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Chapter 5

Trace Elements in the Human Milk

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Additional information is available at the end of the chapter

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Abstract

Human breast milk is considered to be the perfect food for infants, specifically adapted to their needs. Before birth, the mother transfers all the nutrients and bioactive components to the fetus through the placenta. After birth, these substances have to be transferred through colostrum and milk. In particular, human breast milk is supposed to provide all the essential trace elements that are required by the normal term newborn infant. Therefore, the composition of human breast milk and its changes during lactation is a topic of major importance and has been the subject for intensive research. Conversely, human milk can also be a transfer medium of undesirable (toxic) elements from the mother to the infant. An extensive review of the most recent literature was carried out focusing on the current trace elements levels and their changes during lactation. For several elements, there is a consistent knowledge of their characteristic concentrations throughout the various stages of lactation, their dependence on maternal nutritional status, inter-individual and geographical variability, metabolic pathways, inter-elemental relationships, and effects on child development. For many other elements, this knowledge does not exist or is quite limited.

Keywords: breast milk, breastfeeding, micronutrients, trace elements, temporal changes

1. Introduction

The nutritional requirements during breastfeeding are among the most important in human development. The production of 750–1000 ml of human milk per day represents the transfer from the mother to the infant of approximately 2100–2520 kJ, as energy-producing macronutrients (carbohydrates, proteins, and lipids) [1].

Likewise, all the vitamins and minerals (both macrominerals and trace elements) needed to support the child's growth and development are transferred in the same way.

According to current recommendations, the newborn should whenever possible be exclusively breastfed for the first 6 months of life [2]. Breast milk is then the only nutritional source of the child at this stage. Among these nutrients, macrominerals and essential trace elements are particularly noteworthy.

Maternal nutritional deficiencies in these elements may occur during lactation, affecting the mother's health. If this is reflected in the volume and quality of the milk, it will lead to nutritional deficiencies in the child, consequently affecting its development and health status.

The characterization of the composition of the human milk, in relation to these elements, is therefore of the utmost importance and has attracted much attention for many years.

On the other hand, breast milk can be a source of exposure of the child to various xenobiotics, including toxic trace elements.

A systematization of the current knowledge about the typical ("normal") levels of trace elements in human milk and the major factors responsible for their variability was the main objective of the present review. It is expected to be a useful tool for future studies and in the formulation of breast milk substitutes.

2. Human breast milk

Human milk is a complex secretion produced by the mammary glands of postpartum women [3]. It is generally assumed that the average volume of breast milk ingested by a nursing infant is about 600 ml/day.

2.1. Macronutrients

The composition of breast milk in terms of macronutrients varies during lactation. According to a recent review [4], the mean concentration of main macronutrients in mature milk from full-term women is estimated to be approximately 0.9–1.2 g/dL for protein, 3.2–3.6 g/dL for lipids, and 6.7–7.8 g/dL for lactose. The total energy is estimated to be approximately 65–70 kcal/dL, and is highly correlated with the lipids content. These macronutrients have three different sources: synthesis in the lactocyte, dietary origin, and maternal stores [4].

The nutritional quality of breast milk tends to be highly conserved for most of the macronutrients, independently of the maternal diet [4].

2.2. Micronutrients

Micronutrients, usually considered as the vitamins and the minerals (both the macrominerals and the trace elements), are fundamental for the proper development of the child. They are essential in the formation and regeneration of tissues, as well as in regulating most of the functions of the body's systems, leading its deficiency to disease, and serious malformations in

the baby and the child. Many of these micronutrients are also involved in the body's defense functions [1]. Minerals are closely related to the action of the remaining nutrients, affecting their absorption, metabolism, and excretion [1].

Contrarily to the generality of the macronutrients, it is documented that when maternal nutrition is inadequate, significant changes in milk composition may occur for some of its micronutrients (e.g., some fatty acids and vitamins, sodium, potassium, chloride, phosphorus, copper, zinc, manganese, and iron). The correlation between the levels of minerals in breast milk and the mother's diet is variable from element to element, being in some cases strongly linked to the mother's intake and body stores [4].

These changes have important implications for the growth and development of the breastfed infants [5]. It is also documented that there are differences regarding the milk composition between the different races [6].

3. Trace elements in human milk

3.1. Essential trace elements

3.1.1. Boron

Little is known about the biochemical function of boron in human tissues. Signs of boron deficiency depend on the nutritional levels of aluminum, calcium, cholecalciferol, magnesium, methionine, and potassium. It affects calcium and magnesium concentrations in plasma and tissues, plasma alkaline phosphatase, and bone calcification [7]. The toxicity of boron is very low orally. There is no clear definition of symptoms of chronic boron intoxication in humans [7]. The levels of boron in breast milk seem to increase during lactation [8]. Average concentration of 0.14 μg/L was observed in mature milk [8].

3.1.2. Chromium

Chromium, as trivalent chromium, is an essential nutrient that enhances the action of insulin and, consequently, the metabolism of carbohydrates, lipids, and proteins. It has been suggested that the active form of chromium, the so-called "glucose tolerance factor," is a complex of chromium, nicotinic acid, and the amino acids glycine, cysteine, and glutamic acid. Biochemically, it affects the ability of the transmembrane insulin receptor to interact with insulin [7]. Chromium deficiency causes glucose intolerance similar to diabetes mellitus, elevated plasma free fatty acids levels, changes in nitrogen metabolism, weight loss, neuropathy, and respiratory depression [7]. The toxicity of trivalent chromium is so low that no effects of administering excessive amounts of this species could be observed. Hexavalent chromium, by contrast, is extremely toxic [7]. The concentrations of chromium in breast milk are very low and present a great variability [8, 9]. They may be increased during 21–89 and 90–180 days of lactation [8, 9].

