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Zinc and copper requirements in preterm infants: An examination of the current literature

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ABSTRACT

Background: Zinc and copper are essential for preterm infants, but recommended requirements from different groups vary widely. Recommended zinc intakes have steadily increased over the years. Although this would be expected to impair copper absorption, recommended copper intakes have not risen in parallel.
Objectives: To systematically review the literature on zinc and copper retention in preterm infants; to examine the effect on zinc intake on copper retention; and to estimate the zinc and copper intakes required to meet the levels of zinc and copper retention required for normal growth.
Design: Studies reporting zinc and/or copper retention in preterm infants (<36 weeks of gestation) during the first 120 days of life were identified using PubMed. Only studies reporting net retention were included.
Results: Fourteen studies on zinc retention reporting data on 45 different groups were identified. Eleven studies (32 groups) were identified reporting copper retention. Zinc retention was significantly higher at higher zinc intakes, and higher in formula-based diets than in human milk based diets. Zinc intakes of between 1.8–2.4 mg/kg/d (from formula based diets) and 2.3–2.4 mg/kg/d (from human-milk based diets) were required to achieve adequate zinc retention. Copper retention was significantly positively correlated with copper intake and significantly negatively correlated with zinc intake. At the zinc intakes suggested previously (1.8–2.4, 2.3–2.4 mg/kg/d), copper intakes of between 200 and 250 mcg/kg/d are required to ensure adequate copper retention.
Conclusions: Our results support the higher zinc intakes recommended in recent guidelines. However, they suggest that recommended copper intakes have not kept pace with increasing zinc intakes, and that preterm infants may need higher copper intakes than currently recommended.

1. Introduction

Zinc and copper are essential nutrients for human health [1,2] and both zinc and copper deficiencies are well described in preterm infants [3,4].

Early recommendations for the zinc requirements of preterm infants were based on human milk content [5] or on the content of formulas designed for term infants [6]. Enteral zinc intakes of 0.50–0.55 mg/100 kcal (approximately 0.60–0.75 mg/kg/d) were felt appropriate [5,6]. More recent consensus guidelines have increased the recommended enteral zinc intake to 1 mg/kg/d [7] and subsequently to 1–2 mg/kg/d [8,9], or as high as 3 mg/kg/d for infants of birthweight less than 1 kg [10].

Initial estimates for enteral copper requirements were 90–120 mcg/100 kcal (approximately 110–160 mcg/kg/d) [5,6], and have changed little over the past 25 years. The most recent recommendations are for intakes of between 120 and 150 mcg/kg/d [7,8] or between 100 and 130 mcg/kg/d [9]. However, copper requirements are known to be related to zinc intakes, as zinc interferes with the enteral absorption of copper [1]. It is surprising, therefore, that recommended copper requirements have remained the same when recommended zinc intakes have increased 2- to 4-fold.

One approach to estimating mineral requirement for preterm infants is to try to identify an intake that is likely to meet either the *in utero* accretion rate, or the *ex utero* needs for normal growth. Accretion of zinc by the fetus during the third trimester is between about 300 mcg/kg/d [11] and 850 mcg/kg/d [12]; however the requirement for normal growth is less than this. Klein estimated zinc requirements in preterm infants using a factorial method [13]. According to these calculations, the requirement for retained zinc (i.e. the amount that absorbed zinc must exceed zinc losses) steadily declines with increasing post-conceptional age from about 500 mcg/kg at 27 weeks of post-conceptional age, to 400 mcg/kg

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at 30–32 weeks of post-conceptional age and 200–300 mcg/kg at 35–40 weeks of post-conceptional age [13]. *In utero* copper accretion is between 50 and 56 mcg/kg/d [10,13–15], although accretion rates as high as 80 mcg/kg/d have been suggested [11]. A factorial analysis suggests that a net requirement of about 30 mcg/kg/d is adequate to maintain normal growth [13] in preterm infants.

The objectives of this review are to systematically examine the existing literature on the relationship between zinc and copper intakes and their retention in preterm infants; to identify factors that modify zinc and copper retention; and to devise models that predict the zinc and copper intakes required to meet the *in utero* accretion rate or the *ex utero* requirement for normal growth of 0.3–0.4 mg/kg/d (for zinc) and 30–50 mcg/kg/d (for copper) in preterm infants.

