

# Iron and Copper in Human Milk

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The reported concentrations of iron and copper in breast milk show a wide variation. Research published over the past 50 y has reported median values of 0.47 and 0.32 mg/L for iron and copper, respectively. The levels of both metals decrease with the progress of lactation. The calculated iron-to-copper ratio of reported means differs from 0.25 to 6.29 (median = 1.18). Maternal constitutional variables such as undernutrition, iron and copper body reserves, stage of lactation, adolescent motherhood, gestation length, and infection and environmental variables such as iron and copper dietary intake, in addition to supplementation, smoking, vegetarianism, and prolonged use of hormonal contraceptives before and during lactation did not consistently affect the concentrations of iron and copper in breast milk. Extreme cases of either low or high levels of body metal availability or altered metabolism due to chelating therapy or illnesses such as Wilson's disease and infections did not affect metal transfer from blood serum to breast milk. There is no clinical or scientific support for the need of extra iron or copper, besides the quantities provided by milk in the full-term breast-fed infant, at least during the first 6 mo. *Nutrition* 2000;16:209–220. ©Elsevier Science Inc. 2000

Key words: iron, anemia, copper, breast-milk, lactation, prematurity

## INTRODUCTION

When considering changing mineral concentrations in breast milk, any deviations from the central measurement trend can have important consequences on the understanding of infant nutrition requirements and infant formula recommendations. In recognition of this, it is important to account for the factors thought to modulate the secretion of trace elements in human milk. Iron and copper concentrations in human milk are considered below that necessary to meet the infant's requirements for growth and development. It is believed that the newborn's needs are met mainly by reserves accumulated during fetal development, especially during the last trimester of pregnancy.<sup>1,2</sup>

The interest in the variation of iron and copper concentration in human milk stems mainly from the assumption that breast-milk composition naturally reflects the full-term infant's nutrient requirements. In the case of iron, it is believed that some of the bacteriostatic properties of human milk are associated with levels and/or bioavailability of this element in breast milk. In vivo and in vitro studies have demonstrated that breast milk protects against pediatric pathogens, with iron as a key factor in breast milk's bacteriostatic properties.<sup>3,4</sup> There is evidence that iron is a determining factor in fecal flora colonization. The presence of added iron in a formula changed the profile of the fecal flora further away from that of the breast-fed baby.<sup>5</sup> Despite the fact that iron reference values in breast milk are considered low, sometimes the reference value of 0.6–0.9 mg Fe/L<sup>6</sup> is higher than commonly reported.

The secretion of iron and copper in breast milk has been investigated with regard to constitutional (undernutrition, body reserves, stage of lactation, adolescent motherhood, gestational length, infection, or iron and copper metabolism disorders) and environmental (cultural diversities, elemental supplementation, iron and copper dietary intake, vegetarianism, smoking, and prolonged use of hormonal contraceptives) factors. These studies are discussed in this review.

## CONSTITUTIONAL FACTORS

### *Prematurity*

The results of studies dealing with iron and copper levels in breast milk as a function of gestation length are inconsistent. Preterm milk iron concentration may be significantly higher<sup>7,8</sup> than or may be not significantly different than that of full-term milk.<sup>8–10</sup> Also, preterm milk copper concentrations may be significantly higher,<sup>7</sup> lower,<sup>8</sup> or no different from the concentrations of full-term milk.<sup>8,9,11–13</sup> Actually, in both preterm and term milk, the range of means of iron and copper concentrations are comparable (Table I). Therefore, the high demands of the preterm neonate are not physiologically related to a systematic difference in maternal secretion of these trace elements due to length of gestation.

### *Maternal Conditions of Altered Iron and Copper Metabolism*

The maternal iron reserves do not seem to play a significant role in breast-milk iron concentrations. Several studies have not found milk iron to be correlated with the number of pregnancies.<sup>14–16</sup> Celada et al.<sup>14</sup> showed that, despite lower iron stores with increased number of pregnancies, the iron concentration in breast milk is independent of serum ferritin or transferrin saturation. There was no significant difference in the iron content of breast milk from mothers with deficiency, overload, or normal iron status.<sup>17,18</sup> Maternal iron deficiency accompanied by serum iron concentrations of 0.34 mg/L when compared with maternal serum concentrations of 2.35 mg Fe/L showed comparable milk iron concentrations.<sup>17</sup> Chelating therapy with desferrioxamine in lactating mothers with  $\beta$ -thalassemia major does not alter iron excretion in breast milk.<sup>19</sup> Iron supplementation of anemic mothers, which significantly increased blood concentrations of the metal, did not affect milk iron concentrations.<sup>20,21</sup> Contrary to these studies, Fransson<sup>22</sup> reported that severely anemic Indian mothers (<80 mg hemoglobin/L) had total breast-milk iron concentrations (1.4 mg/L) higher than those from mothers with higher hemoglobin levels. The same investigators<sup>23</sup> also reported a significant inverse relation between iron concentration in milk and maternal hemoglobin levels.

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TABLE I.

