytical variability for biotin measurements, losses over shelf life, and history of apparently safe use.

e) Minerals and Trace Elements

Iron

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Iron-~~cow milk and partial hydrolysate~~	mg/ 100 kcal	~~0.3~~ [13] 0.6	~~1.3~~	2.4
	µg/ 100 kJ	~~0.07~~ 0.17	~~0.3~~	0.57

[13] ~~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.~~

~~Nutrient~~	~~Unit~~	~~Minimum~~	~~Maximum~~	~~Guidance upper levels~~
~~Iron - soy~~	~~mg/ 100 kcal~~	~~.45~~	~~2.0~~	
	~~µg/ 100 kJ~~	~~0.1~~	~~0.5~~	

Comment: We recommend deletion of footnote 13. The proposed minimum level for iron in milk-based formulas of 0.3 mg/100 kcal is acknowledged in the footnote to be insufficient for populations where infants are at risk of iron deficiency. We also recommend a minimum level for iron of 0.6 mg/100 kcal to avoid infant formulas that do not meet the nutritional requirements for all infants. Minimum levels for other nutrients have been set at levels that are thought to be adequate for all infants. We do not find a reason to make an exception for iron. Selection of 0.6 mg/100 kcal as the minimum level for iron also eliminates the need for a separate recommendation for soy-based formulas, as this minimum level is also greater than the minimum iron level proposed for soy formulas

Rationale: Iron deficiency is the most common micronutrient deficiency in the world. It is associated with both acute and long-term consequences and the minimum level of iron in infant formula should be selected to help minimize the occurrence of such consequences. Although 0.3 mg/100 kcal may reduce the risk of anemia (the most severe stage of iron depletion), a level of 0.6 mg/100 kcal, the minimum level recommended for infant formulas by the American Academy of Pediatrics, would provide adequate iron to maintain a higher level of iron status and improve iron stores to prevent later development of iron deficiency, not just prevent anemia.

Comment: Based on clinical studies cited in the IEG report, the IEG concluded that iron content higher than 1.3 mg/ 100 kcal would provide no additional benefit with respect to iron status and

noted the potential for adverse effects on copper status. However, the recommendation was not based on a science-based risk assessment.

We support a GUL for iron because data are not sufficient for a science-based risk assessment to establish a maximum value. In our March comments, we remarked on the history of apparently safe use with infant formulas that have stated label content of 1.8 mg iron/100 kcal. After we submitted that comment, we had an opportunity to examine the data provided by ISDI and the IFC. From the data provided, we noted that formulas with a stated label content of 1.8 mg iron/100 kcal, as expected, had analyzed levels that were higher than the stated label value. Based on these data, we propose a GUL of 2.4 mg/100 kcal, reflecting a history of apparently safe use for all types and forms of infant formulas.

Calcium

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Calcium	mg/ 100 kcal	50	~~140~~	140
	mg/ 100 kJ	12	~~35~~	35

Comment: We support a GUL for calcium because data are not sufficient for a science-based risk assessment to establish a maximum value for infant formulas. The proposed maximum values are suitable as guidance upper levels.

Phosphorus

~~Nutrient~~	~~Unit~~	~~Minimum~~	~~Maximum~~	~~Guidance upper levels~~
~~Phosphorus* - cow milk and partial hydrolysate~~	~~mg/ 100 kcal~~	~~25~~		~~90~~
	~~mg/ 100 kJ~~	~~6~~		~~22~~

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Total Phosphorus, ~~soy~~	mg/ 100 kcal	30		100*
	mg/ 100 kJ	7		25*

*These total phosphorus values include the amount of phytate-phosphorus contained in soy protein-based formulas. Levels of phosphorus in milk-based products need not be adjusted to approach the GUL.

Comment: We support a GUL for phosphorus because data are not sufficient for a science-based risk assessment to establish a maximum value for infant formulas. We suggest restructuring the phosphorus section of the table so that the GUL value for phosphorus will include all types of infant formulas and a history of apparently safe use.

Comment: We recommend addition of a footnote to explain that levels of total phosphorus include phytate-phosphorus found in soy protein-based formulas and that phosphorus levels in milk-based formulas need not be adjusted to approach the GUL.

Calcium:Phosphorus Ratio

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Calcium:Phosphorus-Ratio		1:1	2:1	

Comment: The United States supports the proposed range of calcium:phosphorus ratios.

Magnesium

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Magnesium	mg/ 100 kcal	5		15
	mg/ 100 kJ	1.2		3.6

Comment: We support a GUL for magnesium because data are not sufficient for a science-based risk assessment to establish a maximum value for infant formulas. We support the GUL for magnesium as proposed.

Sodium

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Sodium	mg/ 100 kcal	20	60	~~60~~
	mg/ 100 kJ	5	14	~~14~~

Comment: We believe that maximum levels should be assigned for sodium, potassium, and chloride because of their critical role in maintaining electrolyte balance. Maximum levels for these minerals should be considered together because of the adverse effects that occur when electrolyte balance is disrupted.

Potassium

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Potassium	mg/ 100 kcal	50	200	~~160~~
	mg/ 100 kJ	12	38	~~38~~

Chloride

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Chloride	mg/ 100 kcal	50	160	~~160~~
	mg/ 100 kJ	12	38	~~38~~

Manganese

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Manganese	µg/ 100 kcal	1		~~50~~ 100
	µg/ 100 kJ	~~0.25~~ 0.24		~~24 or 12~~ 24

Comment: We support a GUL for manganese because data are not sufficient for a science-based risk assessment to establish a maximum value for infant formulas. Inherent levels of manganese are quite high (and highly variable) in soy protein ingredients. Based on a history of apparently safe use, we suggest a GUL of 100 µg/ 100 kcal that would cover all types and forms of infant formulas.

Iodine

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Iodine	µg/ 100 kcal	10		75
	µg/ 100 kJ	2.5		18

Comment: We support a GUL for iodine because data are not sufficient for a science-based risk assessment to establish a maximum value for infant formulas. The United States supports the proposed GUL for iodine.

Selenium

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Selenium	µg/ 100 kcal	1		9
	µg/ 100 kJ	0.24		2.2

Comment: We support a GUL for selenium because data are not sufficient for a science-based risk assessment to establish a maximum value for infant formulas. The United States supports the proposed GUL for selenium.

Copper[14]

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Copper	µg/ 100 kcal	~~35~~ 60	~~80~~	190
	µg/ 100 kJ	~~8.5~~ 14	~~19~~	45

[14] Adjustments may be needed in these levels for infant formula made in regions with a high content of copper in the water supply.

Comment: In our response to CL 2005/53, we questioned the need to lower the minimum value for copper to 35 µg/100 kcal, a value similar to breast milk content of copper. We continue to have concerns about a minimum value of 35 µg/100 kcal for copper in infant formulas as we are not aware of scientific evidence to support lowering the minimum value for copper in infant formulas. The proposed minimum value of 35 µg/100 kcal proposed in the draft revised standard is more than a 40% reduction from the value of 60 µg/100 kcal in the existing standard (CODEX STAN 72-1981 (amended 1983, 1985, 1987, 1997)), which is known to meet the copper requirement of infants. Without additional scientific evidence, we do not support a reduction of the minimum value for copper. We suggest that the minimum level for copper be maintained at 60 µg/ 100 kcal, a level that has scientific support and was the level recommended in the LSRO 1998 report.

Comment: The recommendation for a maximum value of 80 µg/100 kcal for copper is not based on a science-based risk assessment. We support a GUL for copper because data are not sufficient for a science-based risk assessment to establish a maximum value for infant formulas. With the availability of analytical data from industry reflecting the history of apparently safe use for all types and forms of infant formulas, we support the value of 190 µg/100 kcal as a GUL. The proposed GUL takes into consideration the variability in inherent levels of copper in ingredients, variability among forms of infant formulas, analytical variability for measurement of copper, and history of apparently safe use.

