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Opinion

Similarity Index Between Breast Milk and Infant Formula

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Abstract

Ignoring the low similarity between the composition of breast milk (BM) and that of infant formulas (IF) is one of the factors contributing to the low rate of exclusive breastfeeding. We propose using the Bray-Curtis Similarity Index with minor modifications to quantify this low similarity. Similarity Index between BM and declared components of two popular international IFs was < 0.61 (61%). This similarity index will safeguard against overstated claims made by manufacturers of IFs such as their IF is "closest to breast milk" or "nutritionally closer to breast milk". It will enable objective comparison between available IFs which may help in choosing between them when needed.

Keywords: *Breast Milk; Infant Formula; Bray-Curtis; Similarity Index*

Abbreviations

BM: Breast Milk; IF: Infant Formulas; ASI: Average Similarity Index; ISI: Similarity Index; ESPGHAN: European Society for Pediatric Gastroenterology Hepatology and Nutrition

Introduction

Breast milk (BM) is ideal nutrition during an infant's first six months of life [1]. Even so, the rate of exclusive breastfeeding during an infant's first six months of life is only 38% worldwide [2]. Several factors contribute to this low rate including ignoring the low degree of similarity between the composition of BM and that of infant formulas (IFs) [2]. In 1995 and again in 2004, 45% of American pediatricians surveyed believed that "Breastfeeding and formula feeding are equally acceptable methods for feeding infants" [3]. Some parents believe IF is as good as or even better than BM [4]. Inappropriate promotion of IFs is responsible for this ignorance [1]. For instance, some manufactures of IFs display overstated label claims on their products such as "Closest to breast milk" [5,6]. Therefore, we believe that there is a need to quantify the similarity between BM and IFs. Here, we propose a chemical similarity index between BM and IFs.

Proposed similarity index

The proposed similarity index is based on the Bray-Curtis Similarity Index with minor modifications. The Bray-Curtis Similarity Index is widely used in ecology to quantify similarity between two sites based on the number of species [7,8]. The total number of individuals for each species in each site is denoted by (A1, A2,.....An) and (B1, B2,.....Bn). Then,

$$\text{Bray-Curtis Similarity Index} = \frac{2\sum_{i=1}^{n} \text{minimun (Ai, Mi)}}{\sum_{i=1}^{n} \text{Ai} + \sum_{i=1}^{n} \text{Bi}}$$

The Bray-Curtis Similarity Index in its present form is not suitable to quantify the similarity between BM and IFs. The Bray-Curtis Similarity Index is used to compare between homogenous measurement units whereas measuring units of elements concentration in milk are heterogeneous. The Bray-Curtis Similarity Index is influenced by the absolute value of the data; as the value increases, its influence increases. The absolute concentration values of some low-abundance elements are higher than the values of some abundant elements. For instance, in BM the lactose concentration is 7g/dL, and the glutamic acid concentration is 1175.0 µmol/L (Table 1). Therefore, the influence of glutamic acid will be more than that of lactose. Furthermore, each element of milk has its own benefit; therefore, they should have their weight in the similarity index.

Consequently, we modified the Bray-Curtis Similarity Index to be the following:

Average similarity index (ASI)

$$< \frac{1}{n} \text{ (individual1 similarity index+individual2 similarity index +}\cdots\text{individual n similarity index)}$$

The equal sign was replaced with a less than sign because of our limited knowledge about the composition and function of elements in BM and the limited declaration of elements contained within IFs. In addition to the difference in their abundances (concentrations), many elements in common between BM and IFs also differ in their chemical structure, which cannot be accounted for in ASI. The individual similarity index (ISI) of the composition of elements in BM and IFs was calculated separately, and their average was the ASI.

We used "d" to denote the smallest value of an element in one milk and "D" to denote the largest value of the same element in the other milk. The ISI can then be calculated as follows:

1. By exact values of d and D: $\text{ISI}=\frac{2\times d}{(d+D)}$

Example: Protein is 0.9 g/dL in BM and 1.35 g/dL in an IF:

$$\text{ISI}=\frac{2\times 0.9}{(0.9+1.35)}=0.80(80\%)$$

Microsoft Excel software can be used when ISIs must be calculated by typing the following syntax into a cell: =(2*MIN(number1,number2))/SUM(number1,number2)

The Excel average function of ISIs can be used to calculate the ASI.

N.B. The equation for ISI cannot be applied when both numbers are zero. In this case, the ISI = 1.0 (i.e. complete similarity). In other words, when both numbers are equal then the ISI = 1.0.

2. By magnitude of change: translating the relationship between d and D into an algebraic equation (see 2.1 below) and then using it in the ISI equation listed above.

2.1 D is expressed as y times as much as d. Therefore, D=d×y. Replacing D with (d×y) in the above ISI equation yields $\text{ISI}=\frac{2}{(1+y)}$

Example: Protein in IF is 1.5 times as much as in BM:

$$\text{ISI}=\frac{2}{(1+1.5)}=0.80(80\%)$$

2.2 d is expressed as y times as much as D: $\text{ISI}=\frac{2\times y}{(1+y)}$

Example: Protein in BM is 0.67 times as much as in IF:

$$\text{ISI}=\frac{2\times 0.67}{(1+0.67)}=0.80(80\%)$$

2.3 D is expressed as y-fold higher than in d or d is increased by y: $\text{ISI}=\frac{2}{2+y}$

Example: Protein in BM is 0.5-fold higher than in IF or protein in BM is increased by 50% in IF:

$$\text{ISI}=\frac{2}{(2+0.5)}=0.80(80\%)$$

2.4 D is expressed as reduced by y-fold: $\text{ISI}=\frac{(2-2\times y)}{(2-y)}$

Example: Protein in IF is reduced by 33% in BM

$$\text{ISI}=\frac{(2-2\times 0.33)}{(2-0.33)}=0.80(80\%)$$

Like the Bray-Curtis Similarity Index [7-9], the ISI and ASI all range from zero (no similarity between the BM and IF) to one (100% or complete similarity).