SUMMARY OF STUDIES THAT HAVE REPORTED IRON AND COPPER CONCENTRATIONS (MG/KG OR MG/L) IN TERM AND PRETERM MILK				
Reference	Country	Fe	Cu	Stage of lactation, condition
Agget et al. <sup>100</sup>	UK	0.31	0.34	119 d, preterm
Alkanani et al. <sup>99</sup>	US		0.44	7 d, term
			0.59	7 d, preterm
Friel et al. <sup>101</sup>	Canada		0.85	7 d, term
			0.85	7 d, preterm
			0.82	14 d, term
			0.82	14 d, preterm
			0.82	21 d, term
			0.77	21 d, preterm
			0.79	28 d, term
			0.80	28 d, preterm
			0.75	35 d, term
			0.74	35 d, preterm
			0.77	42 d, term
			0.76	42 d, preterm
			0.74	49 d, term
			0.75	49 d, preterm
			0.77	56 d, term
			0.70	56 d, preterm
			0.69	94 d, term
			0.66	94 d, preterm
Aquilio et al. <sup>12</sup>	Italy		0.27	2–6 d, term
			0.26	12–16 d, term
			0.26	21 d, term
			0.25	2–6 d, preterm
			0.25	12–16 d, preterm
			0.25	21 d, preterm
Atinmo and Omololu <sup>7</sup>	Nigeria	1.05	0.54	1 wk, preterm
		0.84	0.33	1–2 wk, preterm
		0.49	0.31	1–2 wk, term
		0.78	0.30	8 wk, preterm
		0.56	0.34	1 wk, term
		0.43	0.27	8 wk, term
Jirapinyo et al. <sup>13</sup>	Thailand		0.42	28 d, preterm
			0.42	7–28 d, term
Lemons et al. <sup>45</sup>	UK	0.08		7–56 d, preterm
		0.04		7–56 d, term
Mendelson et al. <sup>9</sup>	Canada	1.11	0.72	3–5 d, term
		1.10	0.83	3–5 d, preterm
		0.99	0.73	8–10 d, term
		0.99	0.78	8–10 d, preterm
		0.81	0.57	15–17 d, term
		0.93	0.75	15–17 d, preterm
		0.88	0.58	28–30 d, term
		0.90	0.63	28–30 d, preterm
Moran et al. <sup>102</sup>	US		0.59	7 d, preterm
			0.52	14 d, preterm
			0.38	21 d, preterm
			0.36	28 d, preterm
			0.29	35 d, preterm
			0.23	42 d, preterm
			0.27	49 d, preterm
			1.04	6–10 d, term
			0.51	15 d–15 mo, term
Perrone et al. <sup>8</sup>	Italy	0.49	0.62	1 wk, term
		0.61	0.54	1 wk, preterm
		0.36	0.46	2 wk, term
		0.65	0.57	2 wk, preterm
		0.58	0.62	3 wk, term
		0.54	0.47	3 wk, preterm
		0.38	0.32	4 wk, term
		0.52	0.25	4 wk, preterm
Sann et al. <sup>11</sup>	France		0.63	6 d, preterm
			0.67	6 d, term
			0.72	7–14 d, preterm
			0.63	7–14 d, term
			0.81	>15 d, preterm
			0.48	>15 d, term
Trugo et al. <sup>10</sup>	Brazil	1.04		1–5 d, term
		0.86		1–5 d, preterm
		0.90		6–36 d, term
		0.69		6–36 d, preterm
Valentine et al. <sup>103</sup>	US		0.28	3–23 d, gestation age = 28 wk

Cu, copper; Fe, iron.

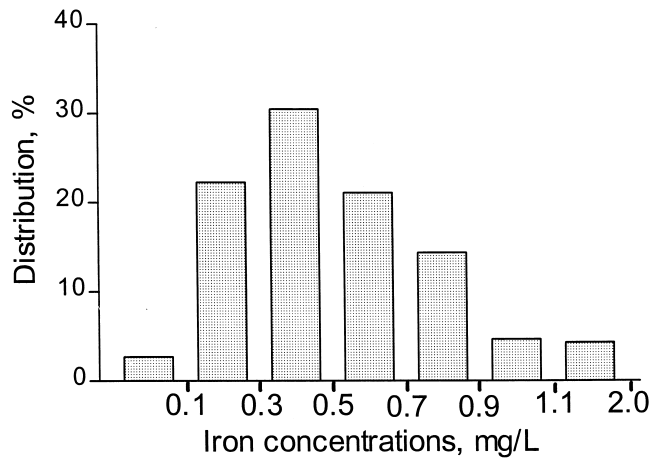


FIG. 1. Distribution of reported means of iron concentrations in human milk.

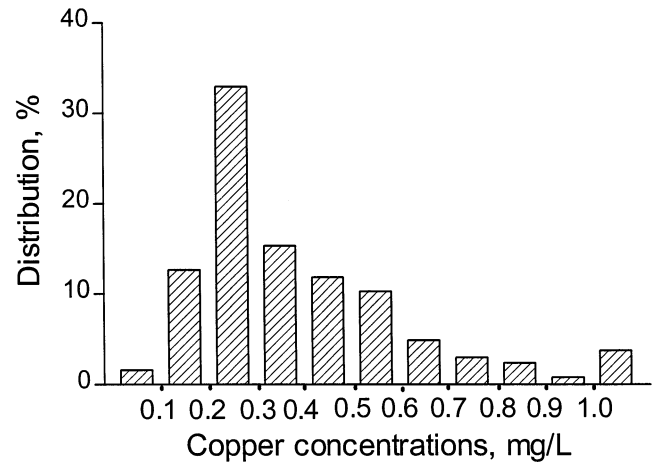


FIG. 2. Distribution of reported means of copper concentrations in human milk.