Zinc

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Zinc, ~~non-phytate~~	mg/ 100 kcal	0.5	~~1.5~~	2.4**
	mg/ 100 kJ	0.12	~~0.36~~	0.75**

~~**For soy protein infant formulas the minimum and maximum values for total zinc should be increased to 0.75 and 2.4 mg/100 kcal, respectively, because of the presence of phytate~~.
**These total zinc values include the amounts added to soy protein-based formulas because of the presence of phytates. Levels of zinc in milk-based products need not be increased to approach the GUL.

Comment: We support a GUL for zinc because data are not sufficient for a science-based risk assessment to establish a maximum value for infant formulas. The values proposed take into account the need to set GULs to cover all types and forms of infant formulas. We suggest restructuring the zinc section of the table so that the GUL value for zinc will include all types of infant formulas and a history of apparently safe use.

f) Other Substances
Choline

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Choline	mg/ 100 kcal	7	~~50~~	50
	mg/ 100 kJ	1.7	~~12~~	12

Comment: We support a GUL for choline because data are not sufficient for a science-based risk assessment to establish a maximum value for infant formulas. The proposed maximum values are suitable as guidance upper levels.

Myo-inositol

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
Myo-inositol	mg/ 100 kcal	4	~~40~~	40
	mg/ 100 kJ	1	~~9.5~~	9.5

Comment: We support a GUL for myo-inositol because data are not sufficient for a science-based risk assessment to establish a maximum value for infant formulas. The proposed maximum values are suitable as guidance upper levels.

L-carnitine

Nutrient	Unit	Minimum	Maximum	Guidance upper levels
L-carnitine	mg/ 100 kcal	1.2	~~N.S~~	N.S.
	mg/ 100 kJ	0.3	~~N.S~~	N.S.

Comment: We support "Not Specified" (N.S.) designation for L-carnitine because data are not sufficient for a science-based risk assessment to establish a maximum value for infant formulas, nor are they sufficient to establish a numerical GUL.

3.2 Optional Ingredients

3.2.2 The suitability for the particular nutritional uses of infants and the safety of these substances shall be scientifically demonstrated. The formula ~~shall~~ should contain sufficient amounts of these substances to achieve the intended effect, taking into account levels in human milk.

Comment: The word "should" should replace "shall".

Rationale: It is not appropriate to say that addition of an optional ingredient is mandatory.

~~3.2.3 The following substances may be added in conformity with national legislation, in which case their content per 100 kcal (100 kJ) in the infant formula ready for consumption shall not exceed:~~ Substances not categorized as essential nutrients for infants may be added in conformity with national legislation. The following list is not all-inclusive, but when the listed ingredients are added, the amount shall not exceed the following values:

Comment: We propose the above edits for section 3.2.3 to clarify that the table in 3.2.3 is not intended to be a comprehensive list.

Rationale: The category of optional ingredients should not imply that only the listed optional ingredients may be added to infant formulas, should future research support the inclusion of additional substances to infant formulas as optional ingredients.

Table: Optional Ingredients

Comment: Proposed additions of optional ingredients and proposed changes in maximum values in the Table are identified in bold.

Nutrient or Constituent	Unit, per 100 kcal	Maximum
Fluoride	µg	60
Taurine	mg	12
Total [~~added~~] nucleotides[15]	mg	~~5~~ 16
Phospholipids	mg	300
Docosahexaenoic acid (DHA)[~~15~~16]		0.5% of total fatty acids

[15]Nucleotides as the 5'-monophosphates may be added to cows' milk infant formulas, provided that the total nucleotides in the formula does not exceed 16 mg/100 kcal. Addition should include at least four nucleotides (two purine and two pyrimidine nucleotides) of the following five nucleotides: adenosine, guanosine and inosine (purines) and cytidine and uridine (pyrimidines), with a maximum of 45% of the total nucleotides added as purine nucleotides. Addition should be in the form of cytidine 5'-monophosphate, uridine 5'-monophosphate, adenosine 5'-monophosphate, guanosine 5'-monophosphate, and inosine 5'-monophosphate. Because of the high endogenous levels of nucleotides in soy protein isolate, there is no need to add nucleotides to soy-based infant formulas.

Addition of Footnote 15

Comment: We suggest addition of the footnote shown above as a replacement for listing individual nucleotides and maximum levels for each nucleotide.

Rationale: Variation in the levels of total nucleotides in cows' milk necessitates flexibility in the levels of addition of individual nucleotides. Specification of use of four of five nucleotides including both purines and pyrimidines would allow for formulation of products more consistent with the composition of human milk. See also the comment under Individual Nucleotides below.

[~~15~~16] If docosahexaenoic acid (22:6 n-3) is added to infant formula, arachidonic acid (20:4 n-6) contents ~~should~~ must reach at least the same concentration as DHA but not exceed 0.75% of total fatty acids. The content of eicosapentaenoic acid (20:5 n-3), ~~which is not a desirable constituent of infant formula but~~ , ~~can occur in~~ which is present in some sources of LC-PUFA, should not exceed the content of docosahexaenoic acid.

Comments on Footnote ~~15~~ 16

Comment: In the first sentence, we suggest replacement of the word "should" by "must."

Rationale: The intent of this sentence is to convey that addition of arachidonic acid is necessary if docosahexaenoic acid is added, thus the word "must" is appropriate.

Comment: A maximum for arachidonic acid should be added to the footnote. We recommend a maximum of 0.75% of total fatty acids as there are scientific data to support this level of addition.

Comment: For the second sentence, we suggest the above edits be made for clarity.

Comment: The 2005 IEG report suggested that conditions or limits are needed on the total amount of EPA that is present and the amount relative to other LCPUFAs in the infant formula. The footnote above states that the EPA content should not exceed the content of DHA (i.e., a ratio as high as 1:1 and as much as 0.5% of total fatty acids). However, the scientific rationale supporting this amount and ratio was has not been explained and we again request clarification of the scientific rationale supporting this amount and ratio.

Comments on Optional Ingredients Listed in Table

Taurine:

Comment: Taurine should be kept in the table of Optional Ingredients as it has not been demonstrated to be an essential nutrient for humans.

Total Nucleotides:

Comment: We recommend use of the term "total nucleotides" and deletion of the word "added," with consideration of a maximum level for total nucleotides of 16 mg/100 kcal.

Rationale: Use of the term "total 'added' nucleotides" is inconsistent with the general principle 5(b) in Annex II that total levels of a nutrient (both naturally occurring nutrients in the ingredients and added nutrients) should be taken into account when establishing minimum and maximum amounts. The maximum level of 16 mg/100 kcal for nucleotides takes into account both added and endogenous levels of nucleotides in cows' milk. Discussion supporting a maximum of 16 mg/100 kcal is included in comments that follow.

Comment: The U.S. position on nucleotides at the 27th session of CCNFSDU supported an allowable maximum level of total nucleotides in infant formula of 16 mg/100 kcal, rather than the 5 mg/100 kcal of added nucleotides that was proposed. Consensus about the level of nucleotides was not reached by the end of the meeting but the final report of the meeting does not reflect the difference of opinion about the nucleotide levels and shows only a level of 5 mg/100 kcal for total nucleotides in the table in Section 3.2.3. We request that the level of 16 mg/100 kcal for total nucleotides be included in the table in Section 3.2.3. The maximum level of 16 mg/100 kcal for total nucleotides takes into account both added and endogenous levels of nucleotides in cows' milk.

Comment: Questions about the maximum level of nucleotides raised by the United States in 2005 resulted in submission of additional information from experts. Based on this additional information and information provided at the 27th session of CCNFSDU by the Mexican Delegation, we recommended a maximum level of 16 mg/100 kcal in 2005. No new scientific information has become available since that meeting that suggests a need to reconsider this assessment and we continue to recommend that the maximum level of total nucleotides be 16 mg/100 kcal, which is at the upper range of the concentration in human milk. This level was also the maximum recommended by the LSRO Expert Panel in 1998.

Rationale: A maximum level of addition for added nucleotides of 5 mg/100 kcal was recommended by the Protein-Calorie Advisory Group (PAG) ad hoc working group meeting on clinical evaluation and acceptable nucleic acid levels recommended by the Scientific Committee on Food. The 5 mg/100

kcal level was based on methodology available at that time that measured only free nucleotides in human milk samples. Newer analytical methods consistently report higher amounts of nucleotides in human milk than previously reported, suggesting that these older methods underestimated the total amount of nucleotides in human milk. Human milk samples have been analyzed for total available nucleotide content across lactation stage, race and diet. Similar mean levels (~72 mg/L) have been reported for samples from Europe, Asia and the United States.