Possible implications of ASI

Help promoting exclusive breastfeeding

Calculating the ASI safeguards against overstated claims made by manufacturers of IFs such as "closest to breast milk" or "nutritionally closer to breast milk". Therefore, it will increase general awareness of the chemical differences between BM and IFs. We present here one example. Table 2 lists the composition of two IFs imported into Saudi Arabia. The ASI between BM and two of these IFs was less than 0.61 (61%) and less than 0.59 (59%). Therefore, these two IFs were roughly 60% similar to BM at the most. The upper limits of these ASIs will decrease if undetectable elements in BM (milk lipid globule membrane, bile salt-stimulated lipase, and 2'-fucosyllactose) or in IFs (β-Lactoglobulin and αS2-Casein) are included.

The limitation of this is that BM composition, is still not well defined: the concentrations of most elements vary between and during feedings and between nursing mothers [10,11]. We propose three suggestions that may overcome this limitation. The first suggestion is to choose one of the suggested elements concentration in the literature such as the one provided in the table 1. The second suggestion is to establish a national or international online database listing the concentrations of elements in BM [12]. The third suggestion is to use point-of-care BM analyzers that can quantitatively measure fat, protein, carbohydrate, total solids, and energy [13]. If the ASI turns to be as useful as we think, then national and international professional health bodies may wish to endorse it.

Enable Objective Comparison Between Various IFS

Comparison between various IFs can be accomplished using two approaches. The first approach involves calculating the ASI between IFs and BM as we have demonstrated above (Table 2). The second approach involves calculating the ASI between IFs and international IF standards including the Codex Alimentarius Commission [14], the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) [15], Commission Directive 2006/141/EC [16], the European Food Safety Authority [17], and the United States Code of Federal Regulations 21CFR107.100 [18].

A recent study cross-referenced the composition of five cow's milk powdered IFs (S26 Gold, Bebelac, NAN, Similac, and Liptomil) imported into the Saudi market with the ESPGHAN standards [19]. Two of these IFs are those we compared with BM in table 1. The study's authors judged that all the five IFs were safe and nutritionally appropriate [19]. They also judged that Bebelac and Liptomil were the most suitable because they contain more elements than the other three IFs [19]. The basis of this conclusion might be flawed. Not every added nutrient can be considered advantageous. Bebelac contains glucose, which is also present in a small amount in BM (0.048 g/dL). However, ESPGHAN advises against adding glucose to IFs because glucose may react with protein and form Maillard products during the manufacture of IF [15]. Two elements (fluoride and eicosapentaenoic acid) are present in Liptomil but not in S26 Gold. Three elements (carotenoids, lutein, and α-lactalbumin) are present in S26 Gold but not in Liptomil. Therefore, it is unclear why the authors preferred Liptomil over S26 Gold, which contains more unique elements than Liptomil. Bebelac declares a concentration of saturated (including trans), monounsaturated, and polyunsaturated fatty acids. Breaking down components of macronutrient does not mean that Bebelac contains these fatty acids and other four IFs do not contain them. It is just a matter of more declaration. Indeed, all five IFs declare the concentration of polyunsaturated fatty acids (linoleic, α-linolenic, arachidonic, and docosahexaenoic). Trans saturated fatty acids may be disadvantageous rather than advantageous, particularly if they are present in quantity that exceeds the allowed amount (≤ 3% of fat) and their source is declared to be commercially hydrogenated oils rather than cows' milk [15,20,21]. Moreover, adding new elements may disturb the concentration of other elements. It has been shown that adding prebiotics to IF increases the concentration of mannitol and glucose and decreases the concentration of phosphate and alanine [22].

Here, we demonstrated a more objective comparison between these five IFs. We calculated the ISI between each claimed element in labels of the five IFs and minimum required elemental concentration endorsed by ESPGHAN. We selected the minimum ESPGHAN values based on the concept that minimum values should be targeted as the maximum values driven mostly by commercial interests that may cause metabolic stress or place a burden on the biological functions of infants [17,23]. The ESPGHAN guidelines do not specify the minimum required values of some elements such as fluoride or they specify some quantities to be zero, like docosahexaenoic acid, taurine, and nucleotides. In such cases, we used the lowest concentration of these elements in the IF that contained them in calculating the ISI. The rationale behind this was as follows: zero values yield an ISI equals zero, which will not differentiate between IFs. The ESPGHAN guidelines against adding glucose to IF as explained above. Therefore, the ISI of such elements was scored as zero if the IF contained it and one if the IF did not contain it. If some manufacturers declared the concentration of elements that are present in BM and are considered by ESPGHAN to be either compulsory or non-compulsory like fluoride and nucleotides then we considered it to be absent in the IFs that did not declare it. We excluded from our calculation elements that are were not present in BM and that ESPGHAN endorses as being non-compulsory such as polysaccharides (starches) or it does not endorse it at all (e.g., maltose).

