# Reference Data for Evaluating Infant Formulas
# Gains in Weight and Length of Term Infants
## Iowa and Iowa/Fels Growth Data

A White Paper

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by

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The purpose of this communication is to examine the Iowa data (Nelson et al., 1989; Fomon and Nelson, 1993) and the Iowa-Fels data (Guo et al., 1991) with respect to their suitability as references for determining adequacy of growth by infants fed a new formula.* Both data sets (the Iowa data; Iowa series) and the Iowa-Fels data (Iowa-Fels data; Iowa-Fels series) were assembled for the purpose of aiding in early detection of infants at risk of growth abnormality, primarily failure to thrive (and in the remainder of this presentation we shall refer only to failure to thrive). Suitability of reference data for early detection of infants who are failing to thrive differs from use of the same reference data for evaluation of growth of a cohort of infants fed a new formula.

## Reference Data as an Aid in Early Identification of Subjects Who are Failing to Thrive

Because of the difference in rate of growth of male and female infants, reference data for any use should be gender-specific. Major characteristics of data (1) The greatest interest in reference data for early identification of infants who are failing to thrive concerns the outlying centiles, usually the 5th. The larger the number of subjects in the reference data, the more stable are these outlying centiles. Because a substantially greater number of subjects may be obtained by combining data on breast-fed and formula-fed infants, the increase in confidence in the outlying centiles may outweigh the advantage of feeding-specific reference data. We considered this to be the case in presenting the Iowa-Fels combined data (Guo et al., 1991). (2) Increments in weight are preferable to increments in length because (a) accurate mesurement of length requires two trained observers and such individuals are rarely simultaneously available in a busy medical office or clinic, (b) a longer time interval is required to evaluate change in length than to evaluate change in weight and abnormally slow gain in length is rarely observed in the absence of abnormally slow gain in weight. (4) Reference data for identification of abnormal growth of individuals during the first two years of life (when failure to thrive is most common) must apply to that entire age span. Thus, for general use in detection of abnormal growth of individual infants, we consider the Iowa-Fels data (Guo et al. 1991) to be the best available.

* Throughout this presentation reference to a "new formula" is meant to include any modification of an existing formula that requires evaluation of growth.

## Reference Data for Evaluation of Growth of a Cohort of Infants Fed A New Formula

Major considerations are as follows: (1) Because the formula is meant to be suitable for all normal term infants, it should be tested over an interval that includes at least a major portion of the neonatal growth spurt (approximately age 8 to 42 days). During the neonatal growth spurt the requirement for a number of nutrients per unit of energy intake is greatest. Therefore, a new formula might appear to be adequate if based on a study that began at or after 42 days of age because the peak of the postnatal growth spurt has been missed. Evaluation of the same formula in a study that began at 14 or even 28 days of age might reveal that the formula did not support adequate growth during the first two months of life.. (2) In order to be as specific as possible, the reference data should be gender-specific and limited to formula-fed infants. (3) Because it is possible that a formula will support normal gain in weight but not gain in length (mainly, excessive accumulation of fat), it is essential that change in length as well as change in weight be determined. Additional measurements (head circumference or measurements of body composition) will rarely aid in distinguishing an adequate from an inadequate formula. (4) Athough 3 months has been suggested as the duration of study, the Iowa data are not adequate after 112 days of age and no comparable incremental data are available. Thus, a study interval beginning no earlier than 8 days of age and no later than 28 days of age and ending at 112 days of age would cover a span of 104 days to 84 days, respectively. Because of practical considerations in recruiting formula-fed infants, we believe that the interval 28 to 112 days may be most feasible and will probably be nearly as satisfactory as an interval beginning at earlier age.

## The Iowa Data and Iowa-Fels Data

QUALITY OF MEASUREMENTS: In both series (Iowa data and Fels data) measurements of weight and length were made by standard anthropometric techniques (Gordon et al., 1989) by trained personnel. Scales for measuring weight were calibrated at regular intervals and the recorded measurement of length in each case was the mean of paired measurements.

