

# Clinical Safety of Iron-Fortified Formulas

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**ABSTRACT.** *Background.* Iron-fortified formulas are recommended throughout infancy and are frequently used beyond, yet safety aspects have been inadequately studied. Iron could theoretically increase pro-oxidant stress, with potential adverse effects, including infection risk, and some clinicians suspect that iron-fortified formulas induce gastrointestinal disturbance.

*Objective.* A planned component of a large intervention trial has been to test the hypothesis that infants receiving iron-fortified formula do not have a higher incidence of infections (primary outcome) or gastrointestinal problems (secondary outcome) than infants on low iron-formulas or cow's milk.

*Methods.* Children ( $n = 493$ ) 9 months old receiving cow's milk were recruited in 3 UK centers and randomized to: 1) cow's milk as before, 2) formula containing .9 mg/L of iron, or 3) an otherwise identical formula but containing 12 mg/L of iron. Children were followed at 3 monthly intervals and the episodes of infections, diarrhea and constipation, and general morbidity to 18 months old were recorded. Hematologic indices of iron status were determined at 18 months old.

*Results.* Serum ferritin concentrations were increased in infants receiving iron-fortified formula but there were no intergroup differences in incidence of infection, gastrointestinal problems, or in general morbidity or weight gain.

*Conclusions.* We were unable to identify adverse health effects in older infants and toddlers consuming a high iron-containing formula (12 mg/L) even when used in populations with a low incidence of iron deficiency. *Pediatrics* 2000;105(3). URL: <http://www.pediatrics.org/cgi/content/full/105/3/e38>; iron, formula, infection.

ABBREVIATION. SD, standard deviation.

The American Academy of Pediatrics recommends that infants up to 1 year old who are not being breastfed should be given iron-fortified formulas rather than cow's milk.<sup>1</sup> The use of such

formulas reduces the high frequency of iron deficiency anemia in infants<sup>2</sup> and in consequence may benefit their long-term cognitive development,<sup>3</sup> although this is now debated.<sup>4,5</sup> A high prevalence of iron deficiency (particularly in some populations<sup>6</sup> has raised the possibility that moderately low iron stores in early life are physiologic rather than pathologic.<sup>7-9</sup> Indeed, theoretical concerns<sup>10</sup> have made some clinicians cautious in their use of iron-fortified formulas.<sup>9,11</sup>

By increasing oxidant stress<sup>10</sup> and providing iron for microorganisms, high levels of body iron may predispose to infections in adults,<sup>12,13</sup> increase mortality in kwashiorkor,<sup>10,14</sup> and theoretically increase the risk of asthma.<sup>15</sup> Parenteral iron supplementation may increase the risk of sepsis,<sup>16</sup> malaria,<sup>17</sup> and respiratory infections<sup>18</sup> in infants; and oral iron supplementation has been associated with growth retardation<sup>19</sup> and changes in gastrointestinal flora in children,<sup>20</sup> and an increased incidence of malaria<sup>12</sup> and amoebiasis<sup>21</sup> in adults. There is also a prevalent view in the United States that infants fed iron-fortified formulas may develop gastrointestinal problems and this belief has encouraged the continued use and manufacture of low iron formulas<sup>11</sup> (recently discussed by Ryan<sup>22</sup>). However, the potential adverse effects of iron-fortified formulas consumed by infants in industrialized countries have not been adequately investigated.