After calculating the ISIs, we calculated the five ASIs. We conducted all of the calculations using Microsoft Excel software. The ASIs of the five IFs in descending order were 0.69, 0.65, 0.64, 0.62, and 0.60 (Table 3). The IF scored the highest ASI (0.69) was neither Bebelac nor Liptomil which is in disagreement with the above cited Saudi study [19]. Another disagreement between our calculation and the Saudi study is the low level of similarity (69 - 60%) between these IFs and the minimum element concentration endorsed by ESPGHAN. These low ASIs challenge the safety of the five studied IFs they may cause metallic stress in infants. Therefore, the ASI may be a useful variable that should be considered in future research looking at the outcomes of various IFs.

The two examples noted above have demonstrated than the ASI enables an objective comparison between various IFs. The ASI makes it possible to compare between all available IFs unbiasedly and robustly. For instance, there are about 18 IFs that are imported into Saudi markets [19]. Therefore, it will be hard, if not impossible, to compare unbiasedly and robustly between all 18 without a tool like the ASI. We accordingly advise that future similar study use the ASI.

Moreover, an objective comparison between all available IFs in a local market may have clinical implications. Prescribing IFs when they are desperately needed is bewildering and daunting, particularly when a manufacturer claims that its IF is nutritionally closer to BM than other IFs [24,25]. However, head-to-head clinical comparisons between most IFs are lacking [17,26]. Therefore, an objective comparison between all available IFs in a local market can help in this regard; it can be assumed that a larger ASI implies a better IF. However, it should be kept in mind that a better IF is the one that more closely emulates the composition of BM as well as the physiologic functions and health outcomes of exclusive breastfeeding [17].

Enable direct comparison between different studies

Chemical and metabolomic studies use different analytic methods and accordingly express their finding using different measurement units. This heterogeneity precludes direct comparisons between studies. Therefore, calculating ASI enables a direct comparison between such studies.

Conclusions

Ignoring the low similarity between BM and IFs is one of the factors contributing to low exclusive breastfeeding rate. We suggested using the Bray-Curtis Similarity Index with minor modifications to quantify this low similarity. We outlined implications and limitations of this index. We demonstrated two methods for comparing between various IFs objectively. This work is the first step in this regard and hopefully will inspire fruitful discussion.

Acknowledgments

We dedicate this work to the great Saudi pediatric nephrologist Dr. Sadek Al-Omran (April 19, 1965-September 3, 2017) who recently died of metastatic rectal adenocarcinoma.

Elements	Concentration	References
Energy (Kcal/dL)	66.0	22, 27-41
Ash (g/dL)	0.2	
Fiber	zero	
Total protein (g/dL)	**0.9**	
Whey (g/dL)	0.7	
α -lactalbumin (g/dL)	0.16	
Lactoferrin (g/dL)	0.17	
Lysozyme (mg/L)	400	
IgA (mg/dL)	119.6	
IgM (mg/dL)	2.9	
IgG (mg/dL)	2.9	
β-Lactoglobulin	Not detected (ND)	
Casein (g/dL)	0.2	
α_{S1}-Casein (% of total casein)	trace	
α_{S2}-Casein (% of total casein)	ND	
β-Casein (% of total casein)	85%	
κ-Casein (% of total casein)	15%	
Casein micelle size (nm)	30-75	
Whey: casein ratio	80:20	
Total fat (98% as triacylglycerol) (g/dL)	**3.4**	
Phospholipid (mg/dL)	27.0	
Cholesterol (mg/dL)	17.0	
Desmosterol (mg/dL)	1.8	
Plant sterols (mg/dL)	0.11	
Sphingomyelin (µmol/L)	110.0	
Gangliosides (mg/L)	20.0	
Total sphingosine (µg/ml per portion)	8.0	
Free sphingosine (ng/ml per portion)	23.0	
Total sphinganine (µg/ml per portion)	0.5	
Free sphinganine (ng/ml per portion)	8.0	
Neutral glycosylceramides (mg/L)	25	
Total carbohydrates (g/dL)	**8.1**	
Lactose (g/dL)	7.0	
Oligosaccharides (g/dL)	1.4	
Sialic acid (g/dL)	7.0	
Glucose (mg/dL)	48.7	
Fructose (mg/dL)	5.2	
Galactose (mg/dL)	7.7	
Myo-inositol (mg/dL)	46.1	
Mannitol (mg/dL)	7.5	
Isomaltulose	ND	
Maltodextrin		

Total Amino Acids	mg/dL	g/100g protein	
Histidine	29.1	2.3	15, 42
Isoleucine	64.7	5.3	
Leucine	118.8	9.4	
Lysine	82.2	6.3	
Methionine	17.8	1.4	
Phenylalanine	46.0	4.5	
Threonine	54.9	4.3	
Tryptophan	24.3	1.8	
Valine	67.0	4.9	
Cystine	23.5	2.1	
Tyrosine	52.8	4.2	
Arginine (mg/dL)	44.5		
Alanine	48.1		
Aspartic acid	107.2		
Glycine	28.9		
Proline	100.3		
Serine	52.7		
Glutamic acid	201.3		
Non-protein nitrogen (NPN)			
NPN (% of total protein)	25.0		27, 43, 44
Urea (mg/L)	217.0		
Uric acid (mg/L)	10.0		
Ammonia (mg/L)	10.6		
N-acetylneuraminic acid (mg/L)	38.0		
Glucosamine nitrogen (mg/L)	88.0		
Creatine (mg/L)	7.2		
Creatinine (mg/L)	11.0		
Hippuric acid (mg/L)	0.014		
Orotic acid (mg/L)	ND		
Free Amino acid (µmol/L)			