Element	Average or interval (mg/L)	Time after delivery[1]	Milk type[2]	n	Country[3]	Analytical technique[4]	[Ref] year
B	0.000145	1–20 mo	M	205	ARE	ICP-MS	[8] 2008
Co	0.00019[b]	—	—	27	AUT	ICP-SFMS	[45] 2000
	0.0002–0.0007	—	—	—	—	—	[20] 2001
	0.00085	2–8 w	M	19	CZE DEU POL	ICP-MS	[46] 2002
	0.000009	1–20 mo	M	205	ARE	ICP-MS	[8] 2008
	0.00069	2 d	C	34	PRT	ICP-MS	[12] 2008
	0.00072	1 mo	M	19			
Cr	0.0243[b]	—	—	27	AUT	ICP-SFMS	[45] 2000
	0.0009–0.0012	0–7 mo	—	6–45	—	—	[20] 2001
	0.0108	2–8 w	M	19	CZE DEU POL	ICP-MS	[46] 2002
	0.017–0.076	1–365 d	—	—	JPN	ICP-AES	[9] 2005
	0.000689	1–20 mo	M	205	ARE	ICP-MS	[8] 2008
	0.000173	1–191 d	M	79	JPN	ICP-MS	[75] 2008
Cu	0.4[b]	—	—	27	AUT	ICP-SFMS	[45] 2000
	0.11–0.62	1–293 d	—	6–50	—	—	[20] 2001
	0.54	1–7 d	C	50	BRA	TXRF	[76] 2002
	0.162	2 mo	M	32	TUR	FAAS	[53] 2005
	0.35	—	M	—	JPN	ICP-AES	[9] 2005
	0.066	1 mo	M	41	IND	ICP-AES	[37] 2006
	0.056	3 d	C	41			
	0.41519	1–20 mo	M	205	ARE	ICP-MS	[8] 2008
	0.403	—	—	120	ARE	ICP-MS	[54] 2008
	0.760	2 d	C	34	PRT	ICP-MS	[12] 2008
	0.498	1 mo	M	19			
	0.506	1 w	C	44	KOR	GFAAS (Zeeman)	[14] 2012
	0.489	2 w	T	32			
	0.384	4 w	M	22			
	0.356	6 w	M	26			
	0.303	8 w	M	22			
	0.301	12 w	M	9			
	0.3	—	—	27	IRN	FAAS	[77] 2015
	0.587	5–17 d	T	55	GTM	ICP-MS	[72] 2016
	0.460	18–46 d	M	73			
	0.262	4–6 mo	M	100			
	0.220	—	—	12	AUS	ICP-MS	[51] 2016

Element	Average or interval (mg/L)	Time after delivery[1]	Milk type[2]	n	Country[3]	Analytical technique[4]	[Ref] year
	0.16952	2–6 w	M	20	USA	ICP-MS	[48] 2017
	0.13094	1–7 w	M	6	NAM		
	0.18687	2–6 w	M	23	POL		
	0.21104	3–7 w	M	21	ARG		
Fe	0.38[b]	—	—	27	AUT	ICP-SFMS	[45] 2000
	0.3–0.6	—	—	—	—	—	[20] 2001
	1.72	1–7 d	C	50	BRA	TXRF	[76] 2002
	1.19	—	M	—	JPN	ICP-AES	[9] 2005
	0.5	30–45 d	M	31	USA (Texas)	AAS	[19] 2008
	0.4	75–90 d		17			
	0.36	—	—	27	IRN	FAAS	[77] 2015
	0.558	5–17 d	T	55	GTM	ICP-MS	[72] 2016
	0.581	18–46 d	M	73			
	0.320	4–6 mo	M	100			
	0.047	—	—	12	AUS	ICP-MS	[51] 2016
	1.27	2–6 w	M	20	USA	ICP-MS	[48] 2017
	1.53	1–7 w	M	6	NAM	ICP-MS	
	1	2–6 w	M	23	POL	ICP-MS	
	0.99	3–7 w	M	21	ARG	ICP-MS	
I	0.098–0.247	14 d–3.5 y	—	14–24	—	—	[20] 2001
	0.0478	30–45 d	M	31	USA (Texas)	NAA	[19] 2009
	0.0423	75–90 d		17			
	0.113	—	—	12	AUS	ICP-MS	[51] 2016
Mn	0.003–0.01	—	—	—	—	—	[20] 2001
	0.000929	1–20 mo	M	205	ARE	ICP-MS	[8] 2008
	0.011	—	M	—	JPN	ICP-AES	[9] 2005
	0.0077	2 d	C	34	PRT	ICP-MS	[12] 2008
	0.0049	1 mo	M	19			
	0.133	1 w	C	44	KOR	GFAAS (Zeeman)	[14] 2012
	0.127	2 w	T	32			
	0.125	4 w	M	22			
	0.123	6 w	M	26			
	0.127	8 w	M	22			
	0.108	12 w	M	9			
	0.012	5–17 d	T	55	GTM	ICP-MS	[72] 2016