Of studies of infant formulas with levels of added nucleotides at or above 5 mg/100 kcal, only two studies have reported any negative morbidity data (upper respiratory infections), which is difficult to assess because of ambiguities in diagnostic criteria and reliance on reports by parents without physician verification. Several additional clinical studies of nucleotides in infant formulas at concentrations higher than 5 mg/100 kcal are available and results of these studies support a recommendation for a maximum level of 16 mg/100 kcal for total nucleotides. These studies have not reported occurrence of adverse effects in infants fed formulas containing total added nucleotides at or above 72 mg/L (~11 mg added nucleotides/100 kcal), including one study with a soy formula with nucleotide levels of about 300 mg/L (~45 mg/100 kcal). Levels of 16 mg/100 kcal of total nucleotides have been present in some infant formulas for more than a decade and there is also a long history of apparently safe use of soy formulas with nucleotide levels well above the 5 mg/100 kcal proposed by the IEG. With the exception of negative findings in two studies (which are based on ambiguous criteria and not verified by physicians), there is no evidence that suggests a safety concern for 16/mg 100 kcal as the maximum level of total nucleotides in infant formulas.

Comment: Because of inherent nucleotide levels of about 40-45 mg/100 kcal in soy infant formulas, there is no need to add nucleotides to soy infant formulas.

Individual Nucleotides:

Comment: Levels of individual nucleotides also needs further consideration. The current Codex proposal in the revised draft for Section 3 prepared by Germany for discussion at the 28th session of CCNFSDU includes specific levels for each of the five nucleotides (3 purines and 2 pyrimidines) that could be added as optional ingredients to infant formula. The Codex proposal could be simplified by using proportions of purines and pyrimidines rather than levels of each of the individual nucleotides. A maximum proportion of purines of 45% would encompass means + 2 standard deviations found in the published literature and the maximum individual levels currently proposed in the table in Section 3.2.3.

Long chain polyunsaturated fatty acids (LCPUFAs):

Comment: We support the proposed level of docosahexaenoic acid (DHA) not to exceed 0.5 % of total fatty acids.

Rationale: This proposed level is based on scientific data and we are not aware of new data to support a higher level of DHA.

3.3 Vitamin Compounds and Mineral Salts

Editorial Comment: Insert revised title: [Advisory List of Nutrient Compounds for Use in Foods for Special Dietary Uses Intended for Use by Infants and Young Children]

3.6 Specific Prohibitions

The product and its components shall not have been treated by ionizing irradiation.

VIET NAM

1. NUCLEOTIDES BRIEF SUMMARY

The traditional measurements of nucleotides level in human milk could assess only the nucleotide in the monomeric form. The levels ranges from 10-29 mg/L.
Later, Leach et al (1995), using the advance techniques, measured the total potentially available nucleotide content in human milk (both monomeric & polymeric nucleotides) and found that it is about 189±70 mmol/L (approx. 72 mg/L).

There are many studies have proved the benefits of nucleotides in enhancing immune system, especially with the content similar to that of human milk (72mg/L).

The Codex draft proposed maximum level of nucleotides in infant formulas (5 mg/100 kcal) is based on the old data about the nucleotide content in the human milk (10-29 mg/L).
This level is far below the total potentially available nucleotide content in human milk.

The ISDI (International Special Food Industries), as in line with USA FDA, requests that the maximum limit should be 16 mg/100 kcal to cover the human milk level (the human milk level is 72 mg/L equivalent to approx. 11mg/100 kcal).

Soy based infants formulas, with a long established history of safe use, have inherent nucleotide levels above 40mg/100 kcal.

Vietnam FA has granted the licences for many infant formulas fortified with nucleotides in variable contents: 26-33 mg/L (Dumex, Duch Lady, Mead Johnson...) and 72 mg/L (Abbott) for many years.

The human milk is the best for the children. To ensure the normal development of the children in the case breastfeeding is not available, the infant formulas should have the nutrients content closest to that of human milk. Therefore we would suggest that upper limit of nucleotide level in the infant formula should be 16mg/100 kcal to cover the human milk nucleotide level (approx. 11mg/100kcal).

2. SUCROSE BRIEF SUMMARY
The Codex draft proposed not to use sucrose in infant formula because of potential life-threatening symptoms in young infants with unrecognised hereditary fructose intolerance.

It is not appropriate and should be deleted, due to the following reasons:

The lactose intolerance is high in the world, around 70%, especially in Asia.

The congenital sucrose-isomaltose malabsortion is a rare inherited metabolic disorder. Only few case have been published, the majority came from European countries. This condition is extremely infrequent in Asia and Latin America.

ISDI

Assuming that the Section A (Infant Formula) should be firstly agreed before adapting the Section B (FSMP for infants), ISDI did not provide comments on the composition of FSMPs for infants in this document but would like to highlight the fact that some changes may be needed and therefore would like to keep the possibility to submit comments later on.

ISDI PROPOSAL	JUSTIFICATION
3.1 Essential Composition	
3.1.3 Infant formula prepared ready for consumption shall contain per 100 kcal (100 kJ) the following nutrients with the following minimum and maximum[1]	Add clear definitions of ‘maximum level’ and ‘guidance upper level’.

or guidance upper[~~1~~2] levels, as appropriate. The general principles for establishing these levels are identified in Annex II of this standard. [1] Maximum levels should not be exceeded in infant formulae. [~~1~~2] Guidance upper levels are for nutrients without sufficient information for a science-based risk assessment. These levels are values derived on the basis of meeting nutritional requirements of infants and an established history of apparently safe use. They may be adjusted based on relevant scientific or technological progress. Levels in infant formulae may exceed the recommended Guidance Upper Levels where it cannot be avoided either due to variable contents of particular nutrients in some components (raw materials or other ingredients) or due to technological reasons such as product integrity, nutrient stability or other justified technological reason.	Rational: ISDI believes that it is important to avoid any confusion between the two terms. Add "apparently. Rational: It is important to be consistent in the wording used in the Standard.
3.1.4 For an equal energy value the formula must contain an available quantity of each essential and semi-essential amino acid at least equal to that contained in the reference protein (breast-milk as defined in Annex I); nevertheless for calculation purposes, the concentrations of methionine and cysteine and of tyrosine and phenylalanine may be added together [~~unless the methionine to cysteine or the phenylalanine to tyrosine ratio are outside the range of 0.7-1.5: 1~~].	Delete "unless the methionine to cysteine or the phenylalanine to tyrosine ratio are outside the range of 0.7-1.5: 1". Rational: cf. annex I
3.1.5 Isolated amino acids may be added to Infant Formula only to improve its nutritional value for infants. Essential and semi-essential amino acids may be added to improve protein quality, only in amounts necessary for that purpose. Only L-forms of amino acids shall be used.	ISDI supports the proposal.
b) Lipids [5)] Lauric and myristic acids are constituents of fats, but combined should not exceed 20% of [total fatty acids]. The content of trans fatty acids shall not be higher than [~~3 %~~] 4% of total fatty acids. Trans fatty acids are endogenous components of milk fat. The acceptance of up to [~~3%~~] 4% of trans fatty acids is intended to allow for the use of milk fat in infant formulae. The erucic acid content shall be less than 1% of total fatty acids.	ISDI believes that the level of total fatty acids should be increased from 3 to 4%. Rational: - No scientific data have established a causal relation between trans fatty acid intake and changes in early development. - Natural trans fatty acid levels of cow's milk fat are often > 5% and vary geographically. - Trans fatty acids in human milk were reported to vary considerably (Spain: 1.3 - 7.2 %; Canada: 0.1 - 17%) Milk-based formulae with more than 60% of the fat as milk fat are not unusual. A maximum trans fatty acid level of 4%

<table>
<tr><td></td><td>seems more appropriate and justified within the context of a global standard.</td></tr>
<tr><td>Linoleic acid (g)<table><tr><td colspan="2">Per 100 kcal</td></tr><tr><td>Min</td><td>Max</td></tr><tr><td>0.3</td><td><s>1.2</s> 1.4</td></tr></table></td><td>Based on the justifications provided by ISDI in the document 06/130 - Annex V “Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation”, ISDI supports 1.4 g/100 kcal as a Maximum level for Linoleic acid.</td></tr>
<tr><td>c) Carbohydrates

6) Lactose and glucose polymers should be the preferred carbohydrates in formula based on cows’ milk protein and hydrolysed protein. Only precooked and/or gelatinised starches may be added to Infant Formula up to 30% of total carbohydrates or up to 2 g/100 ml.