IOWA DATA: The Iowa data are based on studies of Caucasian infants born in or near Iowa City, Iowa from March 1965 through March 1987 (Nelson et al., 1989). The majority were sons or daughters of students or faculty of the University of Iowa. Birth weights were 2500 g or more and, based on physical examination soon after birth, the infants were believed to be normal. Although the studies included both breast-fed and formula-fed infants, we have elected to restrict presentation of the Iowa data to those for formula-fed infants.

The infants were fed commercially available formulas or experimental formulas that were, in most instances, modifications of commercially available formulas. The source of protein was cow milk, cow milk plus cow milk whey, or methionine-fortified isolated soy protein. The formulas were provided ready-to feed, generally 667 kcal/L, but with a range of 640 to 700 kcal/L. Nearly all of the feedings were iron-fortified with 12 mg of iron per L in the form of ferrous sulfate.

Before the mid 1970s, when it was the custom to introduce strained foods to an infant's diet during the early months of life, infants were permitted to receive commercially prepared foods: oatmeal with bananas and applesauce beginning at 28 days of age, pureed pears beginning at 56 days of age, pureed applesauce and pureed bananas beginning at 84 days of age. These foods were supplied by the investigators and amounts consumed were determined by weight and have been published for many of the infants (Fomon et al., 1975). After 1978 foods other than infant formula were not permitted during the first 112 days of life. Analysis of the data did not detect differences in energy intake or growth between infants born before 1978 and those born from 1978 through 1987.

The first summary of the Iowa data (Fomon et al., 1971) presented gender-specific gains in weight and length of 65 male and 77 female infants fed milk-based formulas. In this and subsequent studies, measurements were made within 2 days of ages 8, 14, 28, and 42 days and within 4 days of ages 56, 84 and 112 days. Values for each infant were then adjusted to the target ages by interpolation or extrapolation using three proximate recorded values. In this and subsequent studies of growth from 8 to 112 days of age, each infant was enrolled by 9 days of age and the study was fully longitudinal with no missing data points.

Further data concerning gains in length and weight of normal term infants from 8 to 112 days of age were combined with the data published in 1971 in a summary that concerned a total of 380 male and 340 female formula-fed infants (Nelson et al., 1989). In addition to milk-based formulas (casein predominant or whey predominant), the 1989 summary included data on infants fed formulas that included methionine-supplemented isolated soy protein. Fomon and Ziegler (1979) had detected no difference in gain in weight or gain in length from 8 to 112 days of age by 174 males fed milk-based formulas and 74 males fed methionine-supplemented isolated soy protein-based formulas, nor by 159 females fed milk-based formulas and 67 females fed methionine-supplemented isolated soy protein-based formulas.

Subsequently, we (Fomon and Nelson, 1993) added to these data, a summary of gains in weight and length of 165 males and 188 females from 112 to 196 days of age fed milk-based or methionine-supplemented isolated soy protein-based formulas. The measurements of each subject were made within 4 days of ages 112, 140, 168 and 196 days and adjusted to the target ages as already mentioned. As was the case with the data from 8 to 112 days of age, the data from 112 to 196 days of age were fully longitudinal with no missing data points. The data included gains for 63 males and 74 females studied longitudinally from 8 to 196 days of age. The tabular data presented in the 1993 summary included gains in weight and length of formula-fed male and female infants during each age interval from 8 to 196 days of age.

FELS DATA: The Fels data included in the combined Iowa-Fels series concern 476 term, caucasian infants (240 males and 236 females), mostly formula-fed, with birth weights 2500 g or more and birth dates from 1930 to 1987. The families of the infants differed widely in socioeconomic status. Examinations were scheduled at ages 1, 3, 6, 9, 12, 18, and 24 months and nearly all were examined within a few weeks of these target ages and also at intermediate ages. As in earlier reports from the Fels Institute (Roche et al., 1989a, 1989b; Guo et al., 1990), reference data were derived by fitting mathematical models to serial data for individual subjects with the stipulation that from birth to 24 months of age there must be at least seven data points. The data for each subject were summarized in a few derived parameters and were then used to estimate status values at selected ages and increments during selected age intervals (Guo et al., 1991).