Element	Average or interval (mg/L)	Time after delivery[1]	Milk type[2]	n	Country[3]	Analytical technique[4]	[Ref] year
	0.011	18–46 d	M	73			
	0.0077	4–6 mo	M	100			
	0.00137	—	—	12	AUS	ICP-MS	[51] 2016
	0.00271	2–6 w	M	20	USA	ICP-MS	[48] 2017
	0.0116	1–7 w	M	6	NAM	ICP-MS	
	0.00161	2–6 w	M	23	POL	ICP-MS	
	0.00762	3–7 w	M	21	ARG	ICP-MS	
Mo	0.0002–0.017	1–293 d	—	6–46	—	—	[29] 2000
	0.00072	2–8 w	M	19	CZE DEU POL	ICP-MS	[46] 2002
	0.000348	1–20 mo	M	205	ARE	ICP-MS	[8] 2008
	0.000542	1–191 d	M	79	JPN	ICP-MS	[75] 2008
	0.00037	—	—	12	AUS	ICP-MS	[51] 2016
Se	0.0056–0.08	1–869 d	—	5–241	—	—	[29] 2000
	0.017[b]	—	—	27	AUT	ICP-SFMS	[45] 2000
	0.0163	2–3 mo	M	31	ESP	ICP-AES	[28] 2003
	0.017	—	M	—	JPN	ICP-AES	[9] 2005
	0.010623	1–20 mo	M	205	ARE	ICP-MS	[8] 2008
	0.0159	30–45 d	M	31	USA (Texas)	NAA	[19] 2008
	0.0157	75–90 d		17			
	0.0722	2 d	C	34	PRT	ICP-MS	[12] 2008
	0.0321	1 mo	M	19			
	0.0118	1 w	C	44	KOR	GFAAS (Zeeman)	[14] 2012
	0.0114	2 w	T	32			
	0.0127	4 w	M	22			
	0.0114	6 w	M	26			
	0.0108	8 w	M	22			
	0.0105	12 w	M	9			
	0.017	5–17 d	T	55	GTM	ICP-MS	[72] 2016
	0.017	18–46 d	M	73			
	0.013	4–6 mo	M	100			
	0.0143	—	—	12	AUS	ICP-MS	[51] 2016
Zn	0.8–4.7	2 d–2 y	—	6–71	—	—	[20] 2001
	6.97	1–7 d	C	50	BRA	TXRF	[76] 2002
	1.2	2 mo	M	32	TUR	FAAS	[53] 2005
	1.45	—	M	—	JPN	ICP-AES	[9] 2005

Element	Average or interval (mg/L)	Time after delivery[1]	Milk type[2]	n	Country[3]	Analytical technique[4]	[Ref] year
	0.255	3 d	C	41	IND	ICP-AES	[37] 2006
	0.276	1 mo	M	41			
	2.1	30–45 d	M	31	USA (Texas)	FAAS	[19] 2008
	2	75–90 d		17			
	1.468	1–20 mo	M	205	ARE	ICP-MS	[8] 2008
	2.730	—	—	120	ARE	ICP-MS	[54] 2008
	12.137	2 d	C	34	PRT	ICP-MS	[12] 2008
	2.785	1 mo	M	19			
	7.8	1 w	C	44	KOR	GFAAS (Zeeman)	[14] 2012
	9.1	2 w	T	32			
	7.2	4 w	M	22			
	8	6 w	M	26			
	7.4	8 w	M	22			
	6.6	12 w	M	9			
	2.34	—	—	27	IRN	FAAS	[77] 2015
	4.36	5–17 d	T	55	GTM	ICP-MS	[72] 2016
	3.47	18–46 d	M	73			
	1.44	4–6 mo	M	100			
	1.390	—	—	12	AUS	ICP-MS	[51] 2016
Ag	0.00041[b]	—	—	27	AUT	ICP-SFMS	[45] 2000
	0.00078	2–8 w	M	19	CZE DEU POL	ICP-MS	[46] 2002
	0.000005	1–20 mo	M	205	ARE	ICP-MS	[8] 2008
Al	0.067	—	—	27	AUT	ICP-SFMS	[45] 2000
	0.007056	1–20 mo	M	205	ARE	ICP-MS	[8] 2008
	0.05645	1–4 d	C	45	TWN	GFAAS	[43] 2014
	0.03657	5–10 d	T	45			
	0.01811	30–35 d	M	45			
	0.01344	60–65 d	M	45			
As	0.0067[b]	—	—	27	AUT	ICP-SFMS	[45] 2000
	0.00025–0.003	—	—	—	—	—	[20] 2001
	0.000089	1–20 mo	M	205	ARE	ICP-MS	[8] 2008
	0.000196	—	—	120	ARE	ICP-MS	[54] 2008
	0.0078	2 d	C	34	PRT	ICP-MS	[12] 2008
	0.0058	1 mo	M	19			
	0.00150	1–4 d	C	45	TWN	GFAAS	[43] 2014

Element	Average or interval (mg/L)	Time after delivery[1]	Milk type[2]	n	Country[3]	Analytical technique[4]	[Ref] year
	0.00068	5–10 d	T	45			
	0.00027	30–35 d	M	45			
	0.00016	60–65 d	M	45			
	0.00347	2–6 w	M	20	USA	ICP-MS	[48] 2017
	0.00668	1–7 w	M	6	NAM	ICP-MS	
	0.00386	2–6 w	M	23	POL	ICP-MS	
	0.00451	3–7 w	M	21	ARG	ICP-MS	
	0.00236	—	—	74	LBN	GFAAS	[47] 2018
Au	0.00029[b]	—	—	27	AUT	ICP-SFMS	[45] 2000
	0.0001–0.0021	—	—	—	AUT	ICP-SFMS	[59] 2000
Ba	0.000017	1–20 mo	M	205	ARE	ICP-MS	[8] 2008
Be	0.000008	1–20 mo	M	205	ARE	ICP-MS	[8] 2008
Bi	0.000002	1–20 mo	M	205	ARE	ICP-MS	[8] 2008
Br	0.812	—	—	12	AUS	ICP-MS	[51] 2016
Cd	<0.001	—	—	—	—	—	[20] 2001
	0.000097	2 mo	M	32	TUR	FAAS	[53] 2005
	0.000003	1–20 mo	M	205	ARE	ICP-MS	[8] 2008
	0.00027	—	—	120	ARE	ICP-MS	[54] 2008
	0.00137	1–4 d	C	45	TWN	GFAAS	[43] 2014
	0.00065	5–10 d	T	45			
	0.00049	30–35 d	M	45			
	0.00034	60–65 d	M	45			
	0.00087	—	—	74	LBN	GFAAS	[47] 2018
Ce	0.00012	2–8 w	M	19	CZE DEU POL	ICP-MS	[46] 2002
	0.0000154	—	—	11	DEU	ICP-MS	[56] 2010
	0.0000157	—	—	51	DEU	ICP-MS	
	0.0000139	—	—	26	ESP	ICP-MS	
Cs	0.001–0.005	—	—	—	—	—	[20] 2001
Ga	0.00052	2–8 w	M	19	CZE DEU POL	ICP-MS	[46] 2002
Hg	0.000030–0.00062	—	—	17	CAN	CV-AFS	[78] 1994
	0.000146–0.000237	—	—	33	CAN	—	[79] 1997
	0.001–0.003	—	—	—	—	—	[20] 2001
	0.000008	1–20 mo	M	205	ARE	ICP-MS	[8] 2008
	0.000115	—	—	120	ARE	ICP-MS	[54] 2008

