

# AMERICAN ACADEMY OF PEDIATRICS

Committee on Nutrition

## Iron Fortification of Infant Formulas

**ABSTRACT.** Despite the American Academy of Pediatrics' (AAP) strong endorsement for breastfeeding, most infants in the United States are fed some infant formula by the time they are 2 months old. The AAP Committee on Nutrition has strongly advocated iron fortification of infant formulas since 1969 as a way of reducing the prevalence of iron-deficiency anemia and its attendant sequelae during the first year.<sup>1</sup> The 1976 statement titled "Iron Supplementation for Infants" delineated the rationale for iron supplementation, proposed daily dosages of iron, and summarized potential sources of iron in the infant diet.<sup>2</sup> In 1989, the AAP Committee on Nutrition published a statement that addressed the issue of iron-fortified infant formulas<sup>3</sup> and concluded that there was no convincing contraindication to iron-supplemented formulas and that continued use of "low-iron" formulas posed an unacceptable risk for iron deficiency during infancy. The current statement represents a scientific update and synthesis of the 1976 and 1989 statements with recommendations about the use of iron-fortified and low-iron formulas in term infants.

---

ABBREVIATION. FDA, Food and Drug Administration.

---

### IRON REQUIREMENTS DURING THE FIRST YEAR: INTAKE, ABSORPTION, AND LOSSES

**A**t birth, most term infants have 75 mg of elemental iron per kilogram of body weight, found primarily as hemoglobin (75%), but also as storage (15%) and tissue protein iron (10%).<sup>4</sup> Infants of mothers with poorly controlled diabetes and small-for-gestational-age infants have approximately 10% and 40% of normal storage iron, respectively, meaning that they may have less of a buffer for protection from postnatal iron deficiency.<sup>5,6</sup>

During the first 4 postnatal months, excess fetal red blood cells break down and the infant retains the iron. This iron is used, along with dietary iron, to support the expansion of the red blood cell mass as the infant grows. The estimated iron requirement of the term infant to meet this demand and maintain adequate stores is 1 mg/kg per day.<sup>1</sup>

Because more than 80% of the iron of the newborn term infant is accreted during the third trimester of gestation, infants born before term must accrete more iron postnatally to "catch up" to their term counterparts during the first year. Thus, the requirements for preterm infants range from 2 mg/kg per day for infants with birth weights between 1500 and

2500 g<sup>2</sup> to 4 mg/kg per day for infants weighing less than 1500 g at birth.<sup>7</sup> Preterm infants who receive erythropoietin in lieu of red blood cell transfusions appear to need at least 6 mg/kg per day of iron.<sup>8</sup>

Daily iron dosing recommendations can only be estimates because they represent the "supply side" of iron economics. Multiple postingestion variables alter the amount of metabolizable iron ultimately absorbed and retained by the infant. The greatest of these factors is the percentage of iron absorbed from the diet. Estimates of iron absorption from infant formulas range from less than 5% in term infants fed casein-predominant formula to 40% in very low birth weight infants fed whey-predominant formula.<sup>9-11</sup> Values of 7% to 12% appear to be most representative for term infants fed cow milk formula, with the lower values seen when formulas supplemented with higher concentrations of iron are used.<sup>11</sup> The percentage of iron absorbed from soy formula is lower than from cow milk formula and ranges from less than 1% to 7%.<sup>12</sup> Nevertheless, infants fed soy formula containing 12 mg/L of iron remain comparably iron sufficient to infants fed iron-fortified cow milk formula.<sup>12</sup>

Factors such as the milk source of iron (eg, human vs cow), type of iron compound consumed, the food with which it is eaten, and the iron status of the infant greatly affect iron absorption. For example, greater than 50% of iron from human milk is absorbed compared with typically less than 12% of iron from cow milk-derived formula. In the older infant, iron from meat sources and iron from ferrous sulfate is better absorbed than iron from nonmeat sources or in its pyrophosphate form. Infants with poorer iron status or in negative iron balance absorb a higher percentage of dietary iron. Potential iron losses (such as occult gastrointestinal bleeding associated with exposure to cow milk protein or infectious agents) must also be considered. Larger dietary doses will be necessary under those conditions to maintain iron balance.