2. Methods

2.1. Selection of studies

Potentially relevant studies were identified by search PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez/) using combinations of the terms "newborn", "neonate", "preterm infant", "zinc absorption", "copper absorption", "zinc retention", "copper retention", "zinc balance", and "copper balance". The literature cited by each study was examined to identify other potentially relevant studies that had been overlooked in the PubMed search. English language literature published since 1960 was considered.

Studies were included if they (a) examined preterm infants (gestational age at birth <36 weeks), (b) were carried out during the first 120 days of life, and (c) provided estimates of net zinc (or copper) retention. Stable isotope studies that only measured fractional zinc (or copper) absorption but did not permit calculation of total net balance/retention were excluded.

2.2. Data extraction

Summary data were extracted from the published manuscripts. Some manuscripts included data on a single group of infants (e.g. Reference [16]), and so contributed a single data-point to the analysis. Others contained data on different groups of preterm infants, for example groups receiving different copper intakes [17], receiving preterm formula or fortified human milk [18,19], or preterm infants being studied at different post-natal ages [11]. These studies, therefore, contributed more than one data-point to the analysis.

For each distinctly identifiable group from each manuscript, summary data on birthweight, gestational age at birth, post-natal age and post-conceptional age, body weight, diet (human milk or formula) at the time of the metabolic balance, zinc and copper intakes and copper retention were collected.

2.3. Calculation of missing means and standard deviations

A small number of published studies presented data for zinc intake or zinc retention as median and ranges. In these instances, mean and SD were estimated using the method of Hozo et al. [20].

2.4. Data analysis

Determinants of zinc retention were examined using multiple regression analysis. Explorative models including either zinc intake, gestational age, post-natal age, and feed type (formula or human milk), or zinc intake, post-conceptional age, and feed type (formula or human milk) were used to identify likely determinants of zinc retention. Based on the results of these analyses, the best model (with the minimum number of significant independent variables required) was developed. This model was used to estimate the zinc intake required to achieve zinc retention of 0.4 mg/kg/d and 0.3 mg/kg/d (the estimated requirement for infants of 30–32 weeks and 35–40 weeks post-conceptional age, respectively).

Three different methods of weighting the data were used. Data were analyzed using (a) unweighted data (all groups contributed the same amount to the analysis), (b) weighted by sample size (the largest groups were weighed more heavily) or (c) by the reciprocal of the standard error of the mean (SEM, with more precise data was weighed more heavily).

Similar methods were used for copper retention, and the copper intakes required to achieve retention of 30–50 mcg/kg/d were calculated.

Statistical analysis was carried out using JMP version 7.02 (SAS Institute, Raleigh, NC). Data were considered significant at a $P < 0.05$.

3. Results

3.1. Zinc

A total of fourteen studies on zinc retention were identified [11,17–19,21–30] with data on forty-five distinctly identifiable groups (Tables 1 and 2). All studies were identified in the primary PubMed search.

Two studies provided six or more distinct groups, one because zinc balances were carried out at multiple different postnatal ages [11], and one because several different diets were assessed at multiple different ages [21].

Study subjects had a mean birth weight of 1217 g (SD 371) and mean gestational age of 29.9 weeks (SD 4.4). Balance studies were carried out a mean postnatal age of 28 days (SD 44), post-conceptional age of 33.8 weeks (SD 5.1) and weight of 1.48 kg (SD 0.81). The mean zinc intake at the time of the metabolic balance was 1.13 mg/kg/d (SD 1.79, range 0.18 to 2.36 mg/kg/d).

3.2. Zinc retention

Initial inspection of the zinc dataset (Table 2) revealed one obvious outlier. Group 8 had a mean zinc retention of −2.34 mg/kg/d, more

Table 1
Birth demographics of the groups included in the analysis of zinc retention.