Element	Average or interval (mg/L)	Time after delivery[1]	Milk type[2]	n	Country[3]	Analytical technique[4]	[Ref] year
	0.00289–0.01333	—	—	10–15	IRN	DC/Au-amal	[80] 2012
	0.000008	1–20 mo	M	205	ARE	ICP-MS	[8] 2008
La	0.00007	2–8 w	M	19	CZE DEU POL	ICP-MS	[46] 2002
	0.000002	1–20 mo	M	205	ARE	ICP-MS	[8] 2008
Li	0.000005	1–20 mo	M	205	ARE	ICP-MS	[8] 2008
Nb	0.00004	2–8 w	M	19	CZE DEU POL	ICP-MS	[46] 2002
Ni	0.00079[b]	—	—	27	AUT	ICP-SFMS	[45] 2000
	0.010–0.020	—	—	—	—	—	[20] 2001
	0.48	2 mo	M	32	TUR	FAAS	[53] 2005
	0.0076	2 d	C	34	PRT	ICP-MS	[12] 2008
	0.0058	1 mo	M	19			
	0.002581	1–20 mo	M	205	ARE	ICP-MS	[8] 2008
Pb	0.001–0.005	—	—	—	—	—	[20] 2001
	0.000019	1–20 mo	M	205	ARE	ICP-MS	[8] 2008
	0.00151	—	—	120	ARE	ICP-MS	[54] 2008
	0.00155	2 d	C	34	PRT	ICP-MS	[12] 2008
	0.00094	1 mo	M	19			
	0.01322	1–4 d	C	45	TWN	GFAAS	[43] 2014
	0.00892	5–10 d	T	45			
	0.01172	30–35 d	M	45			
	0.00293	60–65 d	M	45			
	0.00077	2–6 w	M	20	USA	ICP-MS	[48] 2017
	0.00215	1–7 w	M	6	NAM	ICP-MS	
	0.00102	2–6 w	M	23	POL	ICP-MS	
	0.00059	3–7 w	M	21	ARG	ICP-MS	
	0.01817	—	—	74	LBN	GFAAS	[47] 2018
Pt	< 0.00001[b]	—	—	27	AUT	ICP-SFMS	[45] 2000
Rb	0.3–1.2	—	—	—	—	—	[20] 2001
	32.176[a]	2–15 d	T	40	IRN	NAA	[71] 2014
	1.12	5–17 d	T	55	GTM	ICP-MS	[72] 2016
	1.05	18–46 d	M	73			
	0.810	4–6 mo	M	100			
Ru	0.00015	2–8 w	M	19	CZE DEU POL	ICP-MS	[46] 2002

Element	Average or interval (mg/L)	Time after delivery[1]	Milk type[2]	n	Country[3]	Analytical technique[4]	[Ref] year
Sb	0.00014	2–8 w	M	19	CZE DEU POL	ICP-MS	[46] 2002
	0.000352	1–20 mo	M	205	ARE	ICP-MS	[8] 2008
Sc	0.00019[b]	—	—	27	AUT	ICP-SFMS	[45] 2000
Sn	<0.001- < 0.002	—	—	—	—	—	[20] 2001
Sr	0.044	5–17 d	T	55	GTM	ICP-MS	[72] 2016
	0.046	18–46 d	M	73			
	0.046	4–6 mo	M	100			
Ti	0.0063[b]	—	—	27	AUT	ICP-SFMS	[45] 2000
	0.270	2–8 w	M	19	CZE DEU POL	ICP-MS	[46] 2002
Th	0.00002	2–8 w	M	19	CZE DEU POL	ICP-MS	[46] 2002
U	0.00003	2–8 w	M	19	CZE DEU POL	ICP-MS	[46] 2002
V	0.00018[b]	—	—	27	AUT	ICP-SFMS	[45] 2000

[1]d: day(s); w: week(s); mo: month(s); y: year(s); t: term; pt: pre-term.
[2]C: colostrum; T: transition milk; M: mature milk.
[3]Countries according to ISO 3166-1 A3.
[4]ICP-MS: inductively coupled plasma mass spectrometry; ICP-SFMS: inductively coupled plasma sector field mass spectrometry; TXRF: total reflection X-ray fluorescence; FAAS: flame atomic absorption spectroscopy; ICP-AES: inductively coupled plasma atomic emission spectroscopy; GFAAS: graphite furnace atomic absorption spectroscopy; NAA: neutron activation analysis; CV-AFS: cold vapor atomic fluorescence spectroscopy; DC/Au-amal: direct combustion/Au amalgam.
[a]mg/kg, as dry matter.
[b]median.