Serum copper is bound (82.8–99.9%) to ceruloplasmin<sup>24</sup> but does not seem to influence the mammary-gland uptake of copper. In extreme cases of altered copper metabolism, no change in milk copper concentrations seems to occur. In the absence of serum ceruloplasmin and in the presence of high plasma copper concentrations, as in Wilson's disease, fetal tissues showed elevated copper levels,<sup>25</sup> but no exceptional milk copper concentration was observed.<sup>26</sup> Bunke et al.<sup>26</sup> showed that, in one case of Wilson's disease, mean concentration of milk copper was 0.20 mg/L, with a serum-to-milk copper molar ratio of 4.3. Also, in situations of illness that significantly increased serum copper, no significant change was seen in milk copper concentrations.<sup>27</sup> Even intravenous infusion of copper in postpartum women, which raised the serum copper, did not significantly increase the copper level in colostrum.<sup>28</sup> One study showing significant differences in milk copper due to parity was not consistent. Kirsten et al.<sup>29</sup> reported significant differences only on day 3.

For iron or copper, the serum-to-milk ratio is always higher on the part of the serum,<sup>17,20,21,30–33</sup> except in cases of severe anemia, where the milk-to-serum ratio for iron becomes higher.<sup>17</sup> Nevertheless, the secretion mechanism operating in the mammary gland does not seem to be influenced by serum metal concentrations of either iron or copper.

Although maternal copper deficiency during gestation may lead to birth defects, it has been speculated that teratogenesis in experimental diabetes may also be related to maternal copper deficiency.<sup>34</sup> However, Butte et al.<sup>35</sup> found no significant differences in milk copper concentrations between diabetic and non-diabetic mothers.

**Stage of Lactation**

The changes in human milk composition that accompany lactation differ for iron and copper (Figs. 1–3). In several studies there was no correlation between the two elements in breast milk.<sup>15,36</sup> The significant decrease in copper concentration with length of lactation (Tables I–V) also occurred for iron.<sup>9,15,16,33,37,38</sup> A few studies,<sup>20,39,40</sup> however, showed no significant decrease in milk iron. The reason for such discrepancies is not well understood and may be due in part to differences in study design because, during gradual weaning, iron decreases to concentrations ranging from 0.03 to 0.05 mg/mL.<sup>41</sup> Postpartum iron and copper serum levels show a gradual return to prepregnancy levels, but the significant correlation reported between serum and milk copper concentrations is not seen between serum and milk iron concentrations.<sup>36</sup>

The iron and copper secretion in breast milk may be specific because it does not appear to depend on total mineral mass changes in human milk. Even on a dry matter basis, the iron concentrations may vary from 10 to 25 mg/kg<sup>42,43</sup> and copper from 1.7 to 5.9 mg/kg.<sup>42,44</sup> Total mineral mass, or milk ash, is reported to vary from 0.15% to 0.28%,<sup>45–48</sup> with the exception of Vaughan et al.'s<sup>39</sup> findings that reported values between 1.23% and 1.76%. Most of the mineral mass is comprised of calcium and phosphorus that together can reach 15–20% of the total ash.<sup>49</sup> Iron and copper comprise less than 1% of the total mineral mass,<sup>50</sup> and copper concentration in milk ash shows an upward trend during the first 3 mo of lactation. During this same period, total ash does not seem to change.<sup>47,50</sup> The concentrations of iron and copper in breast milk may<sup>15</sup> or may not<sup>36</sup> be significantly correlated.

The distributions of iron and copper in breast-milk fractions occur independently. Studies have shown that iron is bound principally to low-molecular-weight peptides (18–56%), fat globules (15–46%), and lactoferrin (16–40%).<sup>33,51–53</sup> The mean iron saturation of lactoferrin varies from 2.2<sup>52</sup> to 12%.<sup>53</sup> The copper distribution in breast milk may reach 15–20% in the lipid layer,<sup>52,54,55</sup> and studies have shown that ceruloplasmin, the serum copper-containing protein, is also found in human milk and may carry 20–25% of the total milk copper.<sup>56,57</sup>

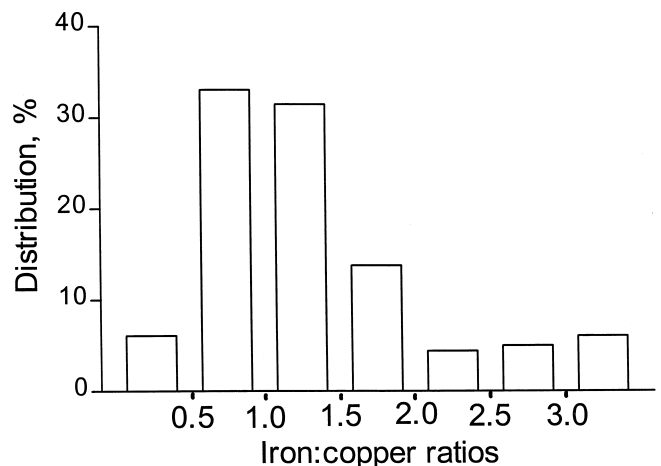


FIG. 3. Distribution of calculated iron:copper ratios in human milk.

TABLE II.