Data suggesting a lack of adverse health outcomes with iron-fortified formulas have been based on epidemiologic studies,<sup>23,24</sup> randomized trials of insufficient power to detect infrequent adverse clinical events,<sup>25-31</sup> or studies in developing countries<sup>27,32</sup> where a greater prevalence and severity of iron deficiency may reduce potential adverse effects of iron supplementation. Many studies have targeted nutritionally vulnerable populations<sup>23,27,29,31-33</sup> and the risks of iron supplementation for the majority of infants who are iron replete are uncertain. Furthermore, few studies have focused on follow-on formulas that are marketed in Europe and a number of countries for consumption by infants over 6 months old<sup>31,33,34</sup> and may have higher iron concentrations (eg, 12 mg/L) than formulas used for younger children (eg, 6.5 mg/L).<sup>31</sup> Therefore, we tested the hypothesis that the incidence of infections (principal outcome), gastrointestinal symptoms, and risk of asthma was greater in infants randomized to high iron-fortified formula (12 mg/L iron), than those randomized to an otherwise identical but low iron

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formula (.9 mg/L) or to pasteurized whole cow's milk. Randomization of infants to cow's milk was ethical because nutritional intervention was confined to infants already on cow's milk and at the time of the study the UK Department of Health accepted the use of cow's milk in infants over 6 months old.

## METHODS

### Subjects

Letters were sent to the parents of potential subjects approaching 9 months old identified from birth registers at the 3 collaborating centers in the United Kingdom (Leicester, Nottingham, and Norwich). If mothers reported that their infant was receiving only cow's milk and no formula, they were sent a second letter with information about the trial. Mothers agreeing to participate were visited at home by a trained research nurse who obtained informed, written consent. The study was approved by the human research ethics committee at each of the collaborating centers.

Healthy infants from singleton pregnancies (or sole survivors of multiple pregnancies) over 36 weeks' gestation with birth weight over 2.5 kg were eligible. Infants with severe chronic disease, congenital anomalies, hematologic disorders, evidence of developmental delay, or other conditions known to affect growth and development were excluded as were those receiving or having previously received iron supplements or blood transfusions. Infants meeting the eligibility criteria, whose parents consented, were randomized from opaque sealed envelopes to: 1) cow's milk (defined as whole, pasteurized fresh milk without added vitamins or minerals, excluding skimmed or semiskimmed milk, and estimated to contain .5 mg/L of iron); 2) iron-fortified formula (containing 12 mg/L iron as ferrous sulfate); or 3) an otherwise identical specially manufactured unfortified formula containing .9 mg/L of iron. Children from Asian families (who are at higher risk for iron deficiency)<sup>6</sup> were separately randomized to ensure balance among groups (only 10 were recruited).

The nutrient composition of the infant formula supplied by Wyeth Laboratories, Maidenhead, United Kingdom is given in Table 1. Solid foods were not restricted, and mothers of infants in the formula groups were asked not to give additional vitamins or mineral supplements. Other than iron contained in the mixed diets of infants, no other sources of iron were given. All infants, mothers, and investigators were blinded to the 2 formulas.

### Sample Size

In a previous study,<sup>27</sup> the standard deviation (SD) of the number of infections per child per year (from 3 to 12 months old, which overlaps with the age range selected by us) in infants fed either iron-fortified or unfortified formula was ~3. Therefore, to detect a difference of 1 infection between infants receiving a high or low iron formula with 80% power and 5% significance required ~144 subjects in each formula group.<sup>35</sup>

### Study Procedures

All participating infants were seen at recruitment at 9 months old and again at 12, 15, and 18 months old. At randomization, a clinical and feeding history, and demographic, social class, and maternal educational attainment data were obtained. Social class was based on the occupation of the parent providing the primary financial support for the family or if both parents worked the father's occupation. The clinical history, repeated at each follow-up visit, specifically included a history of infective episodes, diagnosis of atopic conditions, bowel habits, and stool characteristics, medications given, and any negative events experienced by the infant (such as allergy, rash, or acute illness), during the previous 3 months. The problems of maternal recall of illness are recognized, but because the same data collection methods were used for all 3 dietary groups, comparison among groups may be valid.