Reference	Group	Number per group	Birthweight (g)	Gestational age (weeks)
Dauncey [11]	1–7	29	1191 ± 126	29 ± 1.4
Voyer [21]	8–10	2–3	1262 ± 131	30.0 ± 1.6
Voyer [21]	11–13	6–9	1328 ± 206	31.6 ± 1.1
Voyer [21]	14–16	2–6	1306 ± 159	31.4 ± 1.1
Mendleson [19]	17	6	1152 ± 170	29.1 ± 1.1
Mendleson [19]	18	6	1102 ± 197	28.5 ± 1.0
Mendleson [19]	19	4	1270 ± 171	29.7 ± 1.4
Mendleson [19]	20	6	1108 ± 176	29.2 ± 1.6
Mendleson [19]	21	6	1091 ± 171	29.0 ± 1.5
Mendleson [19]	22	4	1195 ± 128	29.5 ± 0.6
Tyrala [17]	23	5	1478 ± 188	31.2 ± 1.1
Tyrala [17]	24	5	1279 ± 220	30.0 ± 2.5
Higashi [22]	25–28	8–9	NR	<36 weeks
Ehrenkranz [18]	29	7	1275 ± 261	30.3 ± 1.9
Ehrenkranz [18]	30	6	1072 ± 227	28.2 ± 2.3
Ehrenkranz [23]	31	33	1295 ± 238	30.1 ± 1.8
Ehrenkranz [23]	32	7	1189 ± 308	29.0 ± 1.8
Ehrenkranz [23]	33	5	1082 ± 175	29.0 ± 1.8
Ehrenkranz [23]	34	5	1284 ± 220	29.4 ± 1.9
Cooke [24]	35	14	1362 ± 125	32.3 ± 1.7
Wirth [25]	36	8	1223 ± 161	29.4 ± 1.4
Wirth [25]	37	10	1106 ± 70	28.9 ± 1.3
Friel [26]	38	12	1160 ± 290	29 ± 4
Fairly [27]	39	7	1411 ± 87	29.8 ± 0.9
Fairly [27]	40	8	1208 ± 142	29.1 ± 1.1
Wastney [28]	41	9	1440 ± 240	32 ± 3
Loui [29]	42 & 43	10	845 ± 76	25.9 ± 0.6
Martinez [30]	44	20	1189 ± 174	31.8 ± 1.0
Martinez [30]	45	20	1231 ± 210	31.0 ± 0.7

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Table 2
Demographics at the time of the metabolic balance, of the groups included in the analysis of zinc retention.