SUMMARY OF STUDIES THAT HAVE REPORTED IRON AND COPPER CONCENTRATIONS (MG/KG OR MG/L) IN MILK OF MOTHERS TAKING IRON OR COPPER SUPPLEMENTATION				
Reference	Country	Fe	Cu	Stage of lactation, condition
Arnaud et al. <sup>20</sup>	Nigeria	0.27	0.58	5 d, control
		0.28	0.55	5 d, Fe supplemented
		0.24	0.19	90 d, control
		0.23	0.21	90 d, Fe supplemented
		0.22	0.18	180 d, control
		0.24	0.21	180 d, Fe supplemented
Keizer et al. <sup>73</sup>	Canada	0.22		28 d, folic acid (300 mg/d)
		0.25		56 d, folic acid (300 mg/d)
		0.19		84 d, folic acid (300 mg/d)
Murray et al. <sup>17</sup>	Niger	1.20		2 wk, normal
		1.12		2 wk, Fe deficient
		1.16		2 wk, Fe supplemented
		0.30		5 mo
Munch-Petersen <sup>28</sup>	Sweden		0.54	Foremilk
			0.55	Hindmilk
Salmenpera et al. <sup>24</sup>	Finland		0.34	Colostrum, 2–4 mg Cu/d
			0.12	9 mo, 2–4 mg Cu/d
Zapata et al. <sup>72</sup>	Brazil	1.02		1–2 d, control
		0.99		1–2 d, Fe supplemented
		0.75		30–40 d, control
		0.79		30–40 d, Fe supplemented
		0.56		90–100 d, control
Zavaleta et al. <sup>21</sup>	Peru	0.9		2 d, anemic + Fe treatment
		0.8		2 d, non-anemic
		0.4		30 d, anemic + Fe treatment
		0.4		30 d, nonanemic

Cu, copper; Fe, iron.

Major metal-carrier protein decreases as lactation progresses. However, whereas lactoferrin decreased, total iron concentration in milk was unaffected.<sup>33</sup> Breast-milk ceruloplasmin decreases in the first month of lactation,<sup>58,59</sup> but to date no study has demonstrated its role in milk copper concentration.

Despite significant differences in fat content between fore- and hindmilk<sup>60</sup> and significant correlation between iron and fat in milk,<sup>51</sup> the difference in total iron between fore- and hindmilk may<sup>61</sup> or may not<sup>62</sup> be statistically significant. Balance studies have shown a direct correlation between copper and fat in feces of very-low-birth-weight infants.<sup>63</sup> However, no significant differences between fore- and hindmilk copper concentrations could be found.<sup>13,60,64</sup>

## ENVIRONMENTAL FACTORS

### *Maternal Dietary Intake of Iron and Copper*

Based on animal studies it has been proposed<sup>65,66</sup> that maternal iron and copper intake could increase iron content of milk. However, there is no evidence that this situation can also occur in humans. Despite the complex interactions related to different environmental and dietary habits or simple mineral supplementation, increased iron and copper intakes do not affect their concentrations in milk.

No significant correlation was found between iron and copper dietary intake and their concentrations in breast milk.<sup>67</sup> Several studies have shown similar milk iron and copper concentrations when comparing maternal iron and copper intakes between countries and cultures. Different dietary habits in the same culture, such

as vegetarianism,<sup>68</sup> or between races within the same country—e.g., Bantu versus white women in South Africa<sup>43</sup> and Chinese versus Malay versus Indian women in Malaysia<sup>69</sup>—produced no significant differences in milk iron and copper concentrations. The exception was the work of Lipsman et al.<sup>70</sup> who reported significantly lower milk copper in Hispanic mothers than in non-Hispanic white mothers in the United States. Comparing two different cultures with distinct dietary habits and food ingredients such as Nepal and the United States showed that Nepalese mothers had a significantly higher copper intake and a significantly lower iron intake than did American mothers. Despite such opposite trends in mineral intake, no significant difference was found in milk iron and copper concentrations between Nepalese and American mothers.<sup>32</sup> However, Fransson et al.<sup>71</sup> reported a significant difference between milk copper concentrations in Ethiopian and Swedish mothers.

Studies in several countries also did not show significant effects of supplementation on milk metal concentrations. Supplementing iron to mothers in Brazil<sup>33,72</sup> and in the United States<sup>15</sup> during either pregnancy<sup>33</sup> or lactation<sup>15</sup> did not affect milk iron concentrations. Zapata et al.<sup>72</sup> reported that the breast milk of mothers supplemented with 40 mg iron/d had higher total iron-binding capacity but no significant difference in total milk iron concentration. Daily supplementation of 100 mg iron in the last 6 mo of pregnancy also did not change milk iron or copper concentrations in Nigerian mothers.<sup>20</sup> Further, 200 mg/d supplemental iron had no effect on milk copper concentrations.<sup>24</sup> Teenage mothers who took folic acid<sup>73</sup> and mineral<sup>70</sup> supplements also did not show significant differences in milk iron and copper concentrations.

TABLE III.

