



29 September 2006

**ISDI COMMENTS ON  
Draft Revised Standard for Infant Formula and Formula for Special Medical Purposes  
Intended for Infants (A)**

**SECTION 3 ESSENTIAL COMPOSITION**

Answer to CX/NFSDU 06/28/4-Add.3

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
<p><b>3.1 Essential Composition</b></p> <p>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<sup>1</sup> or guidance upper<sup>+2</sup> levels, as appropriate. The general principles for establishing these levels are identified in Annex II of this standard.</p> <p><sup>1</sup> <b>Maximum levels should not be exceeded in infant formulae.</b></p> <p><sup>+2</sup> 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 <b>apparently</b> safe use. They may be adjusted based on relevant scientific or technological progress.</p> <p><b>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</b></p>	<p><u>Add</u> clear definitions of ‘maximum level’ and ‘guidance upper level’.</p> <p><u>Rational:</u> ISDI believes that it is important to avoid any confusion between the two terms.</p> <p><u>Add</u> “apparently.</p> <p><u>Rational:</u> It is important to be consistent in the wording used in the Standard.</p>

<b>reason.</b>		
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 <del>[unless the methionine to cysteine or the phenylalanine to tyrosine ratio are outside the range of 0.7-1.5: 1].</del>		<u>Delete</u> “unless the methionine to cysteine or the phenylalanine to tyrosine ratio are outside the range of 0.7-1.5: 1”.  <u>Rational</u> : 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>b) Lipids</b>  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 <del>{3-%}</del> 4% of total fatty acids. Trans fatty acids are endogenous components of milk fat. The acceptance of up to <del>{3%}</del> 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%.  <u>Rational</u> : - No scientific data have established a causal relation between <i>trans</i> fatty acid intake and changes in early development.  - Natural <i>trans</i> fatty acid levels of cow's milk fat are often > 5% and vary geographically.  - <i>Trans</i> 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 <i>trans</i> fatty acid level of 4% seems more appropriate and justified within the context of a global standard.
<b>g)</b>		Based on the justifications provided by ISDI in the document 06/130 - Annex V “ <i>Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation</i> ”, ISDI supports 1.4 g/100 kcal as a Maximum level for Linoleic acid.
per 100 kcal		
Min	Max	
0.3	<del>1.2</del> 1.4	
<b>c) Carbohydrates</b>  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.  <del>{</del> Sucrose, unless needed, and the addition of fructose, <b>as an ingredient, particularly</b> should be		<u>Rephrase</u> the sentence and delete the square brackets.

avoided in infant formula, because of potential life-threatening symptoms in young infants with unrecognised hereditary fructose intolerance.]		
RE <sup>7)</sup> )		Based on the justifications provided by ISDI in the document 06/130 - Annex V “ <i>Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation</i> ”, ISDI supports 225 µg/100 kcal as a Maximum level for Vitamin A.
Per 100 kcal		
Min	Max	
50	<b>225</b>	
<b>Vitamin K (µg)</b>		Based on the justifications provided by ISDI in the document 06/130 - Annex V “ <i>Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation</i> ”, ISDI supports 35 µg/100 kcal as a GUL for Vitamin K.
Per 100 kcal		
Min	Guidance upper level	
4	<del>25</del> <b>35</b>	
<b>Thiamin (µg)</b>		Based on the justifications provided by ISDI in the document 06/130 - Annex V “ <i>Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation</i> ”, ISDI supports supports 325 µg/100 kcal as a GUL for Thiamin.
Per 100 kcal		
Min	Guidance upper level	
60	<del>300</del> <b>325</b>	
<b>Riboflavin (µg)</b>		Based on the justifications provided by ISDI in the document 06/130 - Annex V “ <i>Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation</i> ”, ISDI supports a GUL of 600 µg/100 kcal for Riboflavin.
Per 100 kcal		
Min	Guidance upper level	
80	<del>400</del> <b>600</b>	
<b>Niacin<sup>11)</sup> (µg)</b>		Based on the justifications provided by ISDI in the document 06/130 - Annex V “ <i>Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation</i> ”, ISDI supports 2650 µg/100 kcal as a GUL for Niacin.
Per 100 kcal		
Min	Guidance upper level	
300	<del>1500</del> <b>2650</b>	
<b>Vitamin B<sub>12</sub> (µg)</b>		Based on the justifications provided by ISDI in the document 06/130 - Annex V “ <i>Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation</i> ”, ISDI supports a GUL of 1.5
Per 100 kcal		