Histidine	21.5		42, 45
Isoleucine	14.2		
Leucine	54.9		
Lysine	58.1		
Methionine	10.1		
Phenylalanine	15.9		
Threonine	79.1		
Taurine	287.1	50 (mg/L)	
Valine	57.4		
Cystine	32.2		
Tyrosine	22.3		
Arginine	30.2		
Alanine	199.9		
Aspartic acid	55.3		
Glycine	84.0		
Proline	49.1		
Serine	99.8		
Glutamic acid	1175.0		
Glutamine	134.6		
Carnitine (mmol/L)	0.1 (1.6 mg/dL)		27
Oligosaccharides (N-Glycome)			
N-glycan number (species-specific number)	38.0 (18.0)		46
Shared N-glycan pool number	20.0		
N-glycolylneuraminic acid number	ND		
Sialylated Complex/Hybrid N-glycans (% of N-glycans)	57%		
Neutral Complex/Hybrid N-glycans (% of N-glycans)	37%		
High Mannose N-glycans (% of N-glycans)	6%		
Fucosylated (% of fucosylated N-glycans)	75%		
Non-Fucosylated (% of fucosylated N-glycans)	25%		
Total nucleotides (mg/dL)	**1994.0**		28
Cytidine monophosphate	461.0		
Uridine monophosphate	179.0		
Adenosine monophosphate	175.0		
Guanosine monophosphate	138.0		
Inosine monophosphate	228.0		
Cytidine diphosphate	474.0		
Uridine diphosphate	174.0		
Adenosine diphosphate	69.0		
Guanosine diphosphate	96.0		

Total saturated fatty acids (FA)	**g/100g FA**	**mg/dL**	**45.33**	**1632**	27,47-49
Butyric acid (C 4:0)			0.19	7.0	
Caproic acid (C6:0)			0.15	5.0	
Caprylic acid (C8:0)			0.46	17.0	
Capric acid (C10:0)			1.03	37.0	
Lauric acid (C12:0)			4.40	158.0	
Tridecanoic acid (C13:0)			ND	2.0	
Myristic acid (C14:0)			6.31	227.0	
Pentadecanoic acid (C:15)			0.64	23.0	
Palmitic acid (C16:0, ≈70% at sn-2 position)			22.17	799.0	
Margaric acid (C17:0)			0.81	29.0	
Stearic acid (C18:0)			8.17	290.0	
Arachidic acid (C20:0)			0.44	16.0	
Heneicosylic acid (C21:0)			0.13	5.0	
Behenic acid (C22:0)			0.12	4.0	
Tricosanoic (C23:0)			0.13	-------	
Lignoceric acid (C24:0)			0.25	9.0	
Total monounsaturated FA			**39.45**	**1420.0**	27, 48, 49
Myristoleic acid (C14:1n5)			0.48	18.0	
Pentadecenoic acid (15:1)			0.11	4.0	
Palmitoleic acid (C16:1n7)			3.65	131.0	
Margaroleic acid (C17:1)			0.37	13.0	
Oleic acid (C18:1n9)			33.9	1223.0	
Eicosenoic acid (C20:1n9)			0.67	24.0	
Erucic acid (C22:1n9)			0.08	3.0	
Nervoic acid (C24:1n9)			0.12	4.0	
Total polyunsaturated FA (PUFA)			**15.27**	**549.0**	27, 48-50
Total n6 series PUFA			**13.59**	**489.0**	
Linoleic (C18:2n6)			12.0	433.0	
γ-Linolenic acid (C18:3n6)			0.25	9.0	
Eicosadienoic acid (C20:2n6)			0.27	10.0	
Dihomo-γ-linolenic acid (C20:3n6)			0.32	12.0	
Arachidonic acid (C20:4n6)			0.29	17.0	
Docosadienoic acid (C22:2n6)			0.11	4.0	
Adrenic acid (C22:4n6)			0.09	3.0	
Docosapentaenoic acid (C22:5n6)			0.09	3.0	
Total n3 series PUFA			**1.68**	**60.0**	27, 32, 48-51
α-Linolenic acid (C18:3n3)			0.67	37.0	
Eicosatetraenoic acid (C20:4n3)			0.18	3.0	
Eicosapentaenoic acid (C20:5n3)			0.12	4.0	
Docosapentaenoic acid (C22:5n3)			0.19	7.0	
Docosahexaenoic acid (C22:6n3)			0.25	9.0	
Vitamins					

Vitamin A (µg/dL)			75		27, 28
Vitamin D (µg/dL)			0.04		
Vitamin E (mg/dL)			0.25		
Vitamin K (µg/dL)			1.5		
Vitamin C (mg/dL)			5.0		
Vitamin B1 (µg/dL)			14.0		
Vitamin B2 (µg/dL)			40		
Vitamin B3 (µg/dL)			160		
Vitamin B6 (µg/dL)			15		
Vitamin B5 (µg/dL)			246		
Vitamin B12 (µg/dL)			0.1		
Folic acid (µg/dL)			0.14		
Biotin (µg/dL)			0.6		
Carotenoids (µg/dL)			218		
Choline (µmol/L)			286 (3.0 mg/dL)		52
Minerals and trace elements					
Sodium (mg/dL)			15.0		28, 41
Potassium (mg/dL)			60.0		
Chloride (mg/dL)			43.0		
Calcium (mg/L)			30.0		
Magnesium (mg/dL)			3.0		
Phosphorus (mg/dL)			13.0		
Iron (mg/dL)			0.03		
Zinc (mg/dL)			0.15		
Copper (mg/dL)			0.03		
Sulfur (mg/dL)			14.0		
Manganese (µg/dL)			1.2		
Iodine (µg/dL)			7.0		
Fluoride (µg/dL)			1.6		
Selenium (µg/dL)			1.6		
Cobalt (µg/dL)			0.01		
Chromium (µg/dL)			0.03		
Molybdenum (µg/dL)			0.30		
Potential renal solute load	mosm/L	mosm/100kcal	93.0	14.0	53
Osmolarity (mosmol/kg of water)			286.0		27, 28
Osmolality (mosmol/kg of water)			290.0		
pH			6.8		
Cells (number/L)			10^8		28, 56
Macrophages			60%		
Neutrophils			40%		
Lymphocytes			10%		