### THE RATIONALE FOR IRON-FORTIFIED INFANT FORMULAS

The American Academy of Pediatrics' Committee on Nutrition stated more than a quarter century ago that "the early use of fortified formula results in augmentation of iron stores which help prevent later development of iron deficiency."<sup>1</sup> The strategy to improve iron stores during the first year was a response to the high rates of iron deficiency before the 1970s when the rate of cow milk consumption during the first year and the concordant rate of iron defi-

---

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

PEDIATRICS (ISSN 0031 4005). Copyright © 1999 by the American Academy of Pediatrics.

ciency were unacceptably high. The strategy was designed to promote at least neutral but preferably positive iron balance after 4 months of age. The rationale for no net loss in iron balance is clear, because humans have relatively low amounts of iron stores compared with total body iron. Thus, there is a relatively small buffer zone to protect developing tissues, such as the brain, heart, skeletal muscle, and gastrointestinal tract, from iron deficiency.

The increased use of iron-fortified infant formulas from the early 1970s to the late 1980s has been a major public health policy success. During the early 1970s, formulas were fortified with 10 mg/L to 12 mg/L of iron in contrast with nonfortified formulas that contained less than 2 mg/L of iron. The rate of iron-deficiency anemia dropped dramatically during that time from more than 20% to less than 3%.<sup>3,13</sup> Nevertheless, *low-iron* formulas, defined by the US Food and Drug Administration (FDA) as containing less than 6.7 mg/L of iron, continue to be available and account for 9% to 30% of elective (non-Women, Infants, and Children program) formula consumption in the United States. Currently, most infants in the United States are not breastfed beyond 3 months of age. Therefore, the number of infants who could potentially receive low-iron formula (or cow milk) during late infancy remains high.

Although anemia is the endpoint of most studies of infant iron supplementation, the physiologic deficits of iron deficiency are apparently not attributable solely to the anemia. The onset of nonheme tissue effects of iron deficiency predate the onset of anemia because the body prioritizes iron for heme synthesis. When iron supply during the first year does not meet the iron demand of the rapidly expanding red blood cell mass, first iron stores in the liver and then nonstorage iron in other tissues will be compromised.<sup>14</sup> These changes take place before any hematologic findings are evident. The nonheme effects, thought to be attributable in part to reduction of iron-containing cellular proteins, are responsible for many of the clinical manifestations of iron deficiency. The combination of hematologic and nonhematologic iron deficiency produces clinical symptoms of weakness, muscle fatigue, abnormal gastrointestinal motility, and, of most concern, permanent reduction of cognitive ability.<sup>14,15</sup>

Because of the prioritization toward the hematopoietic system, many infants consuming low-iron formula who have reduced iron stores or frank tissue iron deficiency will not be given a diagnosis of iron deficiency because they are not anemic when their hemoglobin is routinely assayed at 9 months of age. Studies that assess the iron storage capacity of the infant (serum ferritin) or the infant's compensatory response to reduced iron availability (increased iron binding capacity) are not routinely performed during infancy. Thus, early warning signs of negative iron balance are missed.

#### IRON CONCENTRATIONS IN LOW-IRON VERSUS IRON-FORTIFIED COW MILK FORMULAS

Infant formulas have been classified as low-iron or iron-fortified based on whether they contain less or

more than 6.7 mg/L of iron. Nevertheless, traditional low-iron formula contains the amount of iron inherent to the cow milk plus a small amount added for stabilization during formulation. This results in iron concentrations of approximately 1.1 mg/L to 1.5 mg/L of iron. Recently, one manufacturer increased the iron concentration of low-iron formula to 4.5 mg/L.

In contrast with low-iron formulas, iron-fortified formulas signified a conscious attempt to "fortify" the infant's iron stores to protect against the later development of iron deficiency. In the United States, iron concentrations of iron-fortified formulas range from 10 mg/L to 12 mg/L. In Europe, infant formula tends to contain 4 mg/L to 7 mg/L of iron.