Reference	Group	N	Age (days)	Diet	HM or formula?	Zinc intake (mg/kg/d)	Zinc retention (mg/kg/d)
Dauncey [11]	1	6	10–12	Unfortified human milk	HM	0.621 ± 0.186	−0.437 ± 0.175
Dauncey [11]	2	6	20–22	Unfortified human milk	HM	0.646 ± 0.149	−0.544 ± 0.389
Dauncey [11]	3	5	30–32	Unfortified human milk	HM	0.641 ± 0.177	−0.415 ± 0.438
Dauncey [11]	4	5	40–42	Unfortified human milk	HM	0.642 ± 0.303	−0.198 ± 0.172
Dauncey [11]	5	3	50–52	Unfortified human milk	HM	0.746 ± 0.291	−0.147 ± 0.315
Dauncey [11]	6	3	60–62	Unfortified human milk	HM	0.598 ± 0.221	0.001 ± 0.090
Dauncey [11]	7	2	70–72	Unfortified human milk	HM	0.710 (0.651 to 0.770)[a]	0.151 (0.127 to 0.173)
Voyer [21]	8	3	9 ± 12	25% strength human milk	HM	0.807 (0.580 to 1.019)[a]	−2.338 (−5.822 to −0.552)[a]
Voyer [21]	9	3	22 ± 13	25% strength human milk	HM	0.845 (0.801 to 0.919)[a]	−0.337 (−0.465 to −0.150)[a]
Voyer [21]	10	2	44 ± 5	25% strength human milk	HM	0.707 (0.687—0.727)[a]	−0.208 (−0.447 to 0.032)[a]
Voyer [21]	11	6	19 ± 7	Human Milk with lactalbumin	HM	0.688 (0.292 to 2.716)[a]	−0.667 (−1.656 to 0.311)
Voyer [21]	12	9	30 ± 11	Human milk with lactalbumin	HM	0.627 (0.404 to 0.965)[a]	−0.753 (−2.366 to 0.234)[a]
Voyer [21]	13	8	48 ± 1	Human milk with lactalbumin	HM	0.760 (0.505 to 1.255)[a]	−0.691 (−2.670 to 0.011[a]
Voyer [21]	14	2	15 ± 11	Formula with 40% MCT	Formula	0.223 (0.200 to 0.205)[a]	0.100 (0.043 to 0.158)[a]
Voyer [21]	15	6	22 ± 5	Formula with 40% MCT	Formula	0.272 (0.193 to 0.391)[a]	0.124 (−0.076 to 0.249)[a]
Voyer [21]	16	6	44 ± 6	Formula with 40% MCT	Formula	0.250 (0.206 to 0.303)[a]	0.082 (−0.101 to 0.249)[a]
Mendleson [19]	17	6	7	Unfortified human milk	HM	0.863 ± 0.267	0.140 ± 0.247
Mendleson [19]	18	6	14	Unfortified human milk	HM	0.680 ± 0.206	0.124 ± 0.171
Mendleson [19]	19	4	28	Unfortified human milk	HM	0.623 ± 0.188	0.226 ± 0.150
Mendleson [19]	20	6	7	Term formula	Formula	0.511 ± 0.029	−0.033 ± 0.093
Mendleson [19]	21	6	14	Preterm formula	Formula	0.902 ± 0.135	0.054 ± 0.267
Mendleson [19]	22	4	28	Preterm formula	Formula	0.888 ± 0.100	0.181 ± 0.236
Tyrala [17]	23	5	18	Low copper formula	Formula	2.05 ± 0.11	0.66 ± 0.35
Tyrala [17]	24	5	20	High copper formula	Formula	2.34 ± 0.28	0.68 ± 0.42
Higashi [22]	25	8	7–128	Unfortified human milk	HM	0.177 ± 0.101	−0.173 ± 0.196
Higashi [22]	26	9	7–128	Unfortified human milk	HM	0.279 ± 0.173	0.109 ± 0.213
Higashi [22]	27	8	7–128	Preterm formula	Formula	0.964 ± 0.078	−0.496 ± 0.568
Higashi [22]	28	9	7–128	Preterm formula	Formula	1.376 ± 0.220	0.483 ± 0.284
Ehrenkranz [18]	29	7	36 ± 19	Preterm formula	Formula	1.369 ± 0.228	0.208 ± 0.903
Ehrenkranz [18]	30	6	37 ± 21	Fortified human milk	HM	1.823 ± 0.247	0.685 ± 0.363
Ehrenkranz [23]	31	33	20 ± 12	Preterm formula	Formula	1.808 ± 0.247	0.235 ± 0.551
Ehrenkranz [23]	32	7	33 ± 27	Unfortified human milk	HM	0.656 ± 0.165	0.340 ± 0.134
Ehrenkranz [23]	33	5	29 ± 8	Fortified human milk	HM	1.847 ± 0.199	0.588 ± 0.494
Ehrenkranz [23]	34	5	33 ± 11	Term formula	Formula	1.887 ± 0.358	0.422 ± 0.390
Cooke [24]	35	14	18 ± 9	Preterm formula	Formula	1.2 ± 0.2	0.19 ± 0.18
Wirth [25]	36	8	24 ± 6	Formula with glucose polymers	Formula	2.29 ± 0.14	0.46 ± 0.28
Wirth [25]	37	10	23 ± 3	Formula with lactose	Formula	2.36 ± 0.95	0.60 ± 0.47
Friel [26]	38	12	39 ± 23	Preterm formula or human milk	Formula[b]	1.821 ± 0.330	0.131 ± 0.334
Fairly [27]	39	7	33 ± 6	Formula, low protein: energy ratio	Formula	2.058 ± 0.074	0.259 ± 0.084
Fairly [27]	40	8	33 ± 8	Formula, high protein: energy ratio	Formula	1.937 ± 0.344	0.381 ± 0.297
Wastney [28]	41	9	14 ± 9	Preterm formula	Formula	1.48 ± 0.49	0.27 ± 0.21
Loui [29]	42	10	52 ± 7	Fortified human milk	HM	0.376 ± 0.187	−0.320 ± 0.272
Loui [29]	43	10	60 ± 10	Fortified human milk	HM	0.391 ± 0.557	−0.202 ± 0.631
Martinez [30]	44	20	18 ± 9	Preterm formula	Formula	0.82 ± 0.18	0.44 ± 0.31
Martinez [30]	45	20	13 ± 4	Preterm formula with PCPUFA	Formula	0.81 ± 0.18	0.51 ± 0.27

[a] Range.
[b] 10 subjects received formula, 2 received human milk, so classified as formula.

than 7 standard deviations from the mean of the remaining groups. This group was excluded from analysis.