Hormones (ng/mL)					
Thyroxine (T4)			40.1		28, 55
Triiodothyronine (T3)			0.1		
Cortisol			32.0		
Progesterone			40.0		
Pregnanediol			150.0		
Estrogens			840.0		
Melatonin (pg/mL)			7.3		56
Leptin			4.97		57
Enzymes					
Bile Salt-Stimulated Lipase	units/mL	µg/mL	32.3	200	58-60
α-Amylase (units/mL)			3.5		61, 62
Sulfhydryl Oxidase (nmol/(min.mL))			901.0		63
Glutathione peroxidase (units/L)			77.1		27
Alkaline Phosphatase (units/mL)			147.0		64, 65
Platelet-Activating Factor Acetylhydrolase (nmol/(min.mL))			3.4		27, 66
Adenosine triphosphatase (mg P/mL/min)			5.38		67
Inorganic Pyrophosphatase (mg P/mL/min)			0.14		
Cholinesterase (µmol ester/mL/min)			1.49		
Protease (µmol tyrosine/1000mL/min)			0.76		
Catalase (µmol H_2O_2/mL/min)			2.8		
Peroxidase (units)			0.05		
Lactate dehydrogenase (units)			140.0		70
Malate dehydrogenase (units)			70.0		
Xanthine oxidase (mU/mg)			20.0		69
Glucose-6-phosphate dehydrogenase (units/mL)			1.4		70
Biotinidase (pmol/min/mg)			7.5		71
Ribonuclease (units/mL)			50		72
N-Acetylglucosaminyl transferase (nmol/hr/mg protein)			0.48		73
Folate-Binding Protein (nmol/L)			250.0		74
Vitamin B12-Binding Protein (nmol/L)			25.0		75
Thyroxine-Binding Protein (µg/dL)			27.3		76
Corticosteroid-Binding Protein (L/g protein)			1.3		77
Lactoperoxidase (mg/mL)			13		54
Nutrition antioxidant (µg/L)					
α-carotene			7.7		78
β-carotene			49.1		
β-cryptoxanthin			21.7		
Lycopene			66.1		
Lutein+zeaxanthin			40.1		
Retinol			401.6		
α-tocopherol			5880.8		
γ-tocopherol			1207.1		
Total antioxidant capacity (µM)			642.94		79

Total antioxidant capacity (mM Trolox)			0.43		56
Superoxide dismutase (ng/mL)			229.0		
Glutathione peroxidase 3			1800.0		
Cytokines					
Interleukin (IL)-1β (U/mL)			1130.0		28, 80
IL-4 (pg/mL)			5.6		
IL-5 (pg/mL)			6.2		
IL-6	U/mL	pg/mL	151.0	5.6	
IL-7 (U/mL)			100.0		
IL-8 (U/mL)			3684.0		
IL-10	U/mL	pg/mL	3400.0	19.0	
Tumor necrosis factor-α (U/mL)			620.0		
Granulocyte-colony-stimulating factor (CSF), (U/mL)			351.0		
Macrophage-CSF (U/mL)			17120.0		
Epidermal growth factor (U/mL)			200000.0		
Transforming growth factor (TGF)-α (U/mL)			7200.0		
TGF-β_1 (pg/mL)			125.0		
TGF-β_2	U/mL	pg/mL	130.0	125.0	
Interferon-γ (pg/mL)			67.0		
Biological functional enrichment of protein (enrichment score)					
Immunity			14.32		81
Transport			2.94		
Enzyme			8.99		
Milk Lipid Globule Membrane (MLGM)					
Percent of globules with crescents			7-44		27, 82
Total lipids (mg/mg protein)			1.46		
Phospholipids (mg/mg protein)			0.35		
Neutral lipids (mg/mg protein)			1.1		
Glycosphingolipids (µg/mg protein)			32.0		
Hexoses (pg/mg protein)			45.0		
Hexosamines (µg/mg protein)			44.0		
Sialic acids (µg/mg protein)			18.0		
Glycosaminoglycans (pg/mg protein)			ND		
RNA (µg/mg protein)			15.0		
Triglycerides (% of total lipid)			58.0		
Diacylglycerols (% of total lipid)			8.0		
Monoacylglycerols (% of total lipid)			0.6		
Sterols (% of total lipid)			0.7		
Sterol esters (% of total lipid)			Trace		
Unesterified fatty acids (% of total lipid)			7.3		
Hydrocarbons (% of total lipid)			Trace		
Phospholipids (% of total lipid)			23.0		
Sphingomyelin (% of total phospholipid)			26.0		
Phosphatidyl choline (% of total phospholipid)			30.0		
Phosphatidyl ethanolamine (% of total phospholipid)			37.0		
Phosphatidyl inositol (% of total phospholipid)			5.0		
Phosphatidyl serine (% of total phospholipid)			1.0		
Lysophosphatidyl choline			2.0		
Proteins number (species-specific number)			312 (146)		