Determining the acceptable range of iron concentration in infant formula depends on what standard is used to assess iron sufficiency. The most common approach is to document the prevalence of iron deficiency in populations of infants fed formulas with various iron concentrations with a target of ensuring that all infants are protected from iron deficiency. Numerous studies have documented the unequivocal reduction in iron deficiency (clinical and subclinical) in infants fed iron-fortified vs low-iron formula.<sup>13,16,17</sup> The rate of iron deficiency anemia in 9-month-old infants fed formulas containing 1.1 mg/L of iron has ranged from 28% to 38%,<sup>16,17</sup> even when supplemental foods are consumed. This unacceptably high rate decreases to 0.6% when formula fortified with 12 mg/L or 15 mg/L of iron is used.<sup>16,17</sup> Recently, Fomon et al<sup>18</sup> demonstrated similar iron status in infants fed formula containing 8 mg/L or 12 mg/L of iron. Fewer studies have assessed the long-term effect of intermediate formula iron concentrations (4 mg/L to 7 mg/L) on iron status. Lonnerdal and Hernell<sup>19</sup> recently reported a trend toward higher ferritin concentrations and lower transferrin receptor concentrations in infants fed a cow milk-based formula containing 7 mg/L of iron compared with a group fed a formula containing 4 mg/L. These data suggest that iron balance is stressed by the formulas with lower iron concentration and that iron stores are better in the more highly supplemented group, although there were no differences in hemoglobin at the relatively early study endpoint of 6 months of age. There appeared to be no adverse effect on copper or zinc status in the more highly supplemented iron group.

Hokama<sup>20</sup> estimated that breastfed 4- to 5-month-old infants retain 0.06 mg/kg per day of iron from that source. Using 0.06 mg/kg per day of iron as a target accretion rate assumes that the prevalence of iron deficiency in human milk-fed infants is acceptably low. In studies in which infants were exclusively breastfed, the prevalence of decreased iron stores appears to range between 6% and 20%,<sup>21,22</sup> suggesting that this rate of daily iron accretion may be near the lower borderline of promoting iron sufficiency. Assuming a 12% absorption rate,<sup>11</sup> an infant consuming 130 mL/kg per day of low-iron cow milk formula containing 1.5 mg/L of iron would retain only 0.02 mg/kg of iron daily. Conversely, even with an absorption rate as low as 7%, an infant consuming

a formula fortified with 12 mg/L of iron will retain 0.06 mg/kg of iron per day.

A relatively small percentage of infants continues to be nourished predominantly by formulas made at home by using evaporated milk as the base and fortifying with additional sugar in the form of glucose polymers. These formulas would have the same low-iron availability of nonformula cow milk. Therefore, infants receiving these formulas should receive exogenous iron supplementation from the time of birth to ensure maintenance of iron storage pools as the infant grows.

#### CAUSES OF RESISTANCE TO THE USE OF IRON-FORTIFIED FORMULAS

The persistent use of low-iron formulas despite recommendations of the American Academy of Pediatrics and multiple studies supporting the use of iron-fortified formulas suggests that the reasons for continued use may be multifactorial and largely non-medical. Four issues appear to influence physician-prescribing and consumer-buying practices: 1) the perception that iron fortification causes gastrointestinal or infectious problems, 2) the continued availability of low-iron products to consumers, 3) the low-iron concentration of human milk, and 4) the Infant Formula Act requirement that the phrase "with iron" be prominently displayed on the front label of iron-fortified formula containers.

#### IRON FORTIFICATION AND GASTROINTESTINAL DISTRESS

There is a misconception by some health professionals and parents that infants fed iron-fortified formulas have more gastrointestinal distress, such as colic, constipation, diarrhea, or gastroesophageal reflux. Of these, constipation and irritability appear to be the most common concern. An association between iron and constipation is appealing to mothers who remember the association between taking prenatal iron in large doses and changes in their own gastrointestinal tract function when they were pregnant.

A controlled study by Osiki<sup>23</sup> and a double-blind crossover study by Nelson et al<sup>24</sup> compared iron-fortified and low-iron formulas and found no differences in prevalence of fussiness, cramping, colic, gastroesophageal reflux, or flatulence. Moreover, therapeutic iron up to 6 mg/kg per day given to infants is well-tolerated.<sup>25</sup>

Although these studies are recognized by most pediatricians, dealing with the fussy baby and the frustrated mother who is convinced that the problem is due to iron in the formula remains difficult for some. Parental education (particularly anticipatory guidance) is laudable, yet it may remain temptingly easier to prescribe a low-iron formula, achieve a placebo effect, and ignore the more insidious long-term consequences of iron deficiency.