<s>[</s>Sucrose, unless needed, and the addition of fructose, as an ingredient, <s>particularly</s> should be avoided in infant formula.<s>, because of potential life-threatening symptoms in young infants with unrecognised hereditary fructose intolerance.]</s></td><td><u>Rephrase</u> the sentence and delete the square brackets.</td></tr>
<tr><td>d) Vitamins

Vitamin A (µg RE[7])<table><tr><td colspan="2">Per 100 kcal</td></tr><tr><td>Min</td><td>Max</td></tr><tr><td>60</td><td>225</td></tr></table></td><td>Based on the justifications provided by ISDI in the document 06/130 - Annex V “Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation”, ISDI supports 225 µg/100 kcal as a Maximum level for Vitamin A.</td></tr>
<tr><td>Vitamin K (µg)<table><tr><td colspan="2">Per 100 kcal</td></tr><tr><td>Min</td><td>Guidance upper level</td></tr><tr><td>4</td><td><s>25</s> 35</td></tr></table></td><td>Based on the justifications provided by ISDI in the document 06/130 - Annex V “Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation”, ISDI supports 35 µg/100 kcal as a GUL for Vitamin K.</td></tr>
<tr><td>Thiamin (µg)<table><tr><td colspan="2">Per 100 kcal</td></tr><tr><td>Min</td><td>Guidance upper level</td></tr><tr><td>60</td><td><s>300</s> 325</td></tr></table></td><td>Based on the justifications provided by ISDI in the document 06/130 - Annex V “Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation”, ISDI supports supports 325 µg/100 kcal as a GUL for Thiamin.</td></tr>
<tr><td>Riboflavin (µg)</td><td>Based on the justifications provided by ISDI in the document 06/130 - Annex V “Industry Upper Levels of Nutrients for</td></tr>
</table>

Min	Guidance upper level
80	~~400~~ 600

Infant Formulas: Data on Current Situation", ISDI supports a GUL of 600 µg/100 kcal for Riboflavin.

Niacin[11] (µg)

Per 100 kcal	
Min	Guidance upper level
300	~~1500~~ 2650

Based on the justifications provided by ISDI in the document 06/130 - Annex V "Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation", ISDI supports 2650 µg/100 kcal as a GUL for Niacin.

Vitamin B_{12} (µg)

Per 100 kcal	
Min	Guidance upper level
0.1	~~0.5~~ 1.5

Based on the justifications provided by ISDI in the document 06/130 - Annex V "Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation", ISDI supports a GUL of 1.5 µg/100 kcal for Vitamin B_{12}.

In addition to the justification already provided, one can note that New Zealand milk contains high intrinsic levels (see Annex IV).

Pantothenic acid (µg)

Per 100 kcal	
Min	Guidance upper level
~~60~~ 400	~~300~~ 2000

ISDI would like the typing error in the table corresponding to the minimum & GUL of Pantothenic acid to be corrected as originally set in the SCF Report on Essential Requirements of Infant Formulae and Follow-on-Formulae (2003).

Vitamin C[12] (mg)

Per 100 kcal	
Min	Max/[Guidance upper level
10	~~30~~ 90

Based on the justifications provided by ISDI in the document 06/130 - Annex V "Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation", a GUL of 90 mg/100 kcal for Vitamin C.

Biotin (µg)

Per 100 kcal

Based on the justifications provided by ISDI in the document 06/130 - Annex V "Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation", a GUL of 12 µg/100 kcal for

<table>
<tr><td><table><tr><td>Min</td><td>Guidance upper level</td></tr><tr><td>1.5</td><td><s>7.5</s> 12.0</td></tr></table></td><td>Biotin.</td></tr>
<tr><td>e) Minerals & Trace Elements

Iron (formula based on cows' milk protein and protein hydrolysate) (mg)<table><tr><td colspan="2">Per 100 kcal</td></tr><tr><td>Min</td><td>Guidance upper level</td></tr><tr><td>0.3</td><td><s>1.3</s> 2.5</td></tr></table>Iron (formula based on soy protein isolate) (mg)<table><tr><td colspan="2">Per 100 kcal</td></tr><tr><td>Min</td><td>Guidance upper level</td></tr><tr><td>0.45</td><td>2.0</td></tr></table></td><td>Based on the justifications provided by ISDI in the document 06/130 - Annex V “Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation”, a GUL of 2.5 mg/100 kcal for Iron in formula based on cows' milk protein and protein hydrolysate.</td></tr>
<tr><td>Phosphorus (formula based on cows' milk protein and protein hydrolysate) (mg)<table><tr><td colspan="2">Per 100 kcal</td></tr><tr><td>Min</td><td>Guidance upper level</td></tr><tr><td>25</td><td>90</td></tr></table>Phosphorus (formula based on soy protein isolate) (mg)<table><tr><td colspan="2">Per 100 kcal</td></tr><tr><td>Min</td><td>Guidance upper level</td></tr><tr><td>30</td><td>100</td></tr></table></td><td>ISDI supports the proposal.</td></tr>
<tr><td>Sodium (mg)<table><tr><td colspan="2">Per 100 kcal</td></tr><tr><td>Min</td><td>Guidance upper level</td></tr><tr><td>20</td><td>60</td></tr></table></td><td>ISDI supports the proposal.</td></tr>
<tr><td>Potassium (mg)</td><td>Based on the justifications provided by</td></tr>
</table>

Per 100 kcal Min: 60 Guidance upper level: ~~160~~ 180	ISDI in the document 06/130 - Annex V "Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation", ISDI supports a GUL of 180 mg/100 kcal for Potassium.
Manganese (µg) Per 100 kcal Min: 1 Guidance upper level: ~~50~~ 100	Based on the justifications provided by ISDI in the document 06/130 - Annex V "Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation" and for the seed of consistency, ISDI would like to have one set of levels for Manganese: 1 µg/100 kcal for the minimum and 100 µg/100 kcal for the GUL.
Copper (µg)[14)] Per 100 kcal Min: 35 Max: ~~80~~ 190	Based on the justifications provided by ISDI in the document 06/130 - Annex V "Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation", ISDI supports a Maximum level of 190 µg/100 kcal for Copper.
Zinc (mg) Per 100 kcal Min: 0.5 Max: 1.5	ISDI supports the proposal.
f) Other substances Choline (mg) Per 100 kcal Min: 7 Max: 50	ISDI supports 50 mg/100 kcal as a GUL for Choline as there is no safety issue for this nutrient.
Myo-Inositol (mg) Per 100 kcal	ISDI supports 40 mg/100 kcal as a GUL for Myo-Inositol as there is no safety issue for this nutrient.