Min		Guidance upper level		µg/100 kcal for Vitamin B <sub>12</sub> .						
0.1		<del>0.5</del> 1.5		In addition to the justification already provided, one can note that New Zealand milk contains high intrinsic levels (see Annex IV).						
<b>Pantothenic acid (µg)</b> <table border="1"> <tr> <td colspan="2">Per 100 kcal</td> </tr> <tr> <td>Min</td> <td>Guidance upper level</td> </tr> <tr> <td><del>60</del> 400</td> <td><del>300</del> 2000</td> </tr> </table>			Per 100 kcal		Min	Guidance upper level	<del>60</del> 400	<del>300</del> 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).	
Per 100 kcal										
Min	Guidance upper level									
<del>60</del> 400	<del>300</del> 2000									
<b>Vitamin C<sup>(12)</sup> (mg)</b> <table border="1"> <tr> <td colspan="2">Per 100 kcal</td> </tr> <tr> <td>Min</td> <td>Max/[Guidance upper level</td> </tr> <tr> <td>10</td> <td><del>30</del> 90</td> </tr> </table>			Per 100 kcal		Min	Max/[Guidance upper level	10	<del>30</del> 90	Based on the justifications provided by ISDI in the document 06/130 - Annex V " <i>Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation</i> ", a GUL of 90 mg/100 kcal for Vitamin C.	
Per 100 kcal										
Min	Max/[Guidance upper level									
10	<del>30</del> 90									
<b>Biotin (µg)</b> <table border="1"> <tr> <td colspan="2">Per 100 kcal</td> </tr> <tr> <td>Min</td> <td>Guidance upper level</td> </tr> <tr> <td>1.5</td> <td><del>7.5</del> 12.0</td> </tr> </table>			Per 100 kcal		Min	Guidance upper level	1.5	<del>7.5</del> 12.0	Based on the justifications provided by ISDI in the document 06/130 - Annex V " <i>Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation</i> ", a GUL of 12 µg/100 kcal for Biotin.	
Per 100 kcal										
Min	Guidance upper level									
1.5	<del>7.5</del> 12.0									
<b>e) Minerals &amp; Trace Elements</b> <b>Iron (formula based on cows' milk protein and protein hydrolysate) (mg)</b> <table border="1"> <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><del>1.3</del> 2.5</td> </tr> </table>			Per 100 kcal		Min	Guidance upper level	0.3	<del>1.3</del> 2.5	Based on the justifications provided by ISDI in the document 06/130 - Annex V " <i>Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation</i> ", a GUL of 2.5 mg/100 kcal for Iron in formula based on cows' milk protein and protein hydrolysate.	
Per 100 kcal										
Min	Guidance upper level									
0.3	<del>1.3</del> 2.5									
<b>Iron (formula based on soy protein isolate) (mg)</b> <table border="1"> <tr> <td colspan="2">Per 100 kcal</td> </tr> </table>			Per 100 kcal							
Per 100 kcal										

Min		Guidance upper level		
0.45		2.0		
<b>Phosphorus (formula based on cows' milk protein and protein hydrolysate) (mg)</b>				ISDI supports the proposal.
Per 100 kcal				
Min	Guidance upper level			
25	90			
<b>Phosphorus (formula based on soy protein isolate) (mg)</b>				
Per 100 kcal				
Min	Guidance upper level			
30	100			
<b>Sodium (mg)</b>				ISDI supports the proposal.
Per 100 kcal				
Min	Guidance upper level			
20	60			
<b>Potassium (mg)</b>				Based on the justifications provided by ISDI in the document 06/130 - Annex V " <i>Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation</i> ", ISDI supports a GUL of 180 mg/100 kcal for Potassium.
Per 100 kcal				
Min	Guidance upper level			
60	<del>40</del> <b>180</b>			
<b>Manganese (µg)</b>				Based on the justifications provided by ISDI in the document 06/130 - Annex V " <i>Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation</i> " 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.
Per 100 kcal				
Min	Guidance upper level			
1	<del>50</del> <b>100</b>			