#### CONTINUED MANUFACTURE OF LOW-IRON FORMULAS

The low-iron formulas produced in the United States contain a range of 1.5 mg/L to 4.5 mg/L of

iron, well below the cutoff of 6.7 mg/L as defined by the FDA. All formula manufacturers in the United States who produce low-iron formulas have attempted through their field representatives to discourage the use of formulas that are deficient in iron. Nevertheless, these formulas account for 9% to 30% of elective infant formula sales in the United States. Manufacturers appear reluctant to unilaterally discontinue providing a product for which there is substantial consumer demand. This impasse is unlikely to be resolved without a change in FDA regulations implemented in the Infant Formula Act.

#### HUMAN MILK IS LOW IN IRON

Some physicians rationalize the prescription of low-iron formula by stating that the concentration of iron in human milk is approximately 20% of that found in low-iron cow milk formula (0.3 mg/L vs 1.5 mg/L). Iron found in human milk is far more bioavailable, resulting in much lower rates of iron-deficiency anemia compared with low-iron cow milk formula. Nevertheless, 6% to 20% of exclusively breastfed infants remain at risk for reduced iron stores.<sup>21,22</sup> A higher rate (20%–30%) of iron deficiency has been reported in breastfed infants who were not exclusively breastfed.<sup>17,21</sup> The effect of iron obtained from formula or beikost supplementation on the iron status of the breastfed infant remains largely unknown and needs further study.

#### LABELING REQUIREMENTS

The Infant Formula Act required that formulas fortified with greater than 6.7 mg/L of iron be labeled "with iron." Initially, this label was a positive message because iron fortification was considered desirable given the prevalence of iron deficiency in the population. Over time, however, this type of labeling has come to function as a reminder of the presence of iron in the formula, making it a convenient scapegoat for the many aspects of infant formula intolerance. No other nutrient, supplemented or in natural abundance, in cow milk formula receives special consideration on the front label. It may be appropriate to remove the term "with iron" from the front label of the iron-fortified formulas. Instead, formulas with iron concentrations that promote negative iron balance could be labeled as "nutritionally incomplete," with a warning that "this formula is not a complete diet for your infant because it lacks sufficient iron and may lead to iron deficiency."

#### POTENTIAL CONTRAINDICATIONS TO IRON-FORTIFIED FORMULAS

There are no known medical contraindications to using iron-fortified formulas in formula-fed infants. In light of controlled studies,<sup>23,24</sup> gastrointestinal symptoms are not an indication for switching to a low-iron formula. The condition of the rare infant with an iron overload syndrome can be carefully monitored. However, the dose of iron received from human milk or infant formula is minute in comparison with the total body iron load. Because these infants undergo chelation therapy, the additional iron received from infant formula that then needs to

be chelated is negligible in determining the chelator dose.

A theoretical concern has been raised about the use of iron-fortified formulas as supplements for breastfed infants.<sup>26</sup> The proposed mechanism is that the higher iron content of iron-fortified formulas may saturate lactoferrin, a protein important in protecting the intestine from overgrowth with *Escherichia coli*. Infants fed iron-fortified formula, partially breastfed infants supplemented with iron-fortified formula, and exclusively breastfed infants who receive iron supplements may have a higher prevalence of *E coli* in the fecal flora compared with exclusively breastfed infants who receive no iron supplementation. In the latter, lactobacillus predominates.<sup>27</sup> The physiologic significance of this difference in flora with respect to diarrheal disease remains to be shown. A recent study demonstrated no evidence of increased diarrhea in breastfed infants supplemented with iron-fortified formula compared with those supplemented with low-iron formula.<sup>28</sup> The conclusions of this study were somewhat clouded by the lack of measurement of the amount of formula supplementation and whether iron containing beikost or vitamins was consumed. A well-controlled, dose-response study of iron-fortified infant formula supplementation of breastfed infants with infection and iron endpoints is needed to resolve this issue. Because no data currently support the use of a low-iron formula as an alternative supplement for breastfed infants and low-iron formula is associated with an unacceptably high risk of iron deficiency, the Committee on Nutrition recommends the use of iron-fortified cow milk or soy formula as a supplement for breastfed infants whose mothers choose not to exclusively breastfeed.