MLGM Protein (log_{10} average intensity based absolute quantification)		
Lactotransferrin	6.87	81
Serum albumin	6.02	
Folate receptor α	5.16	
Monocyte differentiation antigen CD14	5.37	
α-lactalbumin	7.16	
Toll-like receptor 2	4.30	
Keratin, type II cytoskeletal 79	4.47	
Plasma membrane calcium-transporting ATPase 2	3.38	
14-3-3 protein zeta/delta	4.29	
Fatty acid synthase	4.02	
Related RAS viral (R-ras) oncogene homolog	3.67	
β-casein	7.23	
Osteopontin	5.06	
Ras-related protein Rab-10	4.55	
Elongation factor 1-α1	4.17	
GTP-binding protein SAR1a	4.35	
Lanosterol synthase	4.27	
Syntaxin-3	4.64	
Ras-related protein Rab-5C	3.58	
CD9 antigen	5.79	
Xanthine dehydrogenase/oxidase	6.11	
Annexin A2	4.20	
Erythrocyte band 7 integral membrane protein	5.28	
Actin, cytoplasmic 2	4.71	
CD59 molecule, complement regulatory protein	6.12	
Fibroblast growth factor-binding protein 1	4.60	
Cell death activator CIDE-A	4.57	
GTP-binding protein SAR1b	3.41	
Heat shock protein HSP 90-α	2.95	
Ras-related protein Rab-1A	4.68	
EH domain-containing protein 4	3.53	
Butyrophilin subfamily 1 member A1	6.80	
Perilipin-2	6.24	
Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit β-1	3.79	
Synaptic vesicle membrane protein VAT-1 homolog	3.98	
14-3-3 protein β/α	3.03	
Polyubiquitin-C	3.56	
Ras-related protein Rab-18	5.29	
Mucin-1	3.79	
Ras-related C3 botulinum toxin substrate 1	3.85	
Ras-related protein Rab-2A	3.93	
Polymeric immunoglobulin receptor	5.17	
Nucleobindin-1	2.58	
Synaptobrevin homolog YKT6	3.68	
Fatty acid-binding protein, heart	5.09	
α-S1-casein	6.69	
ATP-binding cassette, sub-family G, member 2	4.92	
Acyl-CoA synthetase long-chain family member 1	3.64	
Heat shock cognate 71 kDa protein	3.19	
Dehydrogenase/reductase (SDR family) member 1	3.77	
Platelet glycoprotein 4	4.78	
Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit β-2	3.40	
IGL@ protein	4.39	
Lactadherin	4.46	

Milk serum protein (log10 average intensity based absolute quantification)		
Albumin	7.30	81
Fatty acid synthase	4.38	
Xanthine dehydrogenase	5.36	
α-1-antichymotrypsin	5.44	
Lactoferrin	7.17	
α-trypsin chain 1	6.74	
Monocyte differentiation antigen CD14	5.52	
Clusterin	5.74	
β-casein	7.80	
L-lactate dehydrogenase B chain	4.25	
α-1-antitrypsin	5.38	
Polymeric immunoglobulin receptor	6.47	
Vitamin D-binding protein	5.20	
Lipoprotein lipase	4.05	
Osteopontin	6.35	
Heat shock 70 kDa protein 8	3.89	
α-lactalbumin	7.79	
α-2-plasmin inhibitor	3.89	
β-2-microglobulin	5.47	
Butyrophilin subfamily 1 member A1	5.60	
Nucleobindin 2	4.44	
Perilipin-2	4.49	
α-S1-casein	7.33	
Apolipoprotein E	3.81	
Antithrombin-III	3.86	
Ras-related protein Rab-18	3.70	
Lactadherin	4.88	
Epididymal secretory protein E1	4.49	
Complement C3	4.56	
Zinc-α-2-glycoprotein	4.88	
α-2-HS-glycoprotein	4.32	
IGL@ protein	6.19	
Complement factor B	2.66	
α-1-acid glycoprotein 1	4.94	
Fibroblast growth factor-binding protein 1	3.69	
Leucine-rich α-2-glycoprotein	4.25	
Nucleobindin 1	4.05	
Isocitrate dehydrogenase 1	3.00	