			Based on the justifications provided by ISDI in the document 06/130 - Annex V “ <i>Industry Upper Levels of Nutrients for Infant Formulas: Data on Current Situation</i> ”, ISDI supports a Maximum level of 190 µg/100 kcal for Copper.						
Per 100 kcal									
Min		Max							
35		190							
	<p><b>Zinc (mg)</b></p> <table border="1" data-bbox="199 678 703 902"> <tr> <td colspan="2">Per 100 kcal</td> </tr> <tr> <td>Min</td> <td>Max</td> </tr> <tr> <td>0.5</td> <td>1.5</td> </tr> </table>	Per 100 kcal		Min	Max	0.5	1.5	ISDI supports the proposal.	
Per 100 kcal									
Min	Max								
0.5	1.5								
	<p><b>f) Other substances</b></p> <p><b>Choline (mg)</b></p> <table border="1" data-bbox="199 1032 703 1256"> <tr> <td colspan="2">Per 100 kcal</td> </tr> <tr> <td>Min</td> <td>Max</td> </tr> <tr> <td>7</td> <td>50</td> </tr> </table>	Per 100 kcal		Min	Max	7	50	ISDI supports 50 mg/100 kcal as a GUL for Choline as there is no safety issue for this nutrient.	
Per 100 kcal									
Min	Max								
7	50								
	<p><b>Myo-Inositol (mg)</b></p> <table border="1" data-bbox="199 1323 703 1543"> <tr> <td colspan="2">Per 100 kcal</td> </tr> <tr> <td>Min</td> <td>Max</td> </tr> <tr> <td>4</td> <td>40</td> </tr> </table>	Per 100 kcal		Min	Max	4	40	ISDI supports 40 mg/100 kcal as a GUL for Myo-Inositol as there is no safety issue for this nutrient.	
Per 100 kcal									
Min	Max								
4	40								
	<p>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 <b>while ensuring that the formulation is suitable as the sole source of nutrition for the infant.</b></p>	ISDI proposes to rephrase the sentence. <u>Rational</u> : Clarity							
	<p>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</p>	ISDI believes that the sentence is clear enough and therefore does not need any further addition.							

	levels in human milk.													
	3.2.3 The following substances may be added <del>in conformity with national legislation</del> , in which case their content per 100 kcal (100 kJ) in the Infant Formula ready for consumption shall not exceed:	<u>Delete</u> the reference to national legislation. <u>Rational</u> : Following Codex provisions should be enough.												
Per 100 kcal		ISDI believes that there is no need to set a Minimum level for Taurine.												
12														
	<p><b>Total <del>added</del> nucleotides mg</b></p> <table border="1"> <tr><td>Per 100 kcal</td></tr> <tr><td><del>5</del> 16</td></tr> </table> <p><b>Cytidine 5'-monophosphate (CMP) mg</b></p> <table border="1"> <tr><td>Per 100 kcal</td></tr> <tr><td><del>2.5</del> 6</td></tr> </table> <p><b>Uridine 5'-monophosphate (UMP) mg</b></p> <table border="1"> <tr><td>Per 100 kcal</td></tr> <tr><td><del>1.75</del> 2.5</td></tr> </table> <p><b>Adenosine 5'-monophosphate (AMP) mg</b></p> <table border="1"> <tr><td>Per 100 kcal</td></tr> <tr><td><del>1.5</del> 3.4</td></tr> </table> <p><b>Guanosine 5'-monophosphate (GMP) mg</b></p> <table border="1"> <tr><td>Per 100 kcal</td></tr> <tr><td><del>0.5</del> 3.1</td></tr> </table> <p><b>Inosine 5'-monophosphate (IMP) mg</b></p> <table border="1"> <tr><td>Per 100 kcal</td></tr> <tr><td>1.0</td></tr> </table>	Per 100 kcal	<del>5</del> 16	Per 100 kcal	<del>2.5</del> 6	Per 100 kcal	<del>1.75</del> 2.5	Per 100 kcal	<del>1.5</del> 3.4	Per 100 kcal	<del>0.5</del> 3.1	Per 100 kcal	1.0	ISDI does not support the composition criteria for maximum levels of nucleotides set in the Alinorm and suggests new maximum levels. <u>Rational</u> : cf. annex II
Per 100 kcal														
<del>5</del> 16														
Per 100 kcal														
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Per 100 kcal														
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Per 100 kcal														
1.0														
	<p><b>Docosahexaenoic Acid<sup>15)</sup> (% of fatty acids)</b></p> <table border="1"> <tr><td><b>Maximum</b></td></tr> <tr><td><del>0.5</del> 1.0</td></tr> </table>	<b>Maximum</b>	<del>0.5</del> 1.0	<p><u>Change</u> “0.5” into ‘1.0’</p> <p><u>Delete</u> “should reach at least the same concentration as DHA “</p> <p><u>Add</u> “can be added within the range of 0 – 2.0% of total fat”</p>										
<b>Maximum</b>														
<del>0.5</del> 1.0														
	15) If docosahexaenoic acid (22:6 n-3) is added to													