### CONCLUSIONS

1. Iron sufficiency is important for normal human growth and development.
2. The goal of early iron supplementation is to meet the rapidly growing child's need for hemoglobin and tissue iron and to fortify iron stores in anticipation of later switching to an iron-poor cow milk-based diet. The use of iron-fortified formulas has dramatically reduced the rate of iron-deficiency anemia during infancy in the last 25 years.
3. Infants who were growth retarded in utero or were born to mothers with poorly controlled diabetes have reduced iron stores at birth and may require further iron supplementation.
4. Formula-fed infants receiving iron-fortified formula (up to 12 mg/L) during their first year have greater assurance of adequate iron stores and very low rates of iron deficiency between 6 and 18 months of age.
5. Barriers to the use of iron-fortified formula include unsubstantiated fears of gastrointestinal distress, availability of low-iron formula, inappropriate comparisons with the iron content of human milk, and inadequate and potentially misleading rules related to formula labeling.
6. There are no known medical contraindications to iron-fortified formulas (eg, iron overload syn-

dromes, colic, constipation, cramps, or gastroesophageal reflux).

### RECOMMENDATIONS

1. In the absence of underlying medical factors (which are rare), human milk is the preferred feeding for all infants.
2. Infants who are not breastfed or are partially breastfed should receive an iron-fortified formula (containing between 4.0–12 mg/L of iron) from birth to 12 months. Ideally, iron fortification of formulas should be standardized based on long-term studies that better define iron needs in this range.
3. The manufacture of formulas with iron concentrations less than 4.0 mg/L should be discontinued. If these formulas continue to be made, low-iron formulas should be prominently labeled as potentially nutritionally inadequate with a warning specifying the risk of iron deficiency. These formulas should not be used to treat colic, constipation, cramps, or gastroesophageal reflux.
4. If low-iron formula continues to be manufactured, iron-fortified formulas should have the term "with iron" removed from the front label. Iron content information should be included in a manner similar to all other nutrients on the package label.
5. Parents and health care clinicians should be educated about the role of iron in infant growth and cognitive development, as well as the lack of data about negative side effects of iron and current fortification levels.

COMMITTEE ON NUTRITION, 1997–1998  
Susan S. Baker, MD, PhD, Chairperson  
William J. Cochran, MD  
Carlos A. Flores, MD  
Michael K. Georgieff, MD  
Marc S. Jacobson, MD  
Tom Jaksic, MD, PhD  
Nancy F. Krebs, MD

LIAISON REPRESENTATIVES  
Donna Blum, MS, RD  
US Department of Agriculture  
Suzanne S. Harris, PhD  
International Life Sciences Institute  
Van S. Hubbard, MD, PhD  
National Institute of Diabetes and Digestive and  
Kidney Diseases  
Ephraim Levin, MD  
National Institute of Child Health and Human  
Development  
Ann Prendergast, RD, MPH  
Maternal and Child Health Bureau  
Alice E. Smith, MS, RD  
American Dietetic Association  
Elizabeth Yetley, PhD  
Food and Drug Administration  
Stanley Zlotkin, MD  
Canadian Paediatric Society