In a univariate analysis, zinc retention was significantly related to zinc intake (Retention = −0.32 + 0.363 * Intake, $P < 0.0001$, $R^2 = 0.30$). When the data for human milk and formula fed groups were analyzed separately, there was a suggestion that zinc retention was higher in feeds based on formula, especially at lower zinc intakes (Fig. 1).

In a multivariate analysis of unweighted data, zinc retention was significantly related to zinc intake ($P = 0.0101$), and to feed type ($P = 0.0039$) but not to gestational age at birth ($P = 0.07$) or postnatal age ($P = 0.60$). When gestational age and postnatal age were replaced by post-conceptional age, zinc retention was significantly related to zinc intake ($P = 0.0055$) and feed type ($P = 0.0126$) but not to post-conceptional age ($P = 0.52$). Similar results were seen in the two weighted analyses.

Three models predicting zinc retention based on feed type (human milk or formula) and zinc intake were constructed (Table 3). The mean zinc intakes required to lead to a zinc retention of 0.4 mg/kg/d from diets based on formula were 1.83 mg/kg/d (from the unweighted data), 1.99 mg/kg/d (weighted by sample size), and 2.01 mg/kg/d (weighed by 1/SEM); and from diets based on human milk, estimates were 2.31 mg/kg/d (from the unweighted data), 2.94 mg/kg/d (weighted by sample size), and 2.44 mg/kg/d (weighed by 1/SEM). In order to retain 0.3 mg/kg/d of zinc, intakes of 1.46 mg/kg/d, 1.45 mg/kg/d or 1.51 mg/kg/d would be required from formula-based diets, and 1.94 mg/kg/d, 2.40 mg/kg/d or 1.95 mg/kg/d from human milk based diets.

3.3. Copper

Eleven studies measured copper balance [11,17–19,23–25,27,30], all of which also reported data for zinc balance. Thirty-two distinct groups were identified (Table 3).

Subjects were born at a mean gestational age of 29.9 weeks (SD 3.3), and weight of 1.22 kg (SD 0.25). Metabolic balances were carried out at a mean postnatal age of 23 days (SD 32), a post-conceptional age of 33.3 weeks (SD 4.5) and a weight of 1.51 kg (SD 0.78) Table 4.

3.4. Copper retention

A scattergram of copper retention against copper intake (Fig. 2) shows that studies of infants fed a human-milk based diet had a narrower range of copper intakes than in those studies of formula-based diets. Furthermore the human-milk based diets had a significantly

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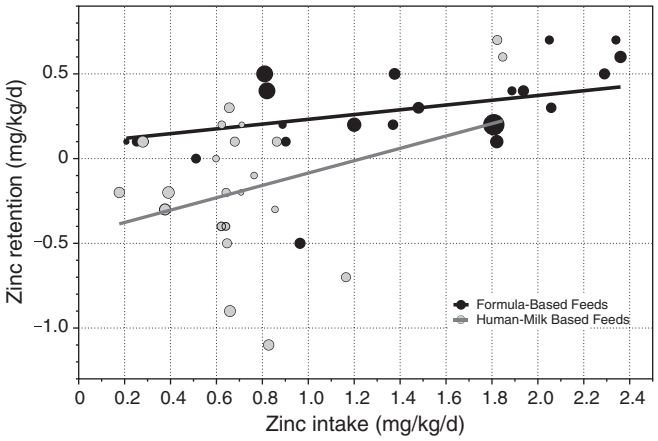

Fig. 1. Scattergram of zinc intake and zinc retention in the formula-based groups (black markers) and human milk based diets (gray markers). The area of the symbols is proportional to the sample size of each group. Separate regression lines for the formula-based diets and the human milk based diets are shown.

lower copper intake (97 ± 21 mcg/kg/d vs. 219 ± 154; P = 0.0042), and zinc intake (0.85 ± 0.44 mg/kg/d vs. 1.54 ± 0.65; P = 0.0013), although the ratio of zinc to copper intake was similar (8.6 mg/mg ± 3.0 vs 8.6 ± 3.4, P = 0.50).