<p>infant formula, arachidonic acid (20:4 n-6) contents <del>should reach at least the same concentration as DHA</del> <b>can be added within the range of 0 – 2.0% of total fat</b>. 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.</p>	<p><u>Rational</u>: cf. annex III</p>																																				
<p><b>3.5 Purity Requirements</b></p> <p>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.</p>	<p>ISDI supports the proposal.</p>																																				
<p><b>3.6 Specific Prohibitions</b></p> <p>The product and its component shall not have been treated by ionizing irradiation.</p>	<p>ISDI supports the proposal.</p>																																				
<p><b>semi-essential amino acids in</b></p> <p>of this Standard the essential and amino acids in breast milk, g per 100 kJ and 100 kcal, are the</p>	<p>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.</p>																																				
<table border="1"> <thead> <tr> <th></th> <th>per 100 kJ</th> <th>per 100 kcal</th> </tr> </thead> <tbody> <tr> <td>Cystine</td> <td><del>11</del> <b>9</b></td> <td><del>44</del> <b>38</b></td> </tr> <tr> <td>Histidine</td> <td><del>12</del> <b>10</b></td> <td><del>47</del> <b>40</b></td> </tr> <tr> <td>Isoleucine</td> <td><del>20</del> <b>22</b></td> <td><del>83</del> <b>90</b></td> </tr> <tr> <td>Leucine</td> <td>40</td> <td><del>167</del> <b>166</b></td> </tr> <tr> <td>Lysine</td> <td><del>28</del> <b>27</b></td> <td><del>119</del> <b>113</b></td> </tr> <tr> <td>Methionine</td> <td><del>6</del> <b>5</b></td> <td>23</td> </tr> <tr> <td>Phenylalanine</td> <td><del>18</del> <b>20</b></td> <td><del>75</del> <b>83</b></td> </tr> <tr> <td>Threonine</td> <td>18</td> <td>77</td> </tr> <tr> <td>Tryptophan</td> <td><del>7</del> <b>8</b></td> <td><del>31</del> <b>32</b></td> </tr> <tr> <td>Tyrosine</td> <td><del>20</del> <b>18</b></td> <td><del>85</del> <b>76</b></td> </tr> <tr> <td>Valine</td> <td><del>24</del> <b>21</b></td> <td><del>99</del> <b>88</b></td> </tr> </tbody> </table>		per 100 kJ	per 100 kcal	Cystine	<del>11</del> <b>9</b>	<del>44</del> <b>38</b>	Histidine	<del>12</del> <b>10</b>	<del>47</del> <b>40</b>	Isoleucine	<del>20</del> <b>22</b>	<del>83</del> <b>90</b>	Leucine	40	<del>167</del> <b>166</b>	Lysine	<del>28</del> <b>27</b>	<del>119</del> <b>113</b>	Methionine	<del>6</del> <b>5</b>	23	Phenylalanine	<del>18</del> <b>20</b>	<del>75</del> <b>83</b>	Threonine	18	77	Tryptophan	<del>7</del> <b>8</b>	<del>31</del> <b>32</b>	Tyrosine	<del>20</del> <b>18</b>	<del>85</del> <b>76</b>	Valine	<del>24</del> <b>21</b>	<del>99</del> <b>88</b>	
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<p><b>ANNEX II</b></p> <p>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.</p> <p>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.</p> <p>The purpose of setting GULs is to provide guidance to manufacturers and GULs should not be interpreted as goal values. When a product <b>type or form ordinarily contains lower levels than the GULs, manufacturers should not increase levels of nutrients to approach the GULs.</b></p>	<p><u>Add</u> the sentences in bold.</p> <p><u>Rational</u>: 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.</p>
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## Annex I

### Comments on requirements for Amino Acids in Infant Formula

The report of the 27<sup>th</sup> 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<sup>6</sup> (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.

\* Data from a manufacturer, USA

	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, 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<sup>4</sup> 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<sup>2</sup> 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<sup>5</sup> *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 alphasalactalbumin 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	<u>Rational:</u> The maximum <b>total</b> 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	<del>4.75</del> 6	ISDI: maximum 6
Uridine 5'- monophosphate (UMP)	mg/100 kcal	0	<del>4.5</del> 2.5	ISDI : maximum 2.5
Adenosine 5'- monophosphate (AMP)	mg/100 kcal	0	<del>4.5</del> 3.4	ISDI: maximum 3.4
Guanosine 5'- monophosphate (GMP)	mg/100 kcal	0	<del>0.5</del> 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.