At the target ages, naked weight was measured accurate to .1 kg (Seca digital baby scales) using standard protocols and by research nurses trained in the techniques involved. Dietary intake was assessed at 9, 12, and 15 months old by a 2-day dietary diary kept by the mother and development assessed at 18 months old using the motor and mental scales of the Bayley Scales of Infant

**TABLE 1.** Nutritional Composition of Infant Formulas

Nutrient	Concentration (per 100 mL)
Energy (kcal)	65
Protein (g)	2.5
Fat (g)	2.8
Saturated %	42.9
Unsaturated %	57.1
Carbohydrate (g)	8.0
Lactose	6.4
Maltodextrin	1.6
Calcium (mg)	100
Phosphorus (mg)	65
Magnesium (mg)	7.5
Iron* (mg)	1.2
Sodium (mg)	30
Potassium (mg)	100
Chloride (mg)	70
Zinc (mg)	.5
Copper (mg)	.08
Iodine ( $\mu$ g)	6.9
Vitamin A ( $\mu$ g)	6.9
Vitamin D ( $\mu$ g)	1.2
Vitamin E ( $\mu$ g)	.75
Vitamin K ( $\mu$ g)	6.6
Thiamine (mg)	.08
Riboflavin (mg)	.12
Pantothenic acid ( $\mu$ g)	.24
Pyridoxine ( $\mu$ g)	48
Cyanocobalamin B <sub>12</sub> ( $\mu$ g)	.12
Vitamin C ( $\mu$ g)	6.6
Niacin ( $\mu$ g)	.61
Folate ( $\mu$ g)	6.0
Biotin ( $\mu$ g)	1.71
Renal solute load (mOsm/L)	158.3

\* 1.2 mg/100 mL iron in iron-fortified formula and .09 mg/100 mL of iron in control formula.

Development II. Growth and development data (the principal efficacy outcomes) are reported elsewhere,<sup>5</sup> and the number of infections (the principal safety outcome) and other clinical safety data are reported here.

### Clinical Events

Maternal reports of the 3 most common infective events in infancy, namely upper respiratory tract infections, chest infections treated with antibiotics, and episodes of diarrhea or vomiting, were recorded at each follow-up visit and the sum of these events per infant taken as an index of morbidity attributable to infection. Any more serious infections were recorded separately. Diarrhea was defined as an increase in stool frequency and loose stools (according to the mother), with the illness episode lasting longer than 24 hours, and vomiting excluded possetting or regurgitation. An index of general morbidity was also obtained from the number of consultations with the family doctor and the number of hospital admissions (defined as at least an overnight stay in hospital). A diagnosis of asthma or eczema (made by the family doctor or pediatrician) and a history of wheeze were also recorded. Other details reported by the mother included the normal stool frequency per week, and normal stool consistency (watery, runny, mushy but formed, soft but formed, or hard)<sup>36</sup> and history of constipation, blood in the stool and use of laxatives in the preceding 3 months.

### Hematology

Blood was obtained by venepuncture (and occasionally if this was unsuccessful from a heel prick) from infants 18 months old. Hemoglobin, serum ferritin, and serum transferrin receptor concentrations were determined at the end of the study in samples stored at -18°C, and all analyses were conducted at the Institute of Food Research, Norwich, UK. Ferritin concentrations were measured using an in house enzyme-linked immunoadsorbent assay and an international ferritin standard (National Institute of Biological Standards and Control, NIBSC, Potters Bar, Hertfordshire, UK) and plasma transferrin receptor concentration using a com-

mercial enzyme-linked immunoadsorbent assay system (R&D Systems, Abingdon, UK).

### Statistical Analysis

A 1-way analysis of covariance was used to detect statistically significant differences in normally distributed variables among the 3 randomized groups with statistical significance defined as  $P < .05$ . If an intergroup difference was identified by this technique, Student's  $t$  test was used to compare means between 2 groups with Bonferroni's  $P$  corrections applied to maintain  $\alpha$  at .05. The Kruskal-Wallis test was used to detect statistically significant differences in nonparametric variables and the  $\chi^2$  test was used to compare the proportions of infants with categorical clinical events or diagnoses. All analyses were conducted and presented on an intention to treat basis, with the denominator for analysis of categorical variables as the number of infants in each dietary group at randomization. Regression analyses were used to adjust associations between formula type and outcome variable for possible confounding factors (gender, birth weight, duration of breastfeeding, maternal education, and social class) and for the number of 3-month follow-up visits attended as part of the trial protocol (maximum = 3).