In multivariate modeling, copper retention was significantly related to copper intake (P < 0.0001), and to zinc intake (P = 0.0051), but unaffected by gestational age (P = 0.39), post-natal age (P = 0.23) or feed type (P = 0.61). When gestational age and post-natal age were replaced by post-conceptional age, the results were similar with copper retention being related to copper intake (P < 0.0001) and zinc intake (P = 0.0043), but not post-conceptional age (P = 0.16) or feed type (P = 0.71). These results were unchanged if the data was weighted by sample size or by 1/SEM, except that fits were somewhat poorer when weighted by 1/SEM.

The simplest model, that related copper retention to zinc and copper intakes weighted by sample size, performed the best of all the models (F-value = 52.9, adjusted R^2 = 0.79).

$$\text{Copper retention(mcg/kg/d)} = 8.553 + 0.637 \times \text{Copper intake(mcg/kg/d)} - 58.9 \times \text{Zinc intake(mg/kg/d)}$$

This model was used in the subsequent analyses.

The copper intake required to achieve a given level of copper retention varied as a linear function of zinc intake (Fig. 3). In order to meet the estimated *ex utero* requirement for copper of 30 mcg/kg/d, a copper intake of about 200 mcg/kg/d is required if the zinc intake is 1.8 mg/kg/d, and about 250 mcg/kg/d if the zinc intake is 2.4 mg/kg/d (Fig. 3). In order to meet the estimated *in utero* accretion rate of 50 mcg/kg/d, copper intakes of 230 and 285 mcg/kg/d respectively, would be required at similar zinc intakes.

4. Discussion

Following a systematic examination of the literature, we estimate that preterm infants require between 1.8–2.4 mg/kg/d of zinc from formula based diets, and 2.3–2.4 mg/kg/d from human milk based diets. Assuming an energy intake of 120 kcal/kg/d, these are equivalent to 1.5–2.0 mg/100 kcal. These estimates are at the higher end of the range of recent recommendations [8–10].

There are relatively few randomized controlled trials comparing different levels of zinc intake in preterm intakes [29,31–33], only two of which have intakes similar to our estimated requirements [32,33]. Diaz-Gomez [32] compared formulas containing either 0.75 mg/100 kcal of zinc or 1.5 mg/100 kcal of zinc in 36 preterm infants. The infants fed the higher zinc intake had higher serum and red cell zinc concentrations, improved linear growth, and higher serum alkaline phosphatase (a zinc containing enzyme) [32]. A potential adverse effect of higher zinc intakes on copper status was seen, with the serum copper concentration being lower in the zinc supplemented group (perhaps reflecting the difference in zinc:copper ratio of 16.7 mg zinc/mg copper, and 12.5 mg zinc/mg copper in the two formulas). Friel et al. studied 52 very-low birthweight infants randomized to formulas containing either 1.0 mg/100 kcal or 1.64 mg/100 kcal of zinc [33]. The higher zinc intake led to improved linear growth, higher serum zinc concentrations, and improved motor scores [33].

There are very few clinical trials of different copper intakes in preterm infants. Enteral feeding of 41–89 μg/kg/d of copper in preterm infants has been associated with copper deficiency [34]. Tyrala [17] showed no clear benefit of a copper intake of 260 μg/100 kcal compared to 120 μg/100 kcal in preterm infants as assessed by copper balance, serum copper and ceruloplasmin. However, no adverse effects were observed in the high copper group.

We found, as expected, that copper requirements varied as a function of zinc intake. In order to meet the estimated requirements for growth, copper intakes of about 200 mcg/kg/d would be required if zinc intakes were 1.8 mg/kg/d, increasing to 250 mcg/kg/d if zinc intakes were 2.4 mcg/kg/d. These intakes are significantly greater than current recommendations for copper intake in preterm infants of 100 to 150 mcg/kg/d [8–10]. However, those recommendations have changed little since the 1980s [5,6] and 1990s [7] when recommended zinc intakes were only 0.5–1.0 mg/kg/d [5–7]. It is noteworthy from Fig. 3 that those lower copper intakes would be expected to provide adequate copper retention (30–50 mcg/kg/d) at those lower zinc intakes. The increased copper requirements we suggest, are therefore, driven by the higher zinc intakes currently recommended.