Table 1: *Concertation of various elements in mature breast milk.*

Elements	BM[a]	IF-A	IF-B	ISI between BM and IF-A	ISI between BM and IF-B
Energy (Kcal/dL)	66.00	66.0	65.0	1.0	(2×65)/(65+66)=0.99
Total protein (g/dL)	0.90	1.30	1.40	0.82	0.78
Whey (g/dL)	0.70	0.80	0.70	0.93	1.00
Casein (g/dL)	0.20	0.50	0.20	0.57	1.00
Total fat (g/dL)	3.40	3.60	3.50	0.97	0.99
Linoleic acid C18:2 (n-6), (mg/dL)	433.00	520.00	600.00	0.91	0.84
α-linolenic acid C18:3 (n-3), (mg/dL)	37.00	42.00	100.00	0.94	0.54
Arachidonic acid C20:4 (n-6), (mg/dL)	17.00	12.00	6.90	0.83	0.58
Docosahexaenoic acid C22:6 (n-3), (mg/dL)	9.00	12.00	6.90	0.86	0.87
Total carbohydrates (g/dL)	8.10	7.30	6.80	0.95	0.91
Lactose (g/dL)	7.00	7.00	6.80	1.00	0.99
Oligosaccharides (g/dL)	1.40	0.30	0.52	0.35	0.54
Nuclotidees (mg/dL)	1181.00	2.60	3.20	0.00	0.01
Taurine (mg/dL)	5.00	4.70	3.80	0.97	0.86
L-carnitine (mg/dL)	1.60	1.00	1.30	0.77	0.90
Lutein ((μg/dL)	40.10	1.00	0.00	0.05	0.00
Vitamin A (μg/dL)	75.00	66.00	63.90	0.94	0.92
Caroten (μg/dL)	218.00	21.00	0.00	0.18	0.00
Vitamin D3 (μg/dL)	0.04	1.20	1.10	0.06	0.07
Vitamin E (mg/dL)	0.25	0.73	1.00	0.51	0.40
Vitamin K (μg/dL)	1.50	6.70	4.50	0.37	0.50
Vitamin B1 (μg/dL)	14.00	100.00	58.00	0.25	0.39
Vitamin B2 (μg/dL)	40.00	110.00	102.00	0.53	0.56
Vitamin B3 (μg/dL)	160.00	500.00	500.00	0.48	0.48
Vitamin B6 (μg/dL)	15.00	55.00	58.00	0.43	0.41
Vitamin B5 (μg/dL)	246.00	350.00	400.00	0.83	0.76
Folic acid (μg/dL)	0.14	11.00	10.00	0.03	0.03
Vitamin B12 (μg/dL)	0.10	0.18	0.20	0.71	0.67
Biotin (μg/dL)	0.60	2.00	1.90	0.46	0.48
Vitamin C (mg/dL)	5.00	9.00	13.00	0.71	0.56
Choline (mg/dL)	218.00	16.00	3.70	0.14	0.03
Myo-inositol (mg/dL)	46.10	4.50	5.10	0.18	0.20
Iron (mg/dL)	0.03	0.80	0.70	0.07	0.08
Calcium (mg/L)	30.00	42.00	45.00	0.83	0.80
Phosphorus (mg/dL)	13.00	24.00	28.00	0.70	0.63
Magnesium (mg/dL)	3.00	4.50	5.10	0.80	0.74
Sodium (mg/dL)	15.00	16.00	19.00	0.97	0.88

Chloride (mg/dL)	43.00	43.00	38.00	1.00	0.94
Potassium (mg/dL)	60.00	65.00	67.00	0.96	0.94
Manganese (μg/dL)	1.20	5.00	7.70	0.39	0.27
Iodine (μg/dL)	7.00	10.00	9.00	0.82	0.88
Selenium (μg/dL)	1.60	1.40	0.90	0.93	0.72
Copper (mg/dL)	0.03	0.05	0.05	0.75	0.80
Zinc (mg/dL)	0.15	0.60	0.60	0.40	0.40
Fluoride (μg/dL)	1.60	0.00	6.40	0.00	0.40
Average similarity index (ASI)				0.61(61%)	0.59 (59%)

Table 2: *Individual (ISI) and average (ASI) similarity index between breast milk (BM) and two cow's milk-based powder infant formulas (IF) for infants 0-6 months.*

[a] References of BM elements concentration are available in table 1.

Elements	IF1[a]	IF2	IF3[a]	IF4[a]	IF5[a]	ESPGHAN minimum required concentration	ISI1	ISI2	ISI3	ISI4	ISI5
Energy (kcal/dL)	66.00	65.00	65.00	64.20	67.00	60.00	0.95	0.96	0.96	0.97	0.94
Protein (g/100kcal)	1.95	2.20	2.04	2.18	1.85	1.80	0.96	0.90	0.94	0.90	0.99
α-lactalbumin (g/100kcal)	0.04	0.00	0.00	0.00	0.00	0.04	0.94	0.00	0.00	0.00	0.00
Total fat (g/100kcal)	5.46	5.30	5.20	5.44	5.34	4.40	0.89	0.91	0.92	0.89	0.90
Linoleic (g/100kcal)	0.79	0.92	0.69	0.08	0.82	0.30	0.55	0.49	0.61	0.41	0.53
α-Linolenic (mg/100kcal)	63.55	150.00	127.16	3.24	90.56	50.00	0.88	0.50	0.56	0.12	0.71
arachidonic acid (mg/100kcal)	18.52	10	9.89	3.24	11.75	As DHA	1.00	1.00	1.00	1.00	1.00
Docosahexaenoic acid (DHA), (mg/100kcal)	18.52	10	9.89	3.24	11.75	3.24[b]	0.30	0.49	0.49	1.00	0.43
Eicosapentaenoic acid (mg/100kcal)	0.00	0.01	0.00	0.00	0.00	AS DHA	0.00	1.00	0.00	0.00	0.00
Carbohydrate (g/100kcal)	10.92	11.000	11.37	10.39	11.14	9.00	0.90	0.90	0.88	0.93	0.89
Galactose (g/100kcal)	0.00	0.00	0.02	0.00	0.00	0.02[b]	0.00	0.00	1.00	0.00	0.00
Glucose (g/100kcal)	0.00	0.00	0.36	0.00	0.00	0.00	1.00	1.00	0.00	1.00	1.00
Dietary fiber (g/100kcal)	0.45	0.80	1.22	0.37	0.00	0.37[b]	0.90	0.63	0.46	1.00	0.00
Nucleotide (mg/100kcal)	3.90	5.00	5.05	0.00	3.01	3.01[b]	0.87	0.75	0.75	0.00	1.00
Taurine (mg/100kcal)	7.02	5.90	8.21	6.96	7.61	5.90[b]	0.91	1.00	0.84	0.92	0.87
L-carnitine (mg/100 kcal)	1.52	2.00	2.32	1.28	1.73	1.20	0.88	0.75	0.68	0.97	0.82
Lutein (μg/100kcal)	17.15	0.00	0.00	0.00	0.00	17.15[b]	1.00	0.00	0.00	0.00	0.00
Vitamin A (μg RE/100kcal)	99.81	98.10	84.00	76.80	101.54	60.00	0.75	0.76	0.83	0.88	0.74
Carotenoids (μg/100kcal)	31.77	0.00	0.00	0.00	0.00	31.77[b]	1.00	0.00	0.00	0.00	0.00
Beta-carotene (μg/100kcal)	0.00	0.00	0.00	10.64	0.00	10.64[b]	0.00	0.00	0.00	1.00	0.00