Table 1. Summary of available data on trace element levels in human milk.

3.1.3. Cobalt

Cobalt is a constituent of vitamin B12 and has been linked to the synthesis of antibodies and phagocytic activity in neutrophils and macrophages [10, 11]. Increased cobalt levels were observed throughout lactation [10, 12]. It has been speculated that this increase would be related to the increased needs arising from the infants' production of humoral antibodies, which starts during the third and fourth month of life, when the passage of the passive acquired immunity to active acquired immunity occurs [13]. Another study reported no significant changes in cobalt levels in breast milk throughout the various stages of lactation [8]. Plasma cobalt was higher in blood plasma of 12–14-week-old infants fed breast milk compared to healthy adults [8]. Cobalt levels in maternal plasma have a negative correlation with their concentration of breast milk [8].

3.1.4. Copper

Copper is present in biological tissues mainly in the form of organic complexes, most of them being enzymatic systems. The metabolic processes in which copper dependent enzymes are

involved include the use of oxygen in cellular respiration and the synthesis of essential biomolecules such as the complex proteins of the skeleton and blood vessels connective tissues and a variety of neuroactive compounds of the central nervous system. It is estimated that an adult individual contains between 50 and 120 mg of copper in the whole body [7]. Copper in the blood is distributed by plasma and erythrocytes, of which 60% is associated with metalloenzyme Cu,Zn-superoxide dismutase (SOD), the rest being linked to other proteins and amino acids [7]. Plasma copper levels in the adult range between 0.8 and 1.2 mg/L and are not significantly influenced by feeding. In women, they are about 10% higher, and may be three times higher during pregnancy [7]. In plasma, about 93% of copper is bound to ceruloplasmin, a protein with multiple functions, particularly involved in the metabolism of iron [7]. In adulthood, copper deficiency is associated with hypochromic anemia, neutropenia, hypopigmentation, deficient bone formation with osteoporosis, and vascular deficiencies [7]. The deficiency of this element in the infant is related to identical symptoms [7, 14]. Copper is mainly accumulated in the liver, especially during the third trimester of pregnancy. Premature infants tend to have lower copper stores compared to full-term children [14]. There is a decrease in copper concentration in milk during lactation, reaching a minimum of 0.08–0.10 mg/L in mature milk between 6 months and 1 year [15]. This trend is consistent with the majority of published results by other authors during this same period of lactation [8, 9, 12, 15]. One author reported a slight increase in copper concentration in breast milk in the first month, from 0.25–0.29 mg/L in colostrum to 0.37–0.41 mg/L in mature milk [15]. The effect of iron dietary supplementation of the mother in serum and milk cooper levels is not clear. Some authors reported a decrease in cooper milk associated with iron supplementation [16, 17], but a noncorrelation have also been reported [18].

3.1.5. Iodine

Iodine is an essential constituent of the thyroid hormones thyroxine (T4) and triiodothyronine (T3). These hormones are involved in the regulation of various enzymes and metabolic processes. The organs most subject to its regulation are the developing brain, muscles, heart, pituitary gland, and kidneys [19, 20]. Iodine is thus absolutely essential for life in mammals [20]. The increase in perinatal mortality associated with iodine deficiency and a reduction in birth weight are described [7]. Since the newborn's brain has only reached about one-third of its size, continuing its accelerated growth until 2 years of age, thyroid hormones and iodine keep playing a key role throughout this period. Populations with severe iodine deficiencies present a high risk of mental retardation and cretinism [7, 19, 21]. Iodine adequate intake is 110 and 130 μg/day for first and second semester of life, respectively [22]. The concentration of iodine in breast milk is strongly correlated with the dietary intake of the mother [19]. The nutritional intake of iodine in the nursing woman (recommended dietary allowance) should be of 220 μg/day [22]. Iodine content in breast milk as shown to be strongly reduced by mother's smoking habits [23].

3.1.6. Iron

Iron is an essential component of several proteins, including enzymes, cytochromes, myoglobin, and hemoglobin. Nearly two-thirds of body iron is found in the hemoglobin of circulating

red blood cells, involved in oxygen transport. About 25% is stored as rapidly mobilizable reserves and the remaining 15% is in muscle myoglobin [22]. The individual iron reserves have a great influence on its absorption. Elevated reserves inhibit the gastrointestinal absorption of iron. Absorption occurs in the small intestine [22]. Iron deficiency results in anemia, which represents the most frequent nutritional deficiency of essential elements. The main symptoms are reduced work capacity and delayed psychomotor development in the child, with cognitive deficit [22]. Anemia is also the most prevalent disease in children [24]. During the first 6 months after delivery, iron concentration in breast milk is relatively stable, ranging from 0.21 to 0.27 mg/L. Some authors have reported that, after this period, iron levels in breast milk tend to fall very significantly to values between 0.08 and 0.10 mg/L [15]. Other authors observed quite constant levels throughout lactation [9]. No differences were found associated with the mother's age, number of children, or number of previously breastfed infants [15]. Likewise, the iron content in the maternal diet did not showed a significant correlation with iron concentration in breast milk [19, 25].