Our estimates were generated from previously published results. As such, they are limited by the nature of the published data. Many studies were relatively old, and it is likely that they were composed of more mature infants than many NICUs now care for. However, we could not identify any effect of gestational age or birth weight on the relationship between zinc (or copper) intake and retention. This may reflect the fact that, by definition, studies were carried out in infants sufficiently mature to be tolerating full enteral feeds, and sufficiently well to tolerate the metabolic balance procedure.

In addition, there were relatively few studies carried out at higher zinc intakes. Of the 45 identifiable groups in the zinc analysis (Table 2)

Table 3
Results of the three models predicting zinc retention based on zinc intakes (in mg/kg/d) and on feeding type (based on formula = 1, based on human milk = 0).

Factor	Intercept		Zinc intake (mg/kg/d)		Feed-type (formula = 1, HM = 0)	
	Coefficient	P-value	Coefficient	P-value	Coefficient	P-value
Unweighted model	−0.2210	0.0424	0.2686	0.0042	0.1289	0.0275
Weighted by N	−0.1472	0.19	0.1861	0.0498	0.1772	0.0054
Weighted by 1/SEM	−0.0912	0.24	0.2006	0.0057	0.0883	0.0883

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Table 4
Demographics at the time of the metabolic balance, of the groups included in the analysis of copper retention.

Reference	Group	Number	HM or formula?	Zinc intake (mg/kg/d)	Copper intake (mcg/kg/d)	Copper retention (mg/kg/d)
Dauncey [11]	1	6	HM	0.621 ± 0.186	83 ± 8	−36 ± 61
Dauncey [11]	2	6	HM	0.646 ± 0.149	82 ± 18	−14 ± 23
Dauncey [11]	3	5	HM	0.641 ± 0.177	87 ± 8	−9 ± 28
Dauncey [11]	4	5	HM	0.642 ± 0.303	90 ± 11	7 ± 23
Dauncey [11]	5	3	HM	0.746 ± 0.291	80 ± 2	35 ± 20
Dauncey [11]	6	3	HM	0.598 ± 0.221	75 ± 2	41 ± 4
Dauncey [11]	7	2	HM	0.710 (0.651 to 0.770) [a]	85 (48 to 85) [a]	30 (3–57) [a]
Mendleson [19]	17	6	HM	0.863 ± 0.267	116 ± 37	59 ± 20
Mendleson [19]	18	6	HM	0.680 ± 0.206	115 ± 37	55 ± 34
Mendleson [19]	19	4	HM	0.623 ± 0.188	98 ± 34	72 ± 34
Mendleson [19]	20	6	Formula	0.511 ± 0.029	54 ± 24	−14 ± 22
Mendleson [19]	21	6	Formula	0.902 ± 0.135	89 ± 12	3 ± 24
Mendleson [19]	22	4	Formula	0.888 ± 0.100	89 ± 10	2 ± 30
Tyrala [17]	23	5	Formula	2.05 ± 0.11	121 ± 30	12 ± 41
Tyrala [17]	24	5	Formula	2.34 ± 0.28	294 ± 19	40 ± 82
Ehrenkranz [18]	29	7	Formula	1.369 ± 0.228	101 ± 11	26 ± 34
Ehrenkranz [18]	30	6	HM	1.823 ± 0.247	108 ± 45	34 ± 13
Ehrenkranz [23]	31	33	Formula	1.808 ± 0.247	189 ± 39	9 ± 4
Ehrenkranz [23]	32	7	HM	0.656 ± 0.165	87 ± 38	6 ± 3
Ehrenkranz [23]	33	5	HM	1.847 ± 0.199	152 ± 34	5 ± 2
Ehrenkranz [23]	34	5	Formula	1.887 ± 0.358	194 ± 28	6 ± 3
Cooke [24]	35	14	Formula	1.2 ± 0.2	146 ± 24	21 ± 8
Wirth [25]	36	8	Formula	2.29 ± 0.14	367 ± 17	69 ± 28
Wirth [25]	37	10	Formula	2.36 ± 0.95	398 ± 16	106 ± 79
Fairly [27]	39	7	Formula	2.058 ± 0.074	528 ± 24	259 ± 84
Fairly [27]	40	8	Formula	1.937 ± 0.344	481 ± 82	220 ± 47
Martinez [30]	44	20	Formula	0.82 ± 0.18	120 ± 21	46 ± 33
Martinez [30]	45	20	Formula	0.81 ± 0.18	120 ± 30	65 ± 47

[a] Range.

only 11 (24%) studied zinc intakes between 1.8 and 2.4 mg/kg/d. All 11 studies also provided data on copper retention at these levels of zinc intake (38% of the 29 identifiable copper groups).