SUMMARY IRON AND COPPER CONCENTRATIONS (MG/KG OR MG/L) IN MILK OF MOTHERS IN STUDIES THAT HAVE COMPARED COUNTRIES, REGIONS, AND RACES				
Reference	Country	Fe	Cu	Stage of lactation, condition
Belavady <sup>104</sup>	India		0.48	<1 mo
			0.28	1-3 mo
			0.21	4-6 mo
			0.17	7-12 mo
			0.21	6-12 wk
Dang et al. <sup>105</sup>	India	0.21	0.51	3-5 d, mid income
			0.61	3-5 d, low income
			0.46	4-6 wk, mid income
			0.41	4-6 wk, low income
Dang et al. <sup>74</sup>	India		0.27	NG, tribal
			0.91	NG, urban
Fransson et al. <sup>71</sup>	Ethiopia	0.47	0.37	Non-privileged
			0.46	Privileged
Lipsman et al. <sup>70</sup>	US	0.50	0.61	NG
			0.23	Hispanic
Loh and Sinnathuray <sup>69</sup>	Malaysia	0.82	0.28	Non-Hispanic
			1.11	2 d, Chinese
			1.16	2 d, Indian
Moser et al. <sup>32</sup>	US		0.27	2-6 mo, American
			0.22	2-6 mo, Nepalese
Parr et al. <sup>106</sup>	Guatemala	0.35	0.26	3 mo
			0.36	3 mo
			0.52	3 mo
			0.72	3 mo
			0.45	3 mo
Rajalakshimi and Srikantia <sup>107</sup>	India	0.56	0.20	3 mo
			0.29	1-3 mo, urban
Villalpando et al. <sup>108</sup>	Mexico	0.19	0.23	1-3 mo, rural
			0.16	4-6 mo, urban
			0.21	4-6 mo, rural
			0.21	7-12 mo, urban
			0.17	7-12 mo, rural
			0.17	>13 mo, urban
			0.16	>13 mo, rural
			0.15	4 mo
			0.23	6 mo
			0.28	4 mo
0.15	6 mo			

Cu, copper; Fe, iron; NG, not given.

Studies in Ethiopia<sup>71</sup> and India<sup>74</sup> have claimed a significant difference in milk copper between socioeconomic groups of lactating women. Milk copper concentrations of 0.91 and 0.27 mg/L were reported for two groups of poverty-stricken lactating women.<sup>75</sup> The same study also reported that malnourished babies were fed breast milk with lower concentrations of trace elements (copper included). However, most studies have shown that maternal dietary copper intake does not affect milk copper.<sup>24,38,75,76</sup> Low (2 mg/d) or high (4 mg/d) copper supplementation during lactation had no significant effect on milk copper concentration. Oral copper supplementation (2 mg/d) significantly raised serum copper but did not affect milk copper concentration.<sup>75</sup> Nepalese mothers with a higher intake of copper had lower serum copper than did American mothers<sup>32</sup> but had similar milk copper levels.

It is clear by now that iron and copper body reserves do not modulate metal transfer from blood serum to milk. Although calcium may impair iron absorption, long-term use of calcium supplementation had no effect on iron stores of lactating women in

Gambia<sup>77</sup> and the United States.<sup>78</sup> Copper metabolism altered by smoking increased copper in the placental cytosolic fraction and amniotic fluid but did not affect milk copper.<sup>79-81</sup>

#### Oral Contraceptives

Since the inception of oral contraceptives (OCs), there have been studies of its effects on lactation and milk composition.<sup>82</sup> These contraceptives are basically the combination (progesterone plus estrogen) and progesterone-only (minipill or injectable progesterone) pills. However, hormonal therapy for control of fertility has undergone considerable change. Formulas for a combined pill have shown a decline in both progesterone and estrogen, with substantially more changes in the former. Progesterone levels also have been changed in both minipills and injectable formulas.<sup>82</sup>

The use of OC seems to affect mineral metabolism.<sup>83</sup> Serum iron and copper metabolism are affected by long-term OC use.<sup>84,85</sup>

TABLE IV.

SUMMARY OF STUDIES THAT HAVE REPORTED IRON AND COPPER CONCENTRATIONS (MG/KG OR MG/L) IN MILK OF MOTHERS UNDER CONDITIONS OF ALTERED METABOLISM						
Reference	Country	Fe	Cu	Stage of lactation, condition		
Bunke et al. <sup>26</sup>	Germany		0.20	10 wk, Wilson's disease		
Butte et al. <sup>35</sup>	US	0.22	0.26	73-115 d, diabetic mothers		
		0.18	0.28	NG, control		
Coni et al. <sup>79</sup>	Italy	0.98	0.37	2 mo, rural non-smokers		
		0.91	0.36	2 mo, rural smokers		
		0.56	0.41	2 mo, urban non-smokers		
		0.69	0.45	2 mo, urban smokers		
		0.1	0.39	8-16 wk, OC users + non-users		
Cumming et al. <sup>30</sup>	Australia	0.1	0.39	8-16 wk, OC users + non-users		
Dorea and Miazaki <sup>36</sup>	Brazil	0.59	0.25	Controls		
		0.42	0.21	Controls		
		0.48	0.25	Before OC, combination pill		
		0.67	0.24	After OC, combination pill		
		0.51	0.25	Before OC, minipill		
		0.46	0.24	After OC, minipill		
		1.4		NG, hemoglobin <80 g/L		
		0.60		NG, hemoglobin 80-110 g/L		
Fransson <sup>22</sup>	Sweden	0.60		NG, hemoglobin >110 g/L		
		0.50		NG, hemoglobin 120 g/L		
Hunt et al. <sup>109</sup>	Ethiopia	0.50		NG, hemoglobin 135 g/L		
		0.50		NG, hemoglobin 135 g/L		
Imamura <sup>18</sup>	Australia	0.66		Monoclyne therapy		
	Japan	0.68		1-3 d, normal		
		0.73		1-3 d, anemic		
		0.76		1-3 d, toxemic		
		0.69		1-3 d, treated anemic		
		0.68		5-7 d, normal		
		0.68		5-7 d, anemic		
		0.73		5-7 d, toxemic		
		0.64		5-7 d, treated anemic		
		0.55		30-40 d, normal		
		0.58		30-40 d, anemic		
		0.59		30-40 d, toxemic		
		0.56		30-40 d, treated anemic		
		Keizer et al. <sup>40</sup>	Canada	0.22		4 wk, folate + placebo
				0.26		8 wk, folate + placebo
0.19				12 wk, folate + placebo		
Kirksey et al. <sup>75</sup>	US	0.45	0.46	3 d, OC before pregnancy		
		0.49	0.40	14 d, OC before pregnancy		
		0.55	0.33	3 d, no OC		
		0.52	0.36	14 d, no OC		
Kirsten et al. <sup>64</sup>	South Africa		0.53	3 d, multipara		
			0.40	3 d, primipara		
			0.58	7 d, multipara		
			0.51	7 d, primipara		
			0.40	6 wk, multipara		
			0.41	6 wk, primipara		
			0.33	12 wk, multipara		
			0.35	12 wk, primipara		
			0.44	24 wk, multipara		
			0.40	24 wk, primipara		
			0.31	36 wk, multipara		
			0.18	36 wk, primipara		
		Lipsman et al. <sup>70</sup>	US	3.10	0.33	30 d, teen age
				2.17	0.29	60 d, teen age
2.45	0.27			90 d, teen age		
2.25	0.25			120 d, teen age		
2.11	0.22			150 d, teen age		
2.12	0.23			180 d, teen age		
0.41	0.33			30 d, adult		
0.30	0.26			60 d, adult		
0.40	0.33			90 d, adult		
0.33	0.26			120 d, adult		
0.28	0.22			150 d, adult		
0.24	0.20			180 d, adult		
0.23	0.17			210 d, adult		