## RESULTS

### Compliance

Initial letters were sent to 11 021 mothers of whom 2043 (19%) replied. Of the mothers replying 592 (29%) were already feeding their infants cow's milk and of these 493/592 (83%) agreed to take part in this study.

The number of infants fed the assigned diet for <6 months was similar for the iron-fortified ( $n = 36/162$ ; 22%) and unfortified groups ( $n = 38/165$ ; 23%) and greater than for subjects fed cow's milk ( $n = 7/166$ ; 4%). Of mothers who stopped the assigned diet before 6 months, a significantly higher proportion refused assessment at 18 months old (51/81, 63%) compared with those who complied (14/412; 3%).

At 18 months old, 160 (96%) of infants fed cow's milk, 135 (82%) fed unfortified formula, and 133 (82%) receiving iron-fortified formula were seen. Subjects not complying were more likely to have mothers with no educational qualifications (26% vs 13%;  $P = .003$ ), come from a lower social class family (67% vs 55%;  $P = .058$ ), and to be significantly lighter at 9 months old (9.0 vs 9.3 kg;  $P = .05$ ).

Energy intake from the assigned milk was similar for the 3 dietary groups at 9 months old (mean, SD: 1.4, .5 MJ/day [ $n = 117$ ] for iron-fortified formula; 1.5, .5 MJ/day [ $n = 120$ ] for unfortified formula; and 1.4, .5 MJ/day [ $n = 145$ ] for cow's milk; analysis of variance  $P = .18$ ) and at 15 months old (1.4, .5 MJ/

day [ $n = 102$ ] for iron-fortified formula; 1.4, .5 MJ/day [ $n = 91$ ] for unfortified formula; and 1.2, .5 MJ/day [ $n = 116$ ] for cow's milk;  $P = .20$ ), but greater in formula than cow's milk fed infants at 12 months old (1.5, .6 MJ/day [ $n = 107$ ] for iron-fortified formula; 1.5, .6 MJ/day [ $n = 105$ ] for unfortified formula; and 1.3, .6 MJ/day [ $n = 143$ ] for cow's milk;  $P = .025$ ).

### Hematology

Blood samples were analyzed for hemoglobin, serum ferritin, and transferrin receptor concentrations after sample subdivision. An unfortunate technical problem resulted in occasional anomalous results for hemoglobin values. Therefore, for this study, we have elected not to include any hemoglobin data, particularly because, as shown below, none of the subjects had significant iron deficiency as evidenced by the serum transferrin receptor concentration results.

At 18 months old, the geometric mean serum ferritin concentrations of children fed iron-fortified formula (21.4, log SD: .22  $\mu\text{g/L}$ ;  $n = 93$ ) was significantly greater than children receiving control formula (13.3, .24  $\mu\text{g/L}$ ;  $n = 81$ ;  $P < .001$ ) or cow's milk (14.3, .28  $\mu\text{g/L}$ ;  $n = 96$ ;  $P < .001$ ). Taking the normal lower range for serum ferritin as 8  $\mu\text{g/L}$ ,<sup>31</sup> fewer infants receiving iron-fortified formula (4/93; 4.3%) had low iron stores than infants receiving low iron formula (13/81; 16%;  $P = .009$ ) or cow's milk (17/96; 17.8%;  $P = .003$ ).