SECTION LIAISON  
Ronald M. Lauer, MD  
Section on Cardiology

## REFERENCES

- American Academy of Pediatrics, Committee on Nutrition. Iron balance and requirements in infancy. *Pediatrics*. 1969;43:134-142
- American Academy of Pediatrics, Committee on Nutrition. Iron supplementation for infants. *Pediatrics*. 1976;58:765-768
- American Academy of Pediatrics, Committee on Nutrition. Iron-fortified infant formulas. *Pediatrics*. 1989;84:1114-1115
- Oski FA. The hematologic aspects of the maternal-fetal relationship. In: Oski FA, Naiman JL, eds. *Hematologic Problems in the Newborn*. 3rd ed. Philadelphia, PA: WB Saunders Co; 1982:32-33
- Petry CD, Eaton MA, Wobken JD, Mills MM, Johnson DE, Georgieff MK. Iron deficiency of liver, heart, and brain in newborn infants of diabetic mothers. *J Pediatr*. 1992;121:109-114
- Georgieff MK, Mills MM, Gordon K, Wobken JD. Reduced neonatal liver iron concentrations after uteroplacental insufficiency. *J Pediatr*. 1995;127:308-311
- Siimes MA, Jarvenpaa AL. Prevention of anemia and iron deficiency in very-low-birth-weight infants. *J Pediatr*. 1982;101:277-280
- Ehrenkranz RA, Sherwonit EA, Nelli CM, Janghorbani M. Recombinant human erythropoietin (r-HuEPO) stimulates incorporation of absorbed iron (Fe) into RBCs in VLBW infants. *Pediatr Res*. 1994;35:311A. Abstract
- Stekel A, Olivares M, Pizarro F, Chadud P, Lopez I, Amar M. Absorption of fortification iron from milk formulas in infants. *Am J Clin Nutr*. 1986;43:917-922
- Ehrenkranz RA, Gettner PA, Nelli CM, et al. Iron absorption and incorporation into red blood cells by very low birth weight infants: studies with the stable isotope <sup>58</sup>Fe. *J Pediatr Gastroenterol Nutr*. 1992;15:270-278
- Saarinén UM, Siimes MA. Iron absorption from infant milk formula and the optimal level of iron supplementation. *Acta Paediatr Scand*. 1977;66:719-722
- Hertrampf E, Cayazzo M, Pizarro F, Stekel A. Bioavailability of iron in soy-based formula and its effect on iron nutrition in infancy. *Pediatrics*. 1986;78:640-645
- Dallman PR, Yip R. Changing characteristics of childhood anemia. *J Pediatr*. 1989;114:161-164
- Dallman PR. Biochemical basis for the manifestations of iron deficiency. *Annu Rev Nutr*. 1966;6:13-40
- Lozoff B, Jimenez E, Wolf AW. Long-term developmental outcome of infants with iron deficiency. *N Engl J Med*. 1991;325:687-694
- Moffatt ME, Longstaffe S, Besant J, Dureski C. Prevention of iron deficiency and psychomotor decline in high-risk infants through use of iron-fortified infant formula: a randomized clinical trial. *J Pediatr*. 1994;125:527-534
- Pizarro F, Yip R, Dallman PR, Olivares M, Hertrampf E, Walter T. Iron status with different infant feeding regimens: relevance to screening and prevention of iron deficiency. *J Pediatr*. 1991;118:687-692
- Fomon SJ, Ziegler EE, Serfass RE, Nelson SE, Frantz JA. Erythrocyte incorporation of iron is similar in infants fed formulas fortified with 12 mg/L or 8 mg/L of iron. *J Nutr*. 1997;127:83-88
- Lonnerdal B, Hernell O. Iron, zinc, copper and selenium status of breast-fed infants and infants fed trace element fortified milk-based infant formula. *Acta Paediatr*. 1994;83:367-373
- Hokama T. A study of the iron requirement in infants, using changes in total body iron determined by hemoglobin, serum ferritin and body weight. *Acta Paediatr Jpn*. 1994;36:153-155
- Pisacane A, De Vizia B, Valiante A, et al. Iron status in breast-fed infants. *J Pediatr*. 1995;127:429-431
- Duncan B, Schiffman RB, Corrigan JJ Jr, Schaefer C. Iron and the exclusively breast-fed infant from birth to six months. *J Pediatr Gastroenterol Nutr*. 1985;4:421-425
- Oski FA. Iron-fortified formulas and gastrointestinal symptoms in infants: a controlled study. *Pediatrics*. 1980;66:168-170
- Nelson SE, Ziegler EE, Copeland AM, Edwards BB, Fomon SJ. Lack of adverse reactions to iron-fortified formula. *Pediatrics*. 1988;81:360-364
- Reeves JD, Yip R. Lack of adverse side effects of oral ferrous sulfate therapy in 1-year-old infants. *Pediatrics*. 1985;75:352-355
- Balmer SE, Wharton BA. Diet and faecal flora in the newborn: iron. *Arch Dis Child*. 1991;66:1390-1394
- Bullen JJ, Rogers HJ, Leigh L. Iron-binding proteins in milk and resistance to *Escherichia coli* infection in infants. *Br Med J*. 1972;1:69-75
- Scariati PD, Grummer-Strawn LM, Fein SB, Yip R. Risk of diarrhea related to iron content of infant formula: lack of evidence to support the use of low-iron formula as supplement for breastfed infants. *Pediatrics*. 1997;99(3). URL: <http://www.pediatrics.org/cgi/content/full/99/3/e2>