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

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.

#### 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  $\beta$ -lactoglobulin were not different. Serum IgG antibodies to  $\beta$ -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.

### I. 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.

### II. 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).**

<b>Maximum (% total fat)</b>	
0.5	1.0

<sup>15)</sup> 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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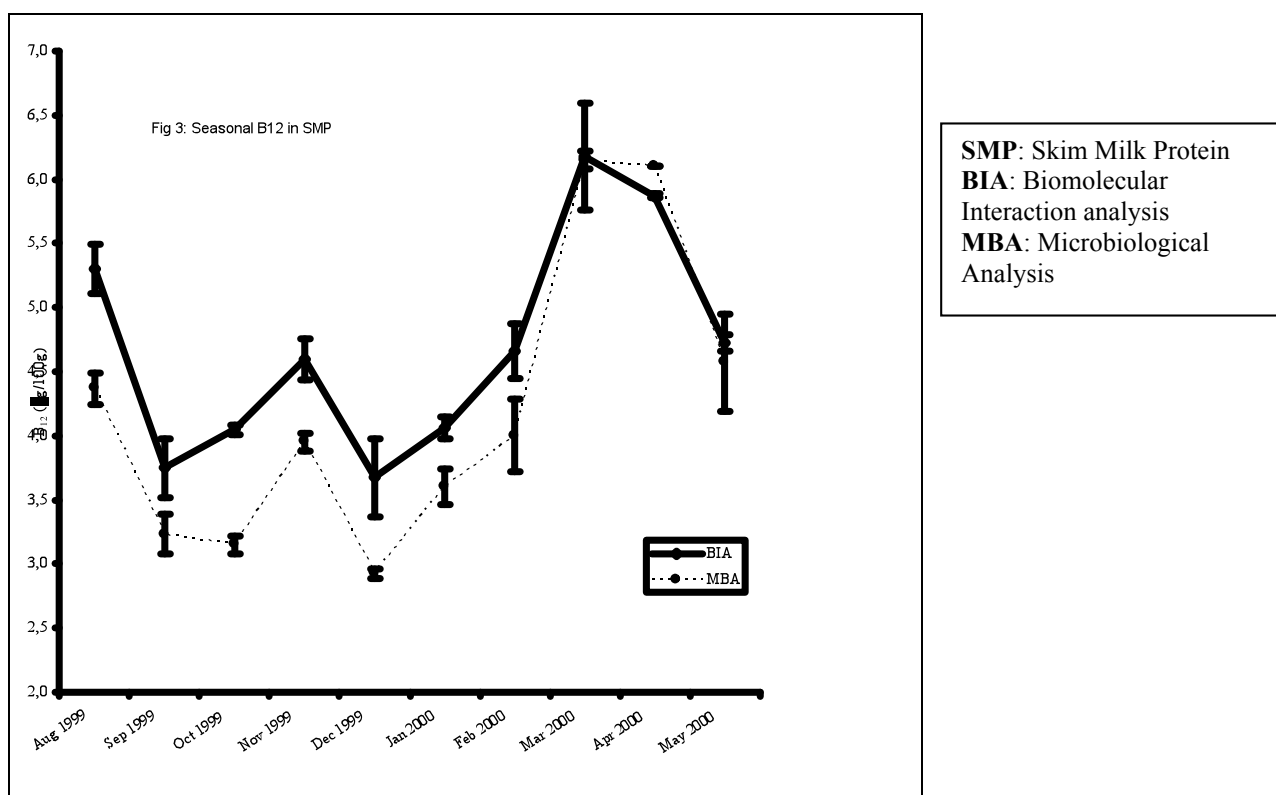
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## Annex IV

### Additional justification for the need of higher levels for Vitamin B<sup>12</sup> 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<sub>12</sub> /100 g milk powder<sup>1</sup> (see graph below).

When used in infant formulae, the vitamin B<sub>12</sub> level may increase into the range of 1 – 1.5 µg vitamin B<sub>12</sub> /100 kcal.



<sup>1</sup> Indyk HE *et al*; (2002). Determination of vitamin B<sub>12</sub> in milk products and selected foods by optical biosensor protein-binding assay: Method comparison. J AOAC 85, 72-81