COMBINED IOWA-FELS DATA (GUO ET AL., 1991): In combining the Iowa data with the Fels data, we elected to include from the Iowa series breast-fed as well as formula-fed infants and to present age intervals beginning at birth or at the monthly anniversaries of birth. For the purpose of early detection of infants at risk of failure to thrive (the major reason for assembling the combined data), we believed, as already mentioned, that the increase in number of subjects was more important than feeding specificity. Data concerning breast-fed infants from 8 to112 days of age in the Iowa series had been published (Fomon et al., 1970, 1978; Nelson et al., 1989). In the Iowa series, both for breast-fed and formula-fed infants, values for weight at birth were based on parental reports and therefore were less reliable than the remainder of the measurements. In the absence of reliable data on length at birth, the value for length at age 8 days was used as a surrogate for length at birth in the belief that gain in length between birth and age 8 days was too small to have a major effect on gain in length over the 3-month interval from birth to 3 months.

Because the Fels series included relatively few subjects less than 3 months of age and the Iowa series included relatively few subjects older than 6 months, the the tables of gains in weight and length were limited to the following: (1) Iowa data only from birth to 3 months of age; (2) combined Iowa and Fels data from 3 to 6 months of age; Fels data only for ages 6 to 24 months of age. The similarity of the Iowa and Fels data at age 3 months (Table 1) gave us some confidence that the two data sets were similar and could be combined.

## Data Considered Most Suitable as Reference for Growth of Infants Fed a New Formula

We consider the Iowa data (Nelson et al., 1989; Fomon and Nelson, 1993) to be completely adequate for evaluation of growth of a cohort of infants fed a new formula during the early months of life. The data cover the most appropriate ages for testing a new formula, and they are completely longitudinal with no missing data points.

For evaluation of formulas for older infants (e.g., an interval from 6 to 9 months of age), the Fels data (Guo et al., 1991) are available as a reference. They are gender-specific and include few, if any, breast-fed infants. However, in the knowledge that formulas designed for older infants are likely to be fed to younger infants as well, it is questionable whether a study that does not include at least a portion of the neonatal growth spurt should be considered adequate.

## Sample Size

As previously stated, we believe it necessary for the interval of study to include at least a major portion of the neonatal growth spurt, and this presents a problem. However desirable it may be for infants to be breast fed, the prevalence of breast feeding during the early weeks of life makes recruitment of formula-fed infants difficult. In our experience, recruitment of formula-fed infants before 42 days of age is difficult and enrollment at 42 days of age is unsatisfactory because an interval beginning at 42 days of age misses the neonatal growth spurt. Nevertheless, we believe that, even in single-center studies (which have many advantages), recruitment of about 30 subjects will be feasible.

Gain in weight of a cohort of infants fed a new formula can be compared directly with Iowa reference data by a two-sample gender-specific analysis, or by a multifactor analysis of variance with gender as a factor. We have based our calculations on the interval 28 to112 days – an interval that covers a substantial portion of the neonatal growth spurt and that, for recruitment purposes, is preferable to an interval beginning at an earlier age. To compare a new formula with the Iowa reference data and be able to detect a difference in weight gain of 3.0 g/d for the age interval 28-112 d with alpha = 0.05 (1-tailed) and power = 0.8 and, assuming a SD in weight gain of 5.6 g/d for this study interval, a sample size of 23 subjects (both genders) is sufficient. The SD of 5.6 g/d is is the approximate mean of the value of 6.2 g/d for males and 5.1 g/d for females (Nelson et al., 1989). However, these standard deviations apply to carefully measured weights using regularly calibrated scales; a larger SD may be necessary under other conditions.

ADVANTAGE OF USING IOWA REFERENCE DATA RATHER THAN A COMPARISON OF TWO COHORTS: If two formulas are compared against one another, and the standard deviation in gain in weight is approximately 5.6 g/d, 45 subjects per cohort would be needed to detect a difference of 0.54 SD or 3 g/d (0.54 x 5.6 g/d). Thus, to detect a 3.0 g/d difference with power 0.8, 90 subjects (45 in each of the two groups) will be needed to compare two cohorts, whereas only 23 subjects (including approximately equal numbers of males and females) will be needed in a study cohort to be compared with the Iowa reference data.