The analysis also suggests that zinc intakes should be higher in preterm infants on human milk than those on formula-based diets. Whether this remains true with more modern human milk fortifiers and infant formulas is unclear. However, there seems to be an urgent need for further research especially as recent recommendations are that all preterm infants should be fed human milk based diets [35].

One shortcoming of the dataset is that the most recent publication was in 2002. The increasing availability of stable isotope methods to study mineral absorption may have resulted in a decrease in interest in more time-consuming and difficult metabolic balance studies [16]. Although stable isotopes are powerful tools to understand mineral absorption in vulnerable populations [36], they have limitations in estimating nutrient requirements unless urinary and fecal losses are either well described or can be estimated [37].

Although the current analyses are imperfect, we believe they provide the best evidence-based guidelines for zinc and copper requirements currently available for preterm infants. Our results support the recent trend towards higher recommendations for zinc intakes in preterm infants. However, they suggest that copper intake recommendations have failed to keep pace with the increase in zinc intakes. Higher copper intakes seem required in preterm infants, especially those on higher zinc intakes.

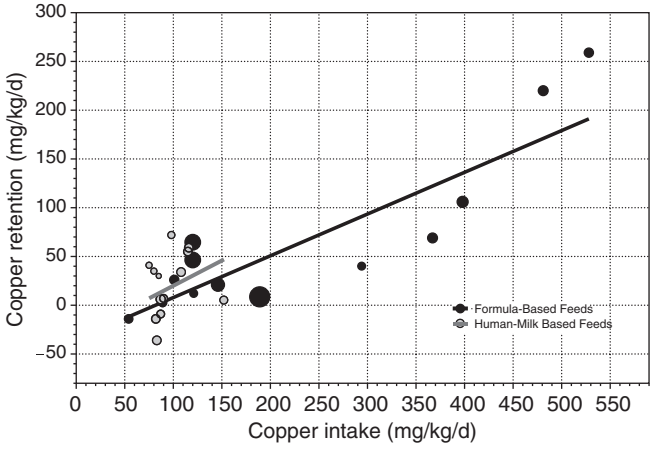

Fig. 2. Scattergram of copper intake and copper retention in the formula-based groups (black markers) and human milk based diets (gray markers). The area of the symbols is proportional to the sample size of each group. Separate regression lines for the formula-based diets and the human milk based diets are shown.

Conflict of interest

This work was originally produced as part of a symposium on neonatal nutrition funded by the Mead Johnson Nutrition (Glenview, IL), and authors were paid an honorarium by Mead Johnson Nutritionals for participation in the symposium. Mead Johnson Nutrition was not involved in the writing or conclusions of this manuscript. None of the authors have a financial conflict related to the conclusions of this review.

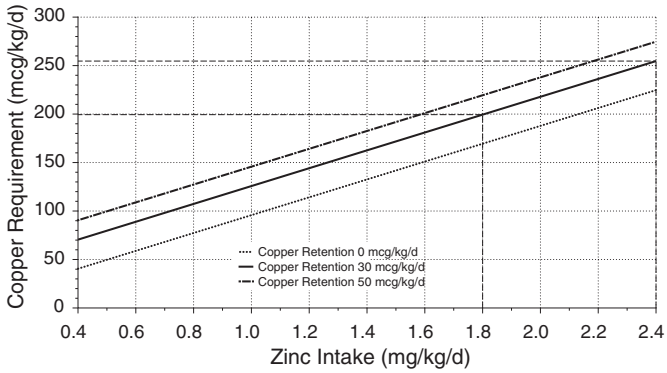

Fig. 3. Regression plot of copper requirement (intake) needed to achieve copper retention on 0, 30 and 50 mcg/kg/day at different zinc intakes.

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