D3 (µg/100kcal)	1.81	1.70	1.83	1.86	1.39	1.00	0.71	0.74	0.71	0.70	0.84
E (mg α-TE/100kcal)	1.11	1.60	1.68	2.56	1.54	0.50	0.62	0.48	0.46	0.33	0.49
K (µg/100kcal)	10.14	6.90	6.74	8.53	8.29	4.00	0.57	0.73	0.75	0.64	0.65
B1 (µg/100kcal)	151.07	89.00	78.32	116.28	111.75	60.00	0.57	0.81	0.87	0.68	0.70
B2 (µg/100kcal)	166.28	158.00	185.47	232.56	231.21	80.00	0.65	0.67	0.60	0.51	0.51
Niacin (µg/100kcal)	755.56	800.00	652.63	1104.65	876.69	300.00	0.57	0.55	0.63	0.43	0.51
B6 (µg/100kcal)	83.04	89.00	57.68	58.14	69.36	35.00	0.59	0.56	0.76	0.75	0.67
B12 (µg/100kcal)	0.27	0.30	0.29	0.29	0.25	0.10	0.54	0.50	0.51	0.51	0.57
Pantothenic (µg/100kcal)	528.85	600.00	518.74	620.16	944.12	400.00	0.86	0.80	0.87	0.78	0.60
Folic acid (µg/100kcal)	16.18	16.00	19.58	14.73	14.26	10.00	0.76	0.77	0.68	0.81	0.82
Vitamin C (mg/100kcal)	13.65	20.00	14.11	10.47	14.26	10.00	0.85	0.67	0.83	0.98	0.82
Biotin (µg/100kcal)	3.12	3.00	2.11	3.88	2.50	1.50	0.65	0.67	0.83	0.56	0.75
Choline (mg/100kcal)	24.17	12.00	18.74	15.50	18.11	7.00	0.45	0.74	0.54	0.62	0.56
Myo-inositol (mg/100kcal)	6.82	7.90	5.89	5.81	15.41	4.00	0.74	0.81	0.81	0.82	0.41
Iron (mg/100kcal)	1.17	1.10	0.82	1.12	1.00	0.30	0.41	0.43	0.54	0.42	0.46
Calcium (mg/100kcal)	63.55	69.00	85.05	77.91	63.58	50.00	0.88	0.84	0.74	0.78	0.88
Phosphorus (mg/100kcal)	36.26	43.00	47.37	42.25	35.26	30.00	0.91	0.82	0.78	0.83	0.92
Magnesium (mg/100kcal)	6.82	7.90	7.79	9.34	8.48	5.00	0.85	0.78	0.78	0.70	0.74
Sodium (mg/100kcal)	24.17	30.00	26.32	27.71	25.05	20.00	0.91	0.80	0.86	0.84	0.89
Chloride (mg/100kcal)	65.50	59.00	71.58	61.43	70.33	50.00	0.87	0.92	0.82	0.90	0.83
Potassium (mg/100kcal)	98.25	102.00	111.37	122.87	62.62	60.00	0.76	0.74	0.70	0.66	0.98
Manganese (µg/100kcal)	7.60	12.00	11.79	20.54	19.27	1.00	0.23	0.15	0.16	0.09	0.10
Iodine (µg/100kcal)	15.20	14.00	18.74	20.54	19.27	10.00	0.79	0.83	0.70	0.65	0.68
Selenium (µg/100kcal)	2.14	1.40	2.53	1.65	2.50	1.00	0.64	0.83	0.57	0.76	0.57
Copper (µg/100kcal)	75.05	69.00	61.47	78.88	77.07	35.00	0.64	0.67	0.73	0.61	0.62
Zinc (mg/100kcal)	0.92	0.90	0.78	0.78	1.04	0.50	0.71	0.71	0.78	0.78	0.65
Fluoride (µg/100kcal)	0.00	9.80	4.21	0.00	0.00	4.21[b]	0.00	0.60	1.00	0.00	0.00
Average similarity index (ASI)							0.69	0.65	0.64	0.62	0.60

Table 3: *Individual (ISI) and average (ASI) similarity index between the minimum required concentration endorsed by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and five cow's milk-based powder infant formulas (IF) for infants 0-6 months.*

[a] *Package label concentrations are not per 100 kcal, thus, we converted concertation to per 100kcal as following: (100×concentration per 100g)/(kcal of energy per 100g)*

[b] *The ESPGHAN either specifies the minimum required amount as zero or it does not specify or address the minimum required amount, thus, lowest declared concentration among compared IFs was used.*

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