4 40	
3.2.1 In addition to the compositional requirements listed under 3.1.3, other ingredients may be added in order to provide substances ordinarily found in human milk ~~and 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 while ensuring that the formulation is suitable as the sole source of nutrition for the infant.	ISDI proposes to rephrase the sentence. Rational: Clarity
3.2.2 The suitability for the particular nutritional uses of infants and the safety of these substances shall be scientifically demonstrated. The formula shall contain sufficient amounts of these substances to achieve the intended effect, taking into account levels in human milk.	ISDI believes that the sentence is clear enough and therefore does not need any further addition.
3.2.3 The following substances may be added ~~in conformity with national legislation,~~ in which case their content per 100 kcal (100 kJ) in the Infant Formula ready for consumption shall not exceed:	Delete the reference to national legislation. Rational: Following Codex provisions should be enough.
Taurine mg Per 100 kcal: 12	ISDI believes that there is no need to set a Minimum level for Taurine.
Total ~~[added]~~ nucleotides mg Per 100 kcal: ~~5~~ 16 Cytidine 5'-monophosphate (CMP) mg Per 100 kcal: ~~2.5~~ 6 Uridine 5'-monophosphate (UMP) mg Per 100 kcal: ~~1.75~~ 2.5 Adenosine 5'-monophosphate (AMP) mg Per 100 kcal: ~~1.5~~ 3.4 Guanosine 5'-monophosphate (GMP) mg	ISDI does not support the composition criteria for maximum levels of nucleotides set in the Alinorm and suggests new maximum levels. Rational: cf. annex II

Per 100 kcal ~~0.5~~ 3.1 Inosine 5'-monophosphate (IMP) mg Per 100 kcal 1.0	
Docosahexaenoic Acid[15)] (% of fatty acids) Maximum ~~0.5~~ 1.0 15) If docosahexaenoic acid (22:6 n-3) is added to infant formula, arachidonic acid (20:4 n-6) contents ~~should reach at least the same concentration as DHA~~ can be added within the range of 0 – 2.0% of total fat. The content of eicosapentaenoic acid (20:5 n-3), which is not a desirable constituent of infant formula but can occur in sources of LC-PUFA, should not exceed the content of docosahexaenoic acid.	Change "0.5" into '1.0" Delete "should reach at least the same concentration as DHA " Add "can be added within the range of 0 – 2.0% of total fat" Rational: cf. annex III
3.5 Purity Requirements All ingredients shall be clean, of good quality, safe and suitable for ingestion by infants. They shall conform with their normal quality requirements, such as colour, flavour and odour.	ISDI supports the proposal.
3.6 Specific Prohibitions The product and its component shall not have been treated by ionizing irradiation.	ISDI supports the proposal.
ANNEX I Essential and semi-essential amino acids in breast milk For the purpose of this Standard the essential and semi-essential amino acids in breast milk, expressed in mg per 100 kJ and 100 kcal, are the following: per 100 kJ — per 100 kcal Cystine ~~11~~ 9 — ~~44~~ 38	ISDI suggests that the figures laid down in the Alinorm are changed in order to reflect the ones indicated in the SCF Report 2003 and taken into account in the upcoming EU Directive on Infant Formulae and Follow-on Formulae.

Histidine	~~12~~ 10	~~47~~ 40	
Isoleucine	~~20~~ 22	~~83~~ 90	
Leucine	40	~~16~~ ~~7~~ 16 6	
Lysine	~~28~~ 27	~~11~~ ~~9~~ 11 3	
Methionine	~~6~~ 5	23	
Phenylalanine	~~18~~ 20	~~75~~ 83	
Threonine	18	77	
Tryptophan	~~7~~ 8	~~31~~ 32	
Tyrosine	~~20~~ 18	~~85~~ 76	
Valine	~~24~~ 21	~~99~~ 88	

ANNEX II 4. In addition to the principles set out in No. 3, when setting minimum and maximum values, consideration will also be given to the safety of such values. For nutrients with a documented risk of adverse health effects the upper levels to be taken into account will be determined using a science-based risk assessment approach. Where scientific data are not sufficient for a science-based risk assessment, consideration should be given to an established history of apparently safe use of the nutrient in infants, as appropriate. Values derived on the basis of meeting the nutritional requirements of infants and an established history of apparently safe use should be considered as interim guidance upper levels. The approach to setting maximum and upper guidance values shall be made transparent and comprehensible. The purpose of setting GULs is to provide guidance to manufacturers and GULs should not be interpreted as goal values. When a product type or form ordinarily contains lower levels than the GULs, manufacturers should not increase levels of nutrients to approach the	Add the sentences in bold. Rational: ISDI believes that it should be clearly stated that manufacturers should not try to equal the GULs but to generally stay below and therefore that the majority of infant formulae will not contain as much as the GULs amounts but less.

GULs.	

Annex I

Comments on requirements for Amino Acids in Infant Formula

The report of the 27th session of the Codex Committee on Nutritional Foods for Special Dietary Uses (CCNFSDU) does not conclude whether the values for methionine and cysteine and those for tyrosine and phenylalanine can be added together to determine whether the needs for the sulphur-containing and aromatic amino acids in infant formula can be met. The report states in section 3.1.4: "…; nevertheless for calculation purposes the concentrations of methionine and cysteine and of tyrosine and phenylalanine may be added together [unless the methionine to cysteine or the tyrosine to phenylalanine ratio are outside the range of 0.7 to 1.5 to 1]. The recommendations for these ratios come from the IEG report[6] (Koletzko et al 2005), but they do not take into account the extensive and current experience with casein-dominant formulas containing protein levels down to 2.09 g/100 kcal and Met: Cys ratios of 2.7-3.0 to 1. They also do not take into account the actual ratios of Tyr: Phe in whey- and casein-dominant formulas. ISDI recommends that the phrase in brackets be deleted.

Methionine: Cysteine Ratio

The attached table shows the Met: Cys ratios in various products with different whey to casein ratios. The ratio in cows' milk is variable and, while not shown in the table, can approach 3.5:1. The consequence of this ratio is that all casein-dominant formulas will be outside the proposed range

Comparison of representative whey to casein ratios and amino acid composition (g amino acid /100 g protein in most cases) of mature human milk from the IEG recommendation, current commercial infant formula formulation, previous commercial formulation of this product and other ingredients.

*

	IEG Values Suggested	Whey adapted Infant Formula**	Casein Predominant Infant Formula*	Whole cow milk protein†	Milk Ingredient*
Whey: Casein	--	48:52	18:82	18:82	18:82
Cystine	2.1	1.92	1.02	0.8	0.8
Methionine	1.4	2.18	2.70	2.5	2.7
Met/Cys Ratio	0.67	1.14	2.65	3.13	3.4
Phenylalanine	4.5	3.92	4.7	4.7	-
Tyrosine	4.2	4.02	4.6	4.8	-

Data from a manufacturer, USA

** Data from a manufacturer, Spain

† O'Connor et. al. Amino acid composition of cow's milk and Human Requirements. In Welch RAS, Burns DWJ, Davis SR et. al. Milk Composition, Production and Biotechnology. Biotechnology in Agriculture Series No. 78. CAB International. Oxon and NewYork. 1997. (Editors are at the N.Z. Pastoral Research

Institute, Hamilton, NZ. O'Connor et al adapted their table from a publication by Heine[4] WE, Klein PD, Reeds PJ. The importance of alphalactalbumin in infant nutrition. J Nutrition 1991; 181:277-283.

Casein-dominant infant formulas have a long established history of safe use. They continue to be fed throughout the world, and include milk-based lactose-free infant formulas. These formulas were studied clinically before being marketed and have been on the market for a number of years with no evidence of inadequacy of protein or essential amino acids.

Lower levels of protein in casein dominant formulas have also been studied. Dr. Sam Fomon[2] and his group published a summary of their growth studies in infants from the University of Iowa in Acta Paediatrica Scandinavica in 1971. They studied groups of infants on formulas based on fat-free cow's milk (no additional whey) that had protein contents ranging from 1.64/100 kcal to 3.13 g/100 kcal. Their research unit used the same methodology for years, which eventually allowed them to analyse the groups from the various studies as if they had conducted a dose-response study. A total of 65 males and 77 females participated. Twenty-five infants were fed a formula with 1.94 g/100 kcal, 18 infants a formula with 1.64 g/100 kcal. Using analysis of variance, Fomon found no effect of protein level on growth in the ranges studied. Although the numbers in each feeding group were not large, as is the case in dose-response studies, the wide range of intakes studied and the method of analysis are compelling.

Clinical studies have also been carried out by a number of companies on different levels of protein and whey to casein ratios. In the case of one formula manufacturer, aggregate 16-week growth studies included over 400 infants, 267 of whom were fed formulas with protein levels between 1.8-2.0 g/100 kcal. These studies found no effect of protein level in these ranges on growth or any other parameter measured, including plasma amino acids in some studies, when compared to commercially available formula with higher protein levels. Of interest, some of these studies included cysteine supplementation – which again showed no measurable effect. Most of these data are not published, as is the case with many infant formula studies. One of these studies did form the basis of a publication by Janas[5] et al (1987).