Mean (SD) serum transferrin receptor levels did not differ in the 3 dietary groups (iron-fortified formula: 2.3 [.6] mg/L [ $n = 90$ ]; low iron formula: 2.4 [.8] mg/L [ $n = 77$ ]; cow's milk: 2.5 [.75] mg/L [ $n = 89$ ]; analysis of variance:  $P = .25$ ) and all had a level below the suggested upper limit of normal of 6.5 mg/L for older infants.<sup>37</sup>

### Morbidity

No clinical events or serious infections were observed. There were no significant differences in demographic details, feeding histories (Table 2), or pre-intervention morbidity (Table 3) in children randomized to the 3 milk groups. By 18 months old, the incidence of asthma, eczema, chest infections, diarrhea and vomiting, and attained weight did not differ statistically in children receiving iron-fortified or unfortified formula or cow's milk (Table 3). Nei-

**TABLE 2.** Characteristics of Infants at Randomization (Mean, SD)

Variable	Cow's Milk ( $n = 166$ )		Standard Formula ( $n = 165$ )		Iron-Fortified Formula ( $n = 162$ )		ANOVA $P$ Value
Age (wk)	41	1.5	41	1.4	41	1.4	.93
Male infants (%)	92	(55)	83	(50)	82	(51)	.58
Gestation (wk)	39.9	1.4	39.9	1.4	39.8	1.4	.52
Birth weight (kg)	3.6	.5	3.5	.5	3.5	.5	.23
Duration of exclusive breast feeding (wk)	4.9	5.8	4.4	5.6	4.6	5.4	.77
Age at weaning (wk)	12.4	4.7	12.0	4.4	12.2	4.0	.68
Age cow's milk introduced (wk)	28.5	5.7	29.2	6.0	29.4	6.0	.39

ANOVA indicates analysis of variance.

**TABLE 3.** Morbidity Before and After Intervention

Variable	Cow's Milk		Standard Formula		Iron-Fortified Formula		P Value						
Number at randomization	166		165		162								
Preintervention													
Number with 1 or more episodes of*													
Hospital admission	19		20		25		.53						
Wheeze	33		31		32		.96						
Asthma	9		8		7		.90						
Eczema	34		37		29		.59						
Chest infection	66		77		76		.33						
Diarrhea and /or vomiting	30		22		31		.33						
Number of clinical events per child (median, interquartile range) <sup>†</sup>	<i>n</i>		<i>n</i>		<i>n</i>								
Visits to family doctor	3.0, 3.0		165		3.0, 3.2		162	3.0, 4.0	161	.44			
URTIs	3.0, 2.0		165		3.0, 2.0		162	2.0, 3.0		160	.16		
Total infective episodes	3.0, 3.0		165		4.0, 4.0		162	3.0, 3.0		161	.39		
Weight (kg; mean, SD) <sup>‡</sup>	9.4, 1.1		165		9.1, 1.1		162	9.2, 1.1		161	.07		
By age 18 mo													
Number with 1 or more episodes of*													
Hospital admission	33		<i>n</i> §		33		<i>n</i> §		39		<i>n</i> §		.57
Wheeze	61		30/156		55		27/123		45		36/121		.22
Asthma	23		22/156		17		14/123		18		17/121		.57
Eczema	58		41/127		54		32/98		45		24/96		.36
Chest infection	104		98/157		97		83/127		103		84/125		.64
Diarrhea and/or vomiting	76		70/156		56		50/123		66		54/121		.09
Number of clinical events per child (median, interquartile range) <sup>†</sup>	<i>n</i>		<i>n</i>		<i>n</i>		<i>n</i>		<i>n</i>		<i>n</i>		
Visits to family doctor	5.0, 5.0		156		5.0, 7.0		123		6.0, 6.0		121		.67
URTIs	6.0, 4.0		155		6.0, 5.0		123		6.0, 4.0		120		.29
Total infective episodes	8.0, 5.0		155		8.0, 5.0		123		7.0, 6.0		121		.48
Weight (kg, mean, SD) <sup>‡</sup>	11.4, 1.4		159		11.3, 1.3		133		11.4, 1.5		133		.64

Total infective episodes = upper respiratory tract infections + diarrhea and/or vomiting + chest infections. *n* = number with data. Analysis on an intention-to-treat basis using \* $\chi^2$  test (with denominator as the number in each dietary group at randomization); †Kruskal-Wallis test; ‡1-way analysis of variance. §Proportions with data to 18 months old.

ther the total number of consultations with the family doctor nor the number of infective episodes per child over 9 months (colds, chest infections, and episodes of diarrhea or vomiting) were significantly different in the 3 dietary groups (Table 3).