**Additional Consideration: Z-scores**

The Iowa data on weight and length (Fomon and Nelson, 1993) could serve as reference for attained weight and weight gain for Z-score analysis but, when incremental data are available, we believe that Z-score analysis is unwieldy and unnecessary. The NCHS data (Ogden et al., 2002) seem to us to be inappropriate for Z-score analysis because of the inclusion of data concerning infants weighing between 1,500 and 2,499 g at birth. Thus, it would be anticipated that the mean Z-score of a study cohort of term infants would be more than 0.

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**TABLES**

TABLE 1

WEIGHT AND LENGTH OF 3-MONTH-OLD INFANTS

IN THE IOWA SERIES AND THE FELS SERIES

| | | Number | Mean | SD | 5th Centile |
|---|---|---|---|---|---|
| Wt, g | Males | | | | |
| | Iowa[1] | 580 | 6,338 | 643 | 5,331 |
| | Fels[2] | 233 | 6,297 | 613 | 5,305 |
| | Females | | | | |
| | Iowa | 562 | 5,770 | 600 | 4,885 |
| | Fels | 224 | 5,750 | 600 | 4,734 |
| L, cm | Males | | | | |
| | Iowa | 580 | 61.0 | 1.9 | 57.8 |
| | Fels | 190 | 61.4 | 1.9 | 58.4 |
| | Females | | | | |
| | Iowa | 562 | 59.4 | 1.8 | 56.7 |
| | Fels | 167 | 59.5 | 2.0 | 56.3 |

[1]From Guo et al., 1991.
[2]From Nelson et al. (1989); formula-fed infants.

TABLE 2

GAINS IN WEIGHT AND LENGTH DURING SELECTED AGE

INTERVALS BY INFANTS IN THE IOWA SERIES[1]

| | Number of subjects | Age Interval, d | Wt gain, g/d mean ( SD) |
|---|---|---|---|
| Males | 380 | 8-112 | 32.3 (5.6) |
| | 380 | 14-112 | 32.1 (5.8) |
| | 63 | 42-140 | 23.7 (5.0) |
| Females | 340 | 8-112 | 27.5 (4.9) |
| | 340 | 14-112 | 27.4 (5.0) |
| | 74 | 42-140 | 23.3 (4.3) |

| | Number of subjects | Age Interval, d | L gain mm/d mean ( SD) |
|---|---|---|---|
| Males | 380 | 8-112 | 1.13 (0.11) |
| | 380 | 14-112 | 1.10 (0.11) |
| | 63 | 42-140 | 0.93 (0.09) |
| Females | 340 | 8-112 | 1.04 (0.09) |
| | 340 | 14-112 | 1.02 (0.09) |
| | 74 | 42-140 | 0.87 (0.11) |

[1]Abstracted from data of Fomon and Nelson, 1993.

TABLE 3

GAINS IN WEIGHT AND LENGTH DURING 3-MONTHLY INTERVALS FOR THE COMBINED IOWA AND FELS SERIES[1]

| | Number of subjects | Age Interval, mo | Wt gain, g/d mean ( SD) |
|---|---|---|---|
| Males | 580 | 0-3 | 31 (5.9) |
| | 65 | 1-4 | 27 (5.1) |
| | 65 | 2-5 | 21 (4.3) |
| Females | 562 | 0-3 | 26 (5.5) |
| | 74 | 1-4 | 24 (5.1) |
| | 74 | 2-5 | 20 (3.9) |

| | Number of subjects | Age Interval, mo | L gain, mm/d mean (SD) |
|---|---|---|---|
| Males | 580 | 0-3 | 1.07 (0.11) |
| | 65 | 1-4 | 1.00 (0.08) |
| | 65 | 2-5 | 0.84 (0.09) |
| Females | 562 | 0-3 | 0.99 (0.10) |
| | 74 | 1-4 | 0.95 (0.10) |
| | 74 | 2-5 | 0.80 (0.10) |

[1]Abstracted from Guo et al., 1991.