Experience with commercially available casein-dominant formulas suggests no relevance of a requirement for a specific Met: Cys ratio at levels down to 2.09 g/100 kcal, and clinical studies extend this assurance down to 1.8 - 2.0 g/100 kcal. Section "3.1.3.a. Protein" of the proposed regulations sets a minimum for cow milk protein in infant formula of 1.8 g/100 kcal and states that "Infant formulae based on non-hydrolysed cows' milk protein containing less than 2 g protein/ 100 kcal . . . should be clinically evaluated."

> We recommend that the requirement for specific Met: Cys ratio be removed and that the sulphur amino acids be permitted to be added together in determining whether formula meets the requirements for essential amino acids. As formulas with protein levels below 2 g/100 kcal will be required to be studied, those studies will be the best way of evaluating whether there is a need for cysteine supplementation.

Tyrosine: Phenylalanine Ratio

Based on our understanding of the amounts of Tyr and Phe in whey- and casein- dominant formulas, all formulas will have Tyr:Phe ratios that fall within the suggested range of 0.7 - 1.7. The following table shows values for Tyr and Phe and the Tyr: Phe ratios in human milk, cows' milk casein and cows' milk whey.

	Human Milk	Cows' Milk	
		Whey	Casein
Tyr	470	320	540
Phe	440	350	460
Tyr:Phe	1.07	0.91	1.17

(Fomon's textbook Nutrition of Normal Infants. P. 126. Note that according to the text, but not stated in the table, values are in mg/g protein, though they appear to be in mg/10 g protein. Nevertheless the ratios are valid. Data are taken from Heine WE, Klein PD, Reeds PJ. The importance of alphalactalbumin in infant nutrition. J Nutrition 1991; 181:277-283.

Any formula based on cows' milk, regardless of the whey to casein ratio, will fall within the proposed standard. Thus, there seems no reason to address this issue in the regulation.

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Annex II

Comments on the Concern about the Safety of Nucleotides Raised in The Expert Report on a Global Standard for the Composition of Infant Formula

&

Clarification on Nucleotide Levels Requested by ISDI

Proposed ISDI levels of nucleotides

Optional ingredients	Unit	Min	Max (Per 100 kcal)	Comments- justification
Total added nucleotides	mg/100 kcal	0	16	Rational: The maximum total level of nucleotides should be increased to 16mg/100kcal. These levels are supported by extensive analytical and clinical data and are in line with the LSRO (Life Sciences Research Office) recommendations (1998). This level of 16mg/100kcal would not apply to formulas made from protein sources whose inherent levels are high in nucleotides, such as formulas made from soy protein isolates.
Cytidine 5'-monophosphate (CMP)	mg/100 kcal	0	~~1.75~~ 6	ISDI: maximum 6
Uridine 5'- monophosphate (UMP)	mg/100 kcal	0	~~1.5~~ 2.5	ISDI : maximum 2.5
Adenosine 5'-monophosphate (AMP)	mg/100 kcal	0	~~1.5~~ 3.4	ISDI: maximum 3.4

Guanosine 5'-monophosphate (GMP)	mg/100 kcal	0	~~0.5~~ 3.1	ISDI : maximum 3.1
Inosine 5'- monophosphate (IMP)	mg/100 kcal	0	1.0	ISDI : maximum 1

Justification

This report will address two issues - the concern about the safety of nucleotides raised by the Expert Report on a Global Standard for the Composition of Infant Formula (IEG Report, 2005); and clarification on the nucleotide levels requested by ISDI.

The Expert Report on a Global Standard for the Composition of Infant Formula (IEG Report, 2005) did not endorse increasing the levels of added nucleotides from the current E.U. upper limit of 5 mg/100 kcal to a level 16 mg/100 kcal, the level proposed by ISDI, previously endorsed by the Life Science Research Office (LSRO) expert consultation in 1998, and accepted by the regulatory authorities of countries such as Canada, China and the United States. Without any discussion, the report raised concern about "adverse effects of higher contents[*] such as increased risk of respiratory infections," citing the article by Yau et al, "Effect of nucleotides on diarrhoea and immune response in healthy term infants in Taiwan" (2003). The suggestion that infant formulas that provide intakes of nucleotides within the ranges found in human milk, and only twice the IEG proposed upper limit, have adverse clinical effects should not be ignored. Whilst it is important that the expert report should consider all papers published on nucleotides, this is a single result and many other studies have shown nucleotides to be safe at the level present in human milk. These and the findings in the clinical trial by Yau et al are examined below.

Since 1991, at least 9 studies have been carried out with infant formula supplemented by nucleotides at different levels, all of which showed that their addition to infant formula was safe and that they either showed an outcome benefit or the potential for one. As is usual in research that extends scientific knowledge, each trial has built upon the findings of earlier research and has been larger and the data collected more robust. These trials reflected not only the scientific knowledge of the day, but also the analytical capabilities for the determination of the level of nucleotides and nucleosides in human milk. Only in one trial - that quoted in the IEG report (2005) - was there a report of adverse events. The trials are listed in chronological order below, and demonstrate both the safety and outcome benefits of the addition of nucleotides to infant formulae.

1991- Carver et al

The Carver study (Carver et al, 1991) lasted 4 months and included 13 infants fed supplemented formula (33mg/L), 15 infants fed unsupplemented formula and included a reference group of 9 breast-fed infants. There were no differences in clinical outcome such as growth or infection rates, but natural killer cell activity and interleukin 2 production of peripheral blood mononuclear cells in vitro was significantly higher in infants fed a formula with nucleotides at 2 months, but not at 4 months.

1994 Brunser et al

The study of Brunser et al (1994) included 194 infants with supplemented formula (14mg/L) and 198 with control formula. Infants less than 6 months of age (mean 90 days) were enrolled and followed for 3 months. The principal focus of the study was the effect of nucleotides on diarrhoea. Trained nurses collected data during weekly home visits. Diarrhoea and other infectious morbidities were not defined in the paper. These authors reported a decrease in the incidence of diarrhoea in the supplemented group. They also stated that "the incidence of diseases such as upper and low respiratory tract, skin infections or infectious diseases were similar in both groups."

1996 Navarro et al

Navarro et al (1996) reported data on the effects of nucleotides (~12mg/L) in two groups of infants, premature infants (n = 24) followed for 3 months and malnourished infants (n = 33) followed during 105 days of inpatient recovery. Data on infections in the premature infants were not reported. In the malnourished group, the infants receiving nucleotide-supplemented formula had a decrease in the number and duration of respiratory infections.

[*] This refers to formulas with approximately 72 mg added nucleotides per litre, slightly less than 11 mg/100 kcal.

1996 Cosgrove et al

The study of Cosgrove et al (1996) was designed to examine the effects of nucleotide supplementation (33mg/L) on catch-up growth in small for gestational age infants. Seventy-four infants were randomised to supplemented formula (n = 39) or control formula (n = 35) and were followed for 6 months. Infants were assessed at 1, 2, 4 and 6 months for growth, and information on parentally reported illness since the last visit was obtained. Data on infections were not presented in the results section of the paper, but in the discussion section the authors stated that there was no effect of supplementation on the incidence of "illnesses collected by parents."

1997 Martinez-Augustin et al

The Martinez-Augustin et al (1997) study evaluated a formula supplementation with 11.6 mg/L nucleotides relative to a control diet in preterm infants. Lactose/mannitol ratios indicating intestinal permeability as well as serum concentrations of β-lactoglobulin were not different. Serum IgG antibodies to β-lactoglobulin on day 30 were higher in the nucleotide supplemented group whereas antibodies to alpha-casein did not differ. There was no reported data on infectious morbidity.

1998 Pickering et al

The study of Pickering et al was a 12-month, randomised feeding study designed to look at the effects of nucleotide supplementation on the development of the immune system. One hundred and seven infants fed supplemented formula (72mg/L) and 101 fed control formula completed the study. The study formulas were cow milk based. A group of breast-fed infants was studied concurrently. The primary outcome was the evolution of serum antibodies in response to childhood immunizations. Data on infections were not routinely collected. Two sites prospectively collected data on diarrhoeal illness (and showed a beneficial effect of nucleotide supplementation), but no other data on infectious morbidity were reported.