(Continued)

TABLE IV.

SUMMARY OF STUDIES THAT HAVE REPORTED IRON AND COPPER CONCENTRATIONS (MG/KG OR MG/L) IN MILK OF MOTHERS UNDER CONDITIONS OF ALTERED METABOLISM ( <i>Continued</i> )				
Reference	Country	Fe	Cu	Stage of lactation, condition
Lonnerdal et al. <sup>27</sup>	Peru	0.50	0.66	1 d, ill
		0.37	0.44	2 d, ill
		0.38	0.46	14 d, ill
		0.55	0.68	1 d, control
		0.35	0.50	2 d, control
		0.47	0.46	14 d, control
Maeda et al. <sup>110</sup>	Japan		2.19	1 wk, primipara
			2.11	1 mo, multipara
			1.38	1 wk, primipara
			1.32	1 mo, multipara
			0.30	3 d, passive smokers
Milnerowicz and Slowinska <sup>81</sup>	Poland		0.27	3 d, active smokers
			0.81	4, 8, 12 mo, control
Ruz et al. <sup>111</sup>	Chile	0.74	0.82	4, 8, 12 mo, undernourished
Surbek et al. <sup>19</sup>	Switzerland	0.04		5 d, $\beta$ -thalassemia major
		0.58		9 d, $\beta$ -thalassemia major
		0.27		11 wk, $\beta$ -thalassemia major
Van der Elst et al. <sup>31</sup>	South Africa		0.59	3 wk, control
			0.53	3 wk, thin mothers
		0.67		4–7 d, control
		0.42		20–60 d, thin mothers
			0.24	1 d, ill
Zavaleta et al. <sup>112</sup>	Peru	0.42	0.27	2 d, ill
		0.36	0.26	14 d, ill
		0.33	0.29	1 d, control
		0.31	0.28	2 d, control
		0.31	0.28	2 d, control
		0.36	0.27	14 d, control

Cu, copper; Fe, iron; NG, not given; OC, oral contraceptive.

In women, contraceptives containing estrogens increased body copper loss<sup>86,87</sup> without affecting its absorption.<sup>88,89</sup> The use of hormonal contraceptives had a marked effect on iron metabolism<sup>90</sup> and a reduction in menstrual blood loss.<sup>91</sup>

There are numerous studies of the effects of hormonal contraceptives on lactation and milk composition, but very little information on the effects of iron and copper in breast milk.<sup>30,75</sup> Kirksey et al.<sup>75</sup> studied the effects of OC taken over long periods before lactation and found no significant effects on iron and copper concentrations in milk but did find a lower concentration of copper in serum of women who took OC before pregnancy. In Australia, Cumming et al.<sup>30</sup> reported that the use of progestin-only (30  $\mu$ g levonorgestrel or 350  $\mu$ g norethisterone/d) during lactation had no effect on either serum or milk metal (Fe and Cu) concentrations. They studied only five mothers and employed simple mean comparisons, without taking into consideration the maternal constitutional variables that may affect lactation and milk components. Besides, progestogens are less likely to interfere with lactation,<sup>92</sup> and their effects on mineral metabolism are not as marked as those of estrogens.<sup>93</sup> Despite reports of urinary<sup>87</sup> and sweat<sup>86</sup> copper losses due to OC use, Dorea and Miazaki<sup>36</sup> did not find significant differences in copper and iron in serum or milk during the relatively short duration of the study (Table III).