**Bowel Habits and Stool Characteristics**

There were no statistically significant differences in the number of children with a history of constipation, laxative use, blood in the stool, or hard or loose

(runny or watery) stool consistency in the 3 dietary groups between 9 and 18 months old (Table 4). By chance, the stool frequency at randomization was higher in children randomized to cow's milk than those receiving low or high iron containing formulas, but this difference was no longer apparent at 18 months old.

After adjusting for possible confounding factors (gender, birth weight, duration of breastfeeding, maternal education, social class, and the number of 3

**TABLE 4.** Stool Characteristics Before and After Intervention

Variable	Cow's Milk		Standard Formula		Iron-Fortified Formula		P Value						
Number at randomization	166		165		162								
Preintervention													
Number with 1 or more episodes of*													
Constipation	7		6		5		.86						
Use of laxatives	4		11		7		.17						
Hard stool consistency	14		18		17		.72						
Blood in stool	12		21		12		.14						
Watery or runny stool consistency	6		7		5		.86						
Number of motions/wk (mean, SD) <sup>†</sup>	15.5, 6.2		<i>n</i>		<i>n</i>		<i>n</i>						
By age 18 mo													
Number with 1 or more episodes of*													
Constipation	19		<i>n</i> §		11		<i>n</i> §		14		<i>n</i> §		.31
Use of laxatives	7		19/156		12		7/123		12		12/133		.40
Hard stool consistency	35		7/160		28		12/135		31		23/110		.64
Blood in stool	17		26/137		23		19/110		19		12/121		.58
Watery or runny stool consistency	31		13/155		25		18/123		28		7/112		.69
Number of motions/wk (mean, SD) <sup>†</sup>	12.0, 5.2		11/137		136		11/106		12.2, 5.2		133		.08

Analysis on an intention to treat basis using \* $\chi^2$  test (with denominator as the number in each dietary group at randomization); †1-way analysis of variance. §Proportions with data to 18 months old. *n* indicates number with data.

monthly follow-up visits attended) using multiple regression analyses, associations between dietary group and outcome variable (morbidity, bowel habits, or stool characteristics at 18 months old) remained nonsignificant (results not presented). Analyses were also repeated on a nonintention-to-treat basis, after restricting the data to subjects with complete follow-up, and showed no significant associations between diet and outcome variables (data not presented).

## DISCUSSION

Iron deficiency is arguably the most common nutritional deficiency in the developed world.<sup>6</sup> Infants in the second 6 months of life are particularly vulnerable and in Europe, follow-on formulas with higher iron concentrations than standard formulas have been specifically developed to enhance iron intake after 6 months old.<sup>6</sup> The use of iron-fortified formulas in the second 6 months of life has been approved by the European Society for Pediatric Gastroenterology<sup>38</sup> and their increased consumption is likely to have contributed to the dramatically reduced incidence of iron deficiency in the United States.<sup>2</sup> However, although heavily promoted and widely used, there are few data to support the safety of iron-fortified formulas, particularly in iron-replete infants.