2002 Ostrom et al and Cordle et al

A large, double blind, randomised trial designed to ascertain the effect of nucleotides on the development of the immune system using vaccine response was published in 2002 (Ostrom et al 2002, Cordle et al 2002). This was a 12-month long feeding trial using soy-based formulas with or without added nucleotides (~72 mg/L). Seventy-three infants randomised to receive unsupplemented soy formula and 73 infants who were fed supplemented formula completed the trial. Sixty-seven breast-fed infants who were enrolled and studied concurrently also completed the study. Morbidity data were collected as follows:

> Beginning at the 1-month visit, parents recorded study infants' illnesses for the duration of the study using calendar-type diary forms. The study staff gave training and written instructions to parents to record the occurrence, symptoms, diagnosis, and treatment of any illness noted by the parents throughout the study. Clinical staff reviewed diaries for completeness at each study visit and by telephone at 9,10, and 11 months of age. The study staff collected and recorded physician-reported data. Medical records for physician-reported illnesses were source-verified by the sponsor's monitors (at 100%) regularly during the study. These records were assessed for reported bronchiolitis, bronchitis, cold, diarrhoea, enterocolitis, fever of unknown origin, non-specific urinary tract infection, otitis media, pneumonia, sinusitis and thrush/candida.

Infectious morbidity was low in all groups. Only parent-reported diarrhoea, physician-recorded diarrhoea and physician-recorded otitis media occurred with a frequency that was sufficiently high to be analysed in a comparative fashion. Breast-fed infants had less physician-reported diarrhoea than either of the formula-fed groups when analysed as "presence or absence" of diarrhoea. This difference was not significant when analysed as frequency. There was no effect of feeding on the incidence of otitis media or on antibiotic usage.

This study is particularly instructive from the point of view safety of nucleotide intakes above the IEG recommendation. Soy formulas have high levels of nucleotides; in fact, as the study's authors pointed out, the formulas in this study would have had inherent levels of nucleotides of approximately 300 mg/L (44.8 mg/100 kcal), mostly as RNA. Clinical studies have documented that a substantial portion of the inherent nucleotides in soy formulas are digestible by the infant (Kuchan et al 2000). While the percentage digested has not been fully quantified, it is clear that the infants receiving supplemented soy formula in this study had effective intakes of nucleotides well above the 72 mg/L that was added and, presumably,

substantially above the ISDI recommended levels of 16 mg/100 kcal (107 mg/L). Despite these high intakes, neither of the formula groups had any suggestion of respiratory infections of any kind (or other infections) that were out of the ordinary or greater than those experienced by the concurrently studied breast-fed infants.

2003 Yau et al

The Yau et al study (2003) referred to in the IEG report was a randomised, double blind trial in healthy infants in Taiwan. Infants were randomised to cow milk formula with or without nucleotides at ~72 mg/L. Infants were fed formula exclusively to 12 weeks of age, after which solid foods were added (with the resulting increase in nucleotide intake). Study formulas were continued to 12 months of age. The primary outcome variable for the trial was the incidence of diarrhoea. Secondary outcomes included respiratory tract infections, serum immunoglobulins and the response to hepatitis B vaccine.

Because of the concern raised in the IEG report related to the incidence of URIs in the study, this discussion will confine itself to the outcomes related to respiratory tract infections. In that regard, it is useful to see how respiratory infections were defined and diagnosed in the study.

> RTI's [respiratory tract infections], including upper respiratory tract infections (URI), lower respiratory tract infections (LRI), and otitis media (OM), were recorded throughout the study. URI was defined as illness with typical symptoms and signs, including increased nasal secretion for more than 12 hours with or without sneezing or fever…. Acute LRI (bronchitis and pneumonia) was identified by the presence of three or more of the following: cough, fever, increased respiratory rate, chest congestion, or the development of/or increase in dyspnoea, rales, rhonchi, percussion dullness, or cyanosis.

Criteria for the diagnosis of otitis media were also carefully defined. Of importance, episodes of URIs were obtained from parental diaries or from physicians' medical records, whereas the diagnoses of LRI and otitis media were based only on physicians' records.

The risk of URI in the infants fed nucleotide-supplemented formula was 1.13 times that of the infants fed unsupplemented formula. In actual fact, the difference between the two groups was quite small – a difference of average daily hazard of 2 episodes per 1000 days (control 20 per 1000 days, supplemented 22 per 1000 days). By contrast, there was no difference between formula groups in the incidence of lower respiratory infection or otitis media. The difference in URIs may have been a "real" finding or may have occurred by statistical chance, as often happens. From a practical point of view a difference of such a small magnitude (2 episodes per 2.7 years) does not appear to be of clinical or health significance, and the data must be interpreted in light of the fact that in this study parental diagnosis of URI was accepted without physician confirmation. Whether these URIs were all infectious also is open to question: for example, the diagnostic criteria would allow an infant with as minor a syndrome as increased nasal secretions for more than 12 hours without fever to be classified as having had a URI. The supposition that the difference in URIs is not of concern is further supported by the fact that there were no differences based on assigned feeding in the physician-diagnosed categories of otitis media, a condition frequently associated with or following a URI, or lower respiratory tract infections.

2004 Schaller et al 2004 Buck et al

The clinical trial reported by Schaller et al (2004) and Buck et al (2004) was set up to replicate the study of Pickering et al and also used cow milk based formula. Their study was a 12 month, randomised, double blind trial in healthy full term infants. Three hundred and eighty-one infants completed the study: 147 infants received control formula and 138 received the same formula supplemented with nucleotides at ~72 mg/L. One hundred and ninety-two breast-fed infants were studied concurrently. Subjects were seen by their physicians per protocol every 4 weeks. There were additional physician visits for illness. All medical records were reviewed blindly by trained personnel to ascertain visits for newly diagnosed illness and for follow-up. Diagnoses were categorized as otitis media, respiratory infection other than otitis media (including upper or lower respiratory infection, respiratory syncytial virus infection, congestion, cough), non-infectious and total. Serious adverse events were monitored throughout the study. There was no difference between the two formula groups or between the formula groups and the breast-fed group in physician visits for otitis media, other respiratory infections without otitis media or any other infections. There were no serious adverse events in any of the three feeding groups.

Comments and Conclusion

Of the nine studies detailed in this report of infant formula supplemented with nucleotides at levels varying from 12-72mg/L (1.8 to 10.75mg/100kcal), the importance of their role in the neonatal immune system is well demonstrated, with the more recent trials at higher levels showing a clear outcome benefit to the infant. Only in one trial, that of Yau et al (2002) was there any report of any adverse effect at the higher level of supplementation. In contrast an extensive literature of studies in animals and in human adults and infants document the integral role that nucleotides play in support of the immune system. While scientists may argue about how robust the data are from a clinical point of view, nucleotides are viewed as a semi-essential nutrient for the human infant (Uauy 1998). The IEG report accepts the safety of nucleotide supplementation at 33.5 mg/L. but not at 72 mg/L. From a biological and nutritional perspective, it is difficult to suppose that the safety profile of nucleotides is so narrow that it differs within the low and mid ranges found in human milk. This belief would imply that the early introduction of solid foods, many of which are rich sources of nucleotides, or the use of soy protein isolates in infant formula puts young infants at risk. Furthermore, it is difficult to postulate a mechanism whereby nucleotides would selectively cause more URIs at the higher intakes and not affect the susceptibility of the infant to other respiratory infections and otitis media. Finally, the IEG acknowledged the value of "an established history of apparently safe use" when assessing upper and lower limits of nutrients. While this should not supplant the results of well done clinical studies, neither should it be overlooked when it exists.

In the case of nucleotides, infant formulas supplemented at 72 mg/L were introduced in 1996 and have been available in countries in all regions of the world since 1998. More than 10 to 15 million infants have been fed such formulas without apparent difficulties. For this reason, we request that the total maximum nucleotide level should be set at 16mg/100kcal. This would permit the fortification of infant formulas to the same levels as those that have shown benefits in recent extensive clinical evaluations, and would allow for variation in inherent nucleotide levels. This level of 16mg/100kcal would not apply to formulas made from protein sources whose inherent levels are high in nucleotides, such as formulas from soy protein isolates.