### INFANT SUSCEPTIBILITY TO VARIATION IN MILK IRON AND COPPER

Despite the wide variation in the median concentrations of iron (0.04–1.92 mg/L) and copper (0.03–2.19 mg/L) in breast milk, there is no proven risk of nutritional deficiencies of these elements

in the child during the first 6 mo of lactation. The neonate is born with hepatic reserves of iron and copper to balance the low concentrations of these elements in human milk.<sup>2</sup> During the first 4 mo, the mineral intake of the breast-fed infant decreases significantly.<sup>94</sup> However, the efficiency of utilization of iron and copper derived from fetal reserves and high bioavailability in breast milk<sup>95</sup> adequately support growth and development in the breast-fed term infant. Despite both decreasing iron and copper concentrations and intakes as lactation progresses, body stores of these metals are satisfactory for breast-fed babies when compared with formula-fed babies.<sup>95–97</sup> Nevertheless, calcium concentrations within the range of reported median values<sup>49</sup> may decrease iron absorption from breast milk.<sup>98</sup> In premature babies, such interactions should be of concern when using human milk fortifiers. One study with a 4-mo-old preterm infant using such fortifiers showed that a negative zinc balance was associated with negative copper balance but not with iron.<sup>99</sup>

### CONCLUSIONS

The mechanisms governing the transfer of iron and copper from blood to breast milk are not fully understood, but they do not seem to depend on either maternal iron and copper intake or maternal metal reserves. Irrespective of factors that affect maternal iron and copper metabolism such as OC use, smoking, or infections, there is no evidence that the milk concentrations of these metals are affected. Also, specific maternal conditions that markedly alter iron (anemia,  $\beta$ -thalassemia major) and copper (Wilson's disease) metabolism have no significant influence on milk iron and copper concentrations. The infant requirements for iron and copper are

TABLE V.

SUMMARY OF STUDIES THAT HAVE MEASURED IRON AND COPPER CONCENTRATIONS (MG/KG OR MG/L) IN BLOOD SERUM AND MILK FROM MOTHERS IN DIFFERENT PARTS OF THE WORLD

Reference	Country	Fe			Cu			Stage of lactation
		Min	Med	Max	Min	Med	Max	
Arnaud and Favier <sup>113</sup>	France	0.31		0.79	1.01		1.11	1-5 d
Arpadjan and Stojanova <sup>114</sup>	Bulgaria		0.56			1.60		NG
Balmer and Wharton <sup>5</sup>	UK		0.80					NG
Benemaryia et al. <sup>115</sup>	Burundi				0.08	0.28	0.59	2 d
Bhatia and Rassin <sup>116</sup>	US					0.30		2-4 wk
Bratter <sup>117</sup>	Germany		0.77			0.90		3 wk
Burguera et al. <sup>118</sup>	Venezuela	0.09	0.20	0.64	0.20	0.53	1.15	1-30 d
Butte et al. <sup>94</sup>	US	0.16	0.18	0.24	0.27	0.28	0.36	1-4 mo
Butte and Calloway <sup>119</sup>	US		0.80			0.30		1 mo
Carias et al. <sup>120</sup>	Venezuela	0.68	0.74	0.84	0.18	0.21	0.25	1 d-6 mo
Carrion et al. <sup>121</sup>	Venezuela	0.22		0.74	0.30		0.78	3-21 d
Casey <sup>122</sup>	New Zealand		0.72			0.40		4-10 d
Casey et al. <sup>76</sup>	US				0.22		0.62	7 d-5 mo
Casey et al. <sup>123</sup>	US				0.41		0.60	7 d-5 mo
Cavell and Widdowson <sup>124</sup>	UK		0.59			0.62		1 wk
Celada et al. <sup>14</sup>	Spain		0.39					10 d
Clemente et al. <sup>125</sup>	Italy		1.5					2-3 mo
Dang et al. <sup>126</sup>	India				0.18	0.27	0.34	
Dauncey et al. <sup>127</sup>	UK				0.31		0.41	Pooled
Davidsson et al. <sup>128</sup>	US		0.14					2-10 mo
Dempster et al. <sup>129</sup>	South Africa					0.54		7 d
Dewey and Lonnerdal <sup>39</sup>	US	0.20	0.22	0.31	0.20	0.24	0.36	1-6 mo
Dewey et al. <sup>130</sup>	US	0.17	0.20	0.27	0.15	0.17	0.23	4-20 mo
Donangelo et al. <sup>33</sup>	Brazil	0.42	0.73	1.23				1-280 d
Dorea et al. <sup>60</sup>	Brazil					0.78		NG
Dorner et al. <sup>131</sup>	Germany		0.43		0.83			NG
Durrand and Ward <sup>132</sup>	UK	0.28		1.92	0.08		1.14	NG
Ehrenkrantz et al. <sup>133</sup>	US					0.29		
Feeley et al. <sup>15</sup>	US	0.76	0.85	0.96	0.84	0.93	1.04	4-45 d
Fransson and Lonnerdal <sup>51</sup>	US		0.41					1-80 wk
Fransson and Lonnerdal <sup>52</sup>	US		0.39			0.32		2-4 mo
Fransson and Lonnerdal <sup>54</sup>	Sweden					0.27		NG
Hambidge <sup>134</sup>	US				0.29	0.49	1.19	2 d-6 mo
Hallberg et al. <sup>98</sup>	Sweden		0.45					
Harzer et al. <sup>135</sup>	Germany				0.35		0.50	5-36 d
Hibberd et al. <sup>136</sup>	Germany				0.34	0.40	0.44	1-36 d
Higashi et al. <sup>137</sup>	Japan				0.22	0.44	0.45	1 wk-5 mo
Hirai et al. <sup>53</sup>	Japan	0.42	0.64	0.67				1-60 d
Hurgoiu and Caseanu <sup>138</sup>	Rumania	0.31	0.45	0.5				7-30 d
Itriago et al. <sup>139</sup>	Venezuela	0.37	0.38	0.49	0.47	0.50	0.52	3-21 d
Iyengar et al. <sup>140</sup>	Germany		0.24					NG
Jochum et al. <sup>141</sup>	Germany					0.27		4 mo
Kirsten et al. <sup>29</sup>	South Africa				0.24	0.38	0.57	3-252 d
Koksal et al. <sup>16</sup>	Turkey	0.21	0.32	0.72	0.15	0.25	0.59	2-40 wk
Krachler et al. <sup>142</sup>	Austria				1.0	1.6	3.7	42-60 d
Lauber and Reinhardt <sup>143</sup>	Ivory Coast	0.54	0.55	0.90	0.13	0.14	0.44	1-18 mo
Li et al. <sup>144</sup>						0.67		6-9 d
Lin et al. <sup>145</sup>	Taiwan	0.09	0.21	0.27	0.09	0.27	0.39	1 d-12 mo
Lonnerdal et al. <sup>146</sup>	US	0.6		1.0	0.3		0.6	Colostrum
		0.2		0.4	0.2		0.3	Mature milk
Mandic et al. <sup>147</sup>	Croatia				0.31	0.37	0.59	<10->60 d
Matsuda et al. <sup>148</sup>	Japan				0.20	0.27	0.44	2 wk-6 mo
Mbofung and Atinmo <sup>149</sup>	Nigeria	0.29		0.52	0.26		0.54	NG
McMillan et al. <sup>95</sup>	US		0.69					NG
Murthy and Rhea <sup>150</sup>	US		0.84			0.24		Pooled
Nagra <sup>48</sup>	Pakistan				0.26	0.28	0.43	1-12 mo
Nassi et al. <sup>151</sup>	Italy	0.36	0.37	0.41	0.29	0.35	0.36	1-15 d
Neville et al. <sup>152</sup>	US					0.19		53-120 d