3.1.7. Manganese

Manganese is an essential nutrient, involved in the formation of bone tissue and in specific reactions related to the metabolism of amino acids, cholesterol, and carbohydrates. Manganese metalloenzymes include arginase, glutamine synthetase, phosphoenolpyruvate decarboxylase, and Mn-superoxide dismutase (Mn-SOD), the mitochondrial correspondent to Cu,Zn-SOD (cytoplasmic) [7]. Only a small part of the manganese ingested is absorbed. Absorption occurs through an active transport process [7]. Although there are symptoms associated with manganese deficiency, it was not possible to clearly establish a relationship between low dietary intakes and health problems. Manganese toxicity causes central nervous system effects similar to those of Parkinson's disease [14, 22]. In one study in Japanese women, the concentrations of manganese in breast milk showed a very low variability throughout the lactation period [9]. Other studies however reported that breast milk concentrations decrease throughout lactation [8]. Also, a direct correlation between maternal plasma levels and breast milk concentration has been observed [8]. A significant reduction in milk manganese content during lactation was also observed in a small study of 29 well-nourished mothers in the United Arab Emirates [8, 12].

3.1.8. Molybdenum

Molybdenum is a cofactor of a small number of enzymes, such as sulfite oxidase, xanthine oxidase, and aldehyde oxidase, involved in the catabolism of sulfur amino acids and heterocyclic compounds such as purines and pyrimidines [20]. In all Mo-enzymes, functional molybdenum is present in the form of an organic component, molybdopterin [20]. Dietary molybdenum deficiencies are associated with growth problems, neurological disorders, and premature death [26]. On the other hand, its excess is associated with an increase in susceptibility to gout, hyperuricemia, and xanthuria [26]. Concentrations of molybdenum in breast milk increase significantly during lactation [8].

3.1.9. Selenium

The best known metabolic role of selenium in mammals was as a component of the enzyme glutathione peroxidase, which, together with vitamin E, catalase, and superoxide dismutase, is a key player of the body's antioxidant defense system. More recently, its role in P-selenoprotein has been discovered, and there is also increasing evidence of the involvement of a selenoprotein in the synthesis of the hormone triiodothyronine from thyroxine [20, 27]. Keshan's disease is a cardiomyopathy associated with selenium deficiency, which mainly affects children and women of childbearing age. Also, Kashin-Beck disease, an osteoarthropathy, is associated with selenium deficiency in soils (and consequently in food), affecting children between 5 and 13 years [7, 28, 29]. Chronic selenium toxicity is characterized primarily by hair loss and changes in nail morphology. In some cases, there is the development of skin lesions and central nervous system disturbances, being the biochemical mechanism unknown [20, 28]. There is evidence of a negative correlation between the supply of selenium and the prevalence of breast, prostate, colon, pancreatic, lung, and bladder cancer [30]. The concentration of selenium in breast milk is directly dependent on the mother's selenium dietary intake [9, 31–33]. In one study, the selenium breast milk concentrations were studied according to the region of residence of the lactating mother. Two selenium-rich regions (Portuguesa) and one control region (Yaracuy) were compared. A significant increase of selenium was observed, from 42.9 μg/L for the control region to 56.6 and 112.2 μg/L for the two seleniferous regions [31]. Other authors reported selenium levels in the first month between 12.7 and 32.1 μg/L [12, 14, 19]. There appears to be a significant inverse correlation between selenium and zinc concentrations in breast milk. Also, mothers with higher dietary selenium intakes present lower concentrations of zinc in breast milk [31]. Studies of zinc binding compounds in breastmilk allowed the identification of six compounds with affinity for selenium too. It was possible to identify one of those compounds as the citrate, which is the main low molecular weight zinc binder. The decrease in zinc concentration in breast milk is then related to the concentration of citrate, which in turn depends on the concentration of selenium in plasma. High levels of selenium observed in seleniferous regions induced reduction of citrate in milk, probably by the suppression of the mechanism of citrate production in the Golgi apparatus described by Linzell [31, 34]. In the case of premature infants, since their reserves of selenium at birth are low, it is of the utmost importance the supply of this element in adequate concentrations through breast milk, which is clearly dependent, as mentioned above, on geographical aspects, the nutritional intake of the mother and the lactation phase [12, 28, 35].

3.1.10. Zinc

In the cell, zinc is involved in catalytic, structural, and regulatory functions [20]. The biochemical role of zinc results from its presence in hundreds of enzymatic systems and as a stabilizer of the molecular structure of cellular substructures. Examples of zinc metalloenzymes are RNA polymerase, alcohol dehydrogenase, carbonic anhydrase, and alkaline phosphatase [20]. Zinc is involved in the synthesis and degradation of carbohydrates, lipids, proteins, and nucleic acids. It plays an essential role in gene expression [7]. The skeletal muscle contains about 60% of the total zinc of the body, being the bone mass

responsible for about 30% [36]. Severe zinc deficiency is associated with clinical symptoms such as delayed growth, delayed sexual and skeletal maturation, dermatitis, diarrhea, alopecia, poor appetite, behavioral changes, and increased susceptibility to disease, as result of immune system malfunction [20, 37]. Generally, mild zinc deficiency occurs without a convenient diagnosis. When detected, it is usually related to a reduced growth rate and poor resistance to infections. Acute zinc poisoning is rare. The manifestations are nausea, vomiting, diarrhea, fever, and lethargy. In the case of chronic exposure to zinc, interference with other elements, particularly with copper, occurs. The zinc/copper interaction causes an excess of zinc to result in a reduction of copper levels (by decreasing its absorption at the gastrointestinal tract) [7]. Zinc metabolism is still subject to interference with other elements. For example, if iron is present at high levels in diet, it may decrease the absorption of zinc, and this aspect should be considered when, during pregnancy and lactation, the control of iron levels is attempted through the use of dietary supplements. Other authors observed that dietary supplementation of the mother with iron did not significantly interfere with their plasma zinc levels nor with zinc levels in breast milk [18, 19, 38]. Also, calcium and phosphorus may interfere with the absorption of zinc, and there are also contradictory studies of the effect of these two elements [20]. Due to the abovementioned zinc/copper antagonism, high concentrations of zinc in breast milk may result in copper deficiency, since zinc can competitively inhibit copper absorption in the gastrointestinal tract of the child. Metallothionein appears to play a relevant role in this process [39]. As for selenium, zinc is accumulated by the fetus during the third trimester of pregnancy [14]. Zinc may be about 15 times more concentrated in breast milk than in the mother's plasma, evidencing an active transport mechanism, and its essential role for the child's development [12, 31]. There is a rapid and significant decrease in the concentration of zinc in breast milk throughout the lactation period, significantly during the first month [12]. This evidence is supported by several published studies [8, 14, 15, 40]. There were no differences associated with the mother's number of children or lactation history. Regarding the age of the mother, it was found that the concentration of zinc tends to increase (higher values for ages greater than 30 years) [15]. Significantly higher zinc values were observed in breast milk between the third and seventh days in mothers with preterm infants, compared to those with full-term infants [37].