Judgments about the safety of any nutrient need to be made with all the available data. The single finding of a small increase in URIs in the Yau study must be interpreted in broader context. Safety studies should not be done with human infants, and nucleotides were added to infant formula only after extensive animal toxicology studies were carried out. These included acute oral, sub chronic oral, chronic oral, multigenerational, mutagenicity and teratology studies. These studies, reviewed by toxicologists at Environ Corporation in Washington D.C. in 2000, raised no concerns and have previously been made available for review. Negative animal toxicology is reassuring, but does not imply that one should not look for or take seriously potentially adverse findings in the controlled studies in infants or in the post-marketing experience that followed. As the above review shows, the two other large trials that specifically looked for adverse effects of nucleotides supplementation at 72 mg/L on respiratory infections or otitis media did not find them. In the Yau trial itself, the effect on URIs – if real – was small, and there was no effect of nucleotide supplementation on physician-diagnosed respiratory tract infections or otitis media. Based on all of the above, we do not believe the safety concerns raised by the IEG Report related to nucleotides at the proposed higher levels are warranted.

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Annex III

Comments on Long-Chain Polyunsaturated Fatty Acids (LCPUFA).

Justification

The basis for revising the compositional criteria of the Codex Infant formula Standard is undoubtedly clear scientific evidence on the safety and efficacy of compositional modification. Within this respect ISDI shares the opinion of the IEG that numerous studies have addressed the potential benefits of LCPUFA supplementation of infant formulae.

The key LCPUFA's are arachidonic acid (AA) and docosahexaenoic acid (DHA). Both AA and DHA are found in human milk at variable concentrations dependent on the maternal diet. Infants fed unsupplemented formulae have lower plasma and erythrocytes concentrations of DHA and AA as compared to breast- or supplemented formula-fed infants (1, 2). Some clinical studies demonstrated that infants fed formulae supplemented with DHA alone or DHA in combination with AA have a better performance in visual and developmental tests than do unsupplemented infants (3-7).

Safety, as measured by infant growth, is still the cornerstone assessment of nutritional health and its validation should remain the basis for modifying the present Codex Infant Formula Standard. Although the effect of DHA and AA on infant growth has been somewhat controversial, a most comprehensive meta-analysis of the effect of LCPUFA supplementation of infant formulae on the growth of term infants has been recently published (8). The analysis, based on a total of 14 clinical trials including 1846 infants (3, 5, 6, 9-20), includes unreported details from published studies (most trials did not publish mean growth data for boys and girls) as well as data from the largest trial that are only available in abstract form. Most trials were conducted to a high standard, all enrolled infants in the first 2 wk of life, and all but one fed the test formulas until infants were at least 4 mo.

The combined data show that no effect of LCPUFA supplementation of infant formula was observed on the growth of term infants at any age. This observation was not influenced by the type of supplementation (n-3 LCPUFA (DHA) alone or n-3 + n-6 LCPUFA (DHA + AA)), the source of supplementation (triacylglycerol or phospholipid), or sex. The results of the meta-analysis are also consistent with the Cochrane systematic review that assessed the effect of LCPUFA interventions on the outcomes of term infants, although the Cochrane review contained less growth data and undertook a less extensive analysis (21).

One of the most hotly debated issues that relates to LCPUFA supplementation of infant formula is whether DHA could be added without a source of AA. Much of this debate originates from the early observations of growth deficits in preterm infants who received formulas that contained only n-3 LCPUFA compared with control formulas (22-24). It was hypothesized that the depression of plasma AA caused by dietary n-3 LCPUFA supplementation may be a factor that contributes to the growth deficit because both observational data (25) and 1 randomized trial (26) indicated an association between plasma AA and weight and length. However, as clearly shown by the recent meta-analysis (8) there is no evidence in term infants of any reduction in weight, length, or head circumference associated with dietary n-3 LCPUFA supplementation in the absence of AA according to 6 trials.

The proposed maximum levels are based on the recent recommendation made by the Scientific Committee on Food (27) which recommends based on the available studies that the concentration of n-6 LCPUFA should not exceed 2% of total fatty acids and that of n-3 LCPUFA 1% of total fatty acids.

Conclusion

Therefore it can be concluded that scientific evidence supports supplementation of infant formula with DHA alone or with a combination of DHA and AA.

As a consequence ISDI proposes the following compositional requirement with respect to LCPUFA's in the Codex Infant Formula Standard (see Table below).

	Maximum (% total fat)
	~~0.5~~ 1.0

[15)] If docosahexaenoic acid (22:6 n-3) is added to infant formula, arachidonic acid (20:4 n-6) contents ~~should reach at least the same concentration as DHA~~ can be added within the range of 0 – 2.0% of total fat. The content of eicosapentaenoic acid (20:5 n-3), which is not a desirable constituent of infant formula but can occur in sources of LC-PUFA, should not exceed the content of docosahexaenoic acid.

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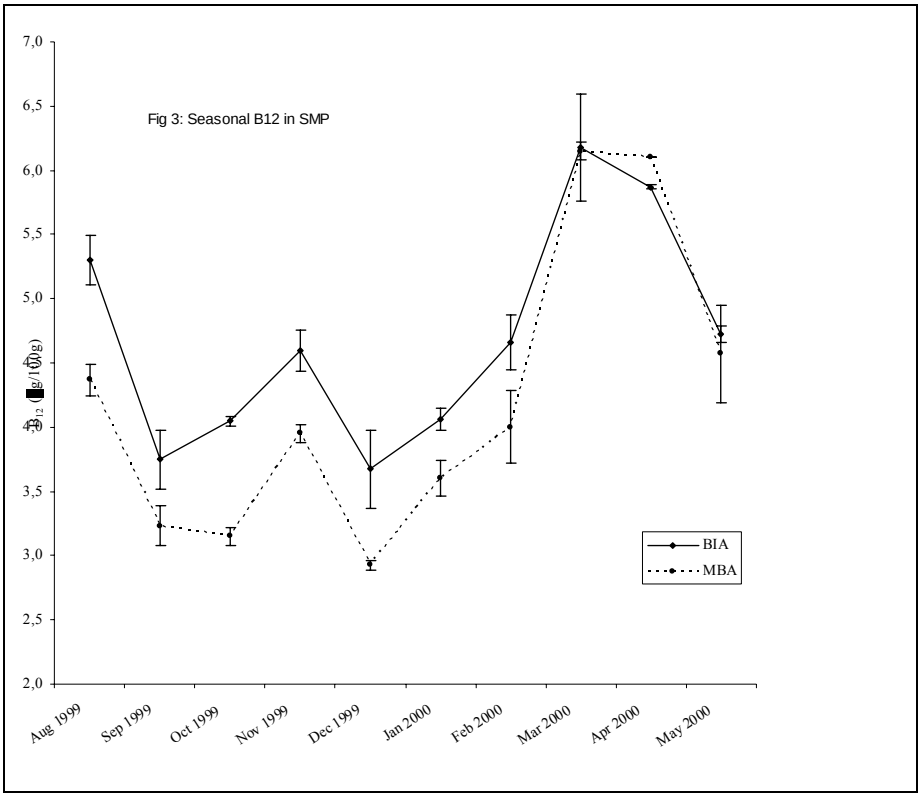
Annex IV

Additional justification for the need of higher levels for Vitamin B^{12} in Infant Formulae

In addition to the justification already provided by ISDI in the document 06/130 - Annex V "Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation", one can note that New Zealand milk contains high intrinsic levels of this vitamin, varying with the season. These levels may be as high as 6.2 µg vitamin B_{12} /100 g milk powder[2] (see graph below).

When used in infant formulae, the vitamin B_{12} level may increase into the range of 1 – 1.5 µg vitamin B_{12} /100 kcal.



SMP: Skim Milk Protein
BIA: Biomolecular Interaction analysis
MBA: Microbiological Analysis

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