The present study found no statistically significant differences in the frequency of adverse events, infections, or general morbidity in infants fed iron-fortified or unfortified formula. Consistent with previous reports,<sup>24–29</sup> stool frequency and character and the incidence of gastrointestinal symptoms also did not differ among dietary groups suggesting that the consumption of iron-fortified formula was not associated with constipation or diarrhea at least in this age group. We would emphasize, therefore, that the common belief that iron-fortified formulas make infants constipated (a belief that may result in inappropriate use of low-iron formulas) is not supported by our study. However, on occasion, iron-fortified formulas have been associated with changes in stool flora,<sup>20</sup> color, or consistency<sup>30</sup> in younger infants; and perhaps with illness in a nonrandomized study from a tropical country.<sup>39</sup>

As expected, mean plasma ferritin concentrations at 18 months old were significantly higher in infants fed iron-fortified rather than standard infant formula or cow's milk and levels were similar to a recent study of inner city infants.<sup>31</sup> However, most infants not receiving iron-fortified formula also had adequate iron stores (consistent with an adequate iron intake from dietary sources other than formula), and infants on cow's milk had similar iron stores to those on low iron formula despite evidence of occult fecal blood loss in studies of younger infants on cow's milk. Furthermore, all children with hematologic data had serum transferrin receptor concentrations  $<6.5$  mg/L (a suggested upper limit of normal with higher concentrations indicating iron deficiency in older infants).<sup>37</sup> Therefore, although low ferritin concentrations indicated depletion of iron stores in

some, no child with hematologic data had evidence of a significant iron deficiency.<sup>37</sup>

Few studies have adequately assessed the safety of iron-fortified formulas particularly in populations with a low incidence of iron deficiency. In an early trial of 1048 infants, significantly fewer infections occurred in iron-supplemented children,<sup>23</sup> but unfortunately this study was not randomized or analyzed on an intention-to-treat basis. More recent epidemiologic studies<sup>24</sup> or randomized trials<sup>34</sup> have not shown an increased risk of infection with iron supplementation, although many had methodological problems such as a high drop-out rate,<sup>28,29</sup> short follow-up ( $<3$  months),<sup>25,30</sup> or lack of a control group simultaneously fed an otherwise identical but low iron formula.<sup>31,33</sup> Two trials (comparing formula with iron concentrations of 58 vs 12 mg/L<sup>27</sup> and 12.7 vs 7.4 mg/L<sup>28</sup>) were difficult to interpret because both index and control subjects received iron-fortified formula. Furthermore, of the studies from developed countries specifically investigating iron-fortified formulas containing 12 mg/L iron in infants over 6 months old, 2 had a cow's milk control group,<sup>31,33</sup> 1 did not report the incidence of adverse clinical events,<sup>40</sup> and 1 had unequal numbers in the index and control groups and did not include morbidity data in the statistical analyses.<sup>34</sup> Nevertheless, a similar infection rate in the present study among infants given formulas containing 12 mg/L or low iron formula was consistent with published data,<sup>29</sup> and with the hypothesis that most adverse effects of iron supplementation are seen in areas where malaria is endemic and rarely in infancy.<sup>22,32</sup>

The longer term risks of iron supplementation in iron-replete populations are uncertain. Theoretical considerations of the role of iron as a pro-oxidant<sup>10</sup> and possible benefits of lower iron stores<sup>7,8</sup> have raised concerns about potential harmful effects of indiscriminate widespread iron supplementation.<sup>9</sup> However, although there are limited long-term data, few harmful clinical consequences of oral iron supplementation in infancy have been described, and in contrast to previous data,<sup>19</sup> we found no adverse effects of iron supplementation on the weight gain of iron-replete infants.

We believe that the present study is the largest randomized, double-blind trial comparing an iron-fortified formula with an identical formula with low iron concentration. Our data are likely to be applicable to infants in the second 6 months of life because this age overlaps with the age range in the present study. Although the sample size was sufficient to detect a statistically significant difference of 1 infection over the study period, we found no difference in infection rates or any other aspect of morbidity or stool characteristics among groups. Thus, in terms of the range of outcomes explored in this study, we did not find that consumption of a high iron-containing formula (12 mg/L) was associated with adverse health outcomes in older infants and toddlers.

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