3.2. Non-essential/toxic trace elements

3.2.1. Aluminum

Brain function of children exposed to this metal can be seriously affected [41]. Relevant sources of exposure are not only breast milk of mothers exposed to relevant levels of aluminum, but also infant Al-adjuvanted vaccination, like hepatitis B [41, 42]. Aluminum milk levels decrease significantly over the nursing, ranging from 0.056 mg/L in colostrum to 0.013 mg/L in mature milk [43]. Older mothers' (>25 years) milk present a higher aluminum concentration than the younger ones [44]. There is no relevant data available related to aluminum exposure during early life, and its correlation with brain function. Concentrations in human milk varying between 7.056 and 67 μg/L are described [8, 43, 45].

3.2.2. Antimony

The calculated transfer factor from food into human milk, calculated as the element concentration in food (g/kg) divided by the element concentration in milk (g/L), has been determined as 13.2 [46]. The reported concentration in human breast milk is between 0.14 and 0.35 μg/L.

3.2.3. Arsenic

Arsenic occurs in trivalent and pentavalent forms in food, water, and the environment. The biological effects of arsenic strongly depend on the actual chemical specie it is present, with inorganic forms being more toxic than most organic forms. Inorganic forms are methylated in the human body, giving rise to less toxic compounds, which are then excreted through urine [7]. Acute intoxication with arsenic is rare and is characterized by nausea, vomiting, diarrhea, and acute abdominal pain. Chronic intoxication is caused by exposure to natural sources, contaminated food, or water, or other accidental source [7]. In a recent study, presence of arsenic was observed in 63.51% of samples, with an average concentration of 2.36 μg/L [47], consistent with results from other authors [12, 20, 45, 48]. Arsenic presence in human milk is associated with cereal and fish intake [47].

3.2.4. Barium

No nutritional requirements are set for barium in mammals, and its origin is probably associated with plant sources, following metabolic pathways similar to the elements of the same group in the periodic table, such as calcium and strontium [11]. Barium levels in milk may be dependent of mother diet [11]. Concentrations of 0.017 μg/L have been reported [8].

3.2.5. Beryllium

Beryllium compounds are very toxic [49], and chronic beryllium disease has been observed in children living near a beryllium factory [50]. There is a high probability that this element can be transferred from mother to child through breast milk [50]. Concentration of 0.008 μg/L has been reported in breast milk [8].

3.2.6. Bismuth

This element has been reported in breast milk at a concentration of 0.002 μg/L [8].

3.2.7. Bromide

Described as having an important function in tissue development, cellular structure and membrane integrity, its presence in breast milk was reported in a recent study at a concentration of 0.812 mg/L [51].

3.2.8. Cadmium

The main source of exposure to cadmium is tobacco smoke. It is estimated that about 10% of mothers smoke during pregnancy, and the percentage of those who return to smoking during

lactation is even higher [23]. Smoking contributes to increased levels of some metals in breast milk. Cadmium is the one of highest concern because it is an IARC type 1 carcinogen, altering the metabolism of other micronutrients, such as copper, iron, magnesium, selenium, and zinc. Cadmium levels are about four times higher in the breast milk of smoking mothers compared to non-smoking ones [23]. It has been reported that metallothionein levels are about half in smoking mothers. This seems to indicate a protective mechanism to the child, since the toxicity of the metallothionein-Cd complex is higher than that of inorganic cadmium [52]. Concentrations of cadmium in human milk varying between 0.003 and 1.37 μg/L are described [8, 20, 43, 47, 53, 54].

3.2.9. Cerium

There is no evidence that it is an essential element [11], neither transport from mother to infant through milk [55, 56]. Concentrations in human milk varying between 0.0139 and 0.12 μg/L are described [46, 56].

3.2.10. Cesium

There is no evidence that it is an essential element [11]. It has been reported ^{137}Cs in breast milk after the reactor accident at Chernobyl [57]. Concentrations in human milk varying between 1 and 5 μg/L are described [20].

3.2.11. Gallium

The presence of ^{67}Ga in human breast milk has been described [58]. A concentration of 0.52 μg/L was reported [46].

3.2.12. Gold

Traces of gold have been found in breast milk, and it is assumed an association with the use of jewelry or dental amalgams [59]. Concentrations varying between 0.1 and 2.1 μg/L are described [45, 59].

3.2.13. Lanthanum

There is no evidence that it is an essential element [11]. The calculated transfer factor from food into the human milk has been determined as 13.8 [46]. The reported concentration in human breast milk is between 0.002 and 0.07 μg/L [8, 46].