(Continued)

TABLE V.

SUMMARY OF STUDIES THAT HAVE MEASURED IRON AND COPPER CONCENTRATIONS (MG/KG OR MG/L) IN BLOOD SERUM AND MILK FROM MOTHERS IN DIFFERENT PARTS OF THE WORLD (Continued)

Reference	Country	Fe			Cu			Stage of lactation
		Min	Med	Max	Min	Med	Max	
Ohtake and Tamura <sup>153</sup>	Japan				0.19	0.29	0.39	1–201 d
Oski et al. <sup>154</sup>	US		0.76					Pooled
Palma et al. <sup>155</sup>	US	0.3		0.7	0.28		0.78	0–240 d
Picciano <sup>61</sup>	US	0.24	0.34	0.42	0.18	0.19	0.20	2–5 mo
Picciano and Guthrie <sup>156</sup>	US		0.20			0.24		6–12 wk
Picciano et al. <sup>157</sup>	US	0.33	0.37	0.41	0.20	0.21	0.21	1–3 mo
Rana et al. <sup>158</sup>	Pakistan		1.7			0.27		2–6 d
Richmond et al. <sup>159</sup>	UK		0.83			0.32		3 mo
Robberecht et al. <sup>160</sup>	Burundi				0.08	0.28	0.59	2–10 d
Rossipal et al. <sup>161</sup>	Austria				0.15	0.24	0.55	1–293 d
Rydzewska and Kro <sup>162</sup>	Poland				0.47		0.60	NG
Sachde and Bundt <sup>163</sup>	Germany				0.58		0.77	NG
Saner and Yuzbaisyan <sup>62</sup>	Turkey	0.23		0.58				1–3 mo
Schulz-Lell et al. <sup>164</sup>	Germany		0.44			0.84		NG, 2300 samples
Schamel et al. <sup>165</sup>	Germany		0.38		0.34		0.37	NG
Silva et al. <sup>166</sup>	Brazil		0.56			0.26		1–6 mo
Sharda et al. <sup>167</sup>	India				0.10	0.21	0.41	2 d >6 mo
Shaw <sup>168</sup>	UK				0.28	0.49	0.52	2 wk–6 mo
Siimes et al. <sup>37</sup>	Finland	0.30		0.56				0.5–5 mo
Stolley et al. <sup>46</sup>	Germany	0.36	0.48	0.62	0.30	0.46	0.67	1–3 wk
Simmer et al. <sup>169</sup>	Bangladesh				0.12	0.19	0.24	1–12 mo
Vaughan et al. <sup>38</sup>	US	0.38	0.42	0.49	0.24	0.29	0.43	1–31 mo
Vuori et al. <sup>67</sup>	Finland	0.29		0.40	0.21		0.36	6–22 wk
Vuori et al. <sup>170</sup>	Finland				0.25		0.60	2–30 wk
Vuori and Kuitunen <sup>171</sup>	Finland				0.17	0.32	0.60	2–37 wk
Williams et al. <sup>172</sup>	US					0.8		NG
Wooten et al. <sup>57</sup>	US					0.60		1 wk
Yamamoto et al. <sup>173</sup>	Japan	0.29	0.40	0.56	0.18	0.32	0.64	3 d–13 mo
Yoshinaga et al. <sup>174</sup>	Japan					0.69		Colostrum

Cu, copper; Fe, iron; Max, maximum; Med, medium; Min, minimum; NG, not given.

met in part by liver reserves of these metals. The low levels of iron and copper in milk are important for the bacteriostatic properties of human milk and do not pose a risk to the nutritional status of these metals in the breast-fed term infant, at least during the first 6 mo of life.

## ACKNOWLEDGMENT

I thank Dr. Connie McManus for redactional suggestions.

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