3.2.14. Lead

Lead blood levels in the worldwide population have been decreasing significantly since the 1970s, largely due to the reduction of sources of environmental contamination, mainly the virtual elimination of this element from automobile fuels, but also from other sources of exposure such as paints, plumbing, ceramics, cosmetics, welding of food cans, etc. [60]. In young American children, it is reported that the levels of lead above 100 μg/L will mainly be related to exposure to particulate matter resulting from the degradation of paints used in homes [60]. The relationship between elevated levels of lead in children's blood and the

occurrence of intellectual development deficits (decreased IQ) is well known [60, 61]. In the human body, most of the lead is deposited in the bones (bones and teeth contain more than 90% of the body's total lead load) [62]. Lead mobilization of the human skeleton during pregnancy and lactation has been described [63, 64], resulting in a transgenerational transfer from the mother to the child. The mother consumption of calcium-rich foods reduces the risk of increased concentrations of lead in breast milk (>100 μg/L) [65, 66]. Iron also interferes with the absorption and toxicity of lead in children, causing a reduction of lead absorption. The hematological effects and intellectual deficit caused by lead are antagonized by an iron-rich diet [60]. A great inter-individual variability was observed in the concentration of lead in breast milk, which may be three orders of magnitude [67]. Concentrations varying between 0.019 and 18.17 μg/L are reported [8, 12, 20, 43, 47, 48, 54].

3.2.15. Lithium

Although clinical recommendations discourage the treatment of lactating mothers with lithium for bipolar disorder, studies demonstrate a concentration reduction in half from mother serum to milk, and also from milk to infant plasma, in the same proportions, with no serious adverse effects [68]. Concentrations of 0.005 μg/L in human milk are reported [8].

3.2.16. Mercury

Mercury is a highly toxic metal. Like lead, it causes depletion of glutathione as well as the protein sulfhydryl binding groups, resulting in the production of reactive oxygen species, such as superoxide anion and hydroxyl radicals [69]. Mercury levels in breast milk vary considerably depending on the mother's place of residence, lactation stage, age, and diet. An increase in mercury levels in mother's plasma and breast milk during lactation is described [8]. Concentrations varying between 0.008 and 3 μg/L are reported [70].

3.2.17. Nickel

Nickel role in some human physiological function is unknown [11]. However, it is reported that in case of severe nickel depletion, growth and hematopoiesis are depressed [7]. Due to its high homeostatic regulation, the symptoms of nickel poisoning are simply related to gastrointestinal irritation [7]. A decrease in nickel concentration throughout lactation is described [12]. Concentrations varying between 0.79 and 480 μg/L are reported [8, 12, 20, 45, 53].

3.2.18. Niobium

The calculated transfer factor from food into human milk was determined as 20.7 [46]. A mean concentration of 0.04 μg/L in human milk was reported [46].

3.2.19. Platinum

Undetectable levels were reported for platinum in human milk [45].

3.2.20. Rubidium

A relatively abundant element in body fluids and tissues, rubidium is also present in breast milk, having a behavior similar to that of potassium, although no rubidium-dependent biochemical functions are known [71]. Concentrations of rubidium in human milk ranging from 0.3 to 1.2 μg/L have been reported [20, 71, 72].

3.2.21. Ruthenium

The calculated transfer factor from food into human milk was determined as 4.1 [46]. Concentrations of 0.15 μg/L in human milk have been reported [46].

3.2.22. Scandium

Median concentrations of scandium in human milk of 0.19 μg/L are reported [45].

3.2.23. Silver

Silver has been found in breast milk, and it is speculated that it also originates from the use of jewelry or dental amalgams [59]. Concentrations varying between 0.005 and 0.78 μg/L are reported [8, 45, 46].

3.2.24. Strontium

There is no evidence of the nutritional importance of this element, although it is known that it is concentrated in the bone mass [11]. Biokinetic model for strontium in the lactating woman from bone to milk have been described [73]. Concentrations in human milk varying between 44 and 46 μg/L are reported [72].

3.2.25. Thorium

The calculated transfer factor from food into human milk was determined as 20.2 [46]. A concentration of 0.2 μg/L in human milk was reported [46].

3.2.26. Tin

There is no evidence that tin is an essential element [11]. Signs of chronic exposure to inorganic tin include decreased growth and anemia [7]. Also, organic tin compounds were studied and no significant transport could be observed from mother diet to milk [74]. Undetectable levels were reported [20].

3.2.27. Titanium

The calculated transfer factor from food into human milk for titanium was determined as 5.6 [46]. Concentrations in human milk varying between 6.3 and 270 μg/L are reported [45, 46].

3.2.28. Uranium

The calculated transfer factor from food into human milk for uranium was determined as 21.3 [46]. A concentration of 0.03 μg/L in the human milk was reported [46].

3.2.29. Vanadium

No defined biochemical function has been identified for vanadium in the higher animals. Vanadium is a relatively toxic element, with the most frequent symptoms being intestinal disturbances and greenish tongue [7]. A concentration of 0.18 μg/L in human milk was reported [45].

4. Concluding remarks

Breast milk is for many children, in the first months of life, their unique source of nutrients, including trace elements essential for their healthy growth and development.

Although by definition trace elements are present in breast milk at relatively low concentrations, they play a crucial role in multiple physiological processes.

All of them show a great inter-individual variability in the breast milk, generally tending to decrease during lactation.

The variability of trace element levels in breast milk related to geographic, environmental, and dietary factors is well studied for several of them. For others, there is still insufficient knowledge about these aspects.

The advances in sensitivity and specificity of the analytical instrumentation occurred in recent years have made it possible to determine several elements which had not been studied until then. On the other hand, the higher reliability of current analytical techniques and the higher awareness about the importance of contamination control makes the more recently published results much more reliable.

It should be noted that the nutritional value of breast milk regarding a particular trace element does not depend on its total analytical concentration but on its bioavailable fraction; however, studies on this topic are very scarce.

Knowing to what extent the mother's supplementation can adequately correct any deficiencies in milk quality in terms of trace element levels is another important issue that should be studied.

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