Estimated folate intakes: data updated to reflect food fortification, increased bioavailability, and dietary supplement use[1,2]

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See corresponding editorial on page 177.

ABSTRACT

Background: There is a critical need to estimate dietary folate intakes for nutrition monitoring and food safety evaluations, but available intake data are seriously limited by several factors.

Objective: Our objective was to update 2 national food consumption surveys to reflect folate intakes as a result of the recently initiated food fortification program and to correct folate intakes for the apparently higher bioavailability of synthetic folic acid (SFA; ie, folate added to foods or from dietary supplements) than of naturally occurring folate so as to express intakes as dietary folate equivalents.

Design: It was not possible to chemically analyze foods, so adjustments were made to food-composition data by using information about food ingredients and characteristics. Total folate intakes were estimated for several sex and age groups by using the modified data coupled with dietary supplement use.

Results: Within the limitations of the data, our findings suggested that 67–95% of the population met or surpassed the new estimated average requirement, depending on the sex and age group and survey. Nonetheless, some subgroups had estimated intakes below these standards. Estimated SFA intakes suggested that ≈15–25% of children aged 1–8 y, depending on the survey, had intakes above the newly established tolerable upper intake level. We estimated that 68–87% of females of childbearing age had SFA intakes below the recommended intake of 400 μg/d, depending on the age group and survey.

Conclusion: There is a need to explore ways to improve folate intakes in targeted subgroups, including females of childbearing age, while not putting other population groups at risk of excessive intakes.   *Am J Clin Nutr* 1999;70:198–207.

INTRODUCTION

Estimates of dietary folate intakes are currently a topic of considerable interest. Recent public health recommendations have focused on the folate needs of females of childbearing age to reduce the risk of babies born with neural tube defects (NTDs) (1). In addition, considerable attention is being paid to total folate intakes relative to serum homocysteine concentrations and, in turn, the risk of cardiovascular disease, although a specific relation between homocysteine concentrations and cardiovascular disease risk has not been firmly established (2). These interests are set against concerns about folate intakes obscuring vitamin B-12 deficiency as well as a lack of data indicating the safety of high folate intakes.

In early 1998, 2 events intensified the focus on dietary folate intakes. First, regulations requiring the fortification of certain cereal-grain products with folate [in practice, this requirement results in fortification with synthetic folic acid (SFA)] became effective (3, 4). Discussions about fortifying the food supply with SFA began in earnest in the early 1990s when the Food and Drug Administration (FDA) and other Public Health Service agencies reviewed the relation between folate and the incidence of NTDs relative to a health claim for use on food labels (5). At the time of the decision to implement the program, it was considered desirable to monitor folate intakes to ensure that, in reaching the target population, others in the population did not exceed an intake of 1 mg folate/d.

Second, the National Academy of Sciences' Institute of Medicine (IOM) published a report establishing dietary reference intakes (DRIs) for folate as well as for several other B vitamins (6). The report provided an estimated average requirement (EAR; an intake below which, on a population basis, inadequate intake may be a concern), a recommended dietary allowance (RDA), and, for the first time, a tolerable upper intake level (UL) for folate. Moreover, the EARs and RDAs are expressed as dietary folate equivalents (DFEs), which were adjusted for the apparent greater bioavailability of SFA than that of the same amount of naturally occurring folate (NF). The report provides estimated intakes of folate from 2 national surveys—the 1994–1996 Continuing Survey of Food Intakes by Individuals (CSFII; 7) and the third National Health and Examination Survey (NHANES III; 8)—but acknowledges that the estimates were incomplete for monitoring purposes.

The purpose of our study was to provide updated estimates of total folate intake that would account for the missing components highlighted by the IOM report, specifically the increased contribution of SFA to the overall intake of folate resulting from food fortification, from dietary supplements, and from adjustments made for its greater bioavailability than that of NF. An estimation of total folate intake from all sources was needed because FDA monitoring efforts focus on overall intakes in their efforts to ensure a safe and adequate food supply. Clinical measures are the preferred indicators of nutritional status, but estimates of dietary intake may serve as early warnings of marginal status as well as of excess intakes. Whereas available food-composition data for folate are less than satisfactory, analyses of estimated intakes are nonetheless useful for monitoring purposes. Additionally, our study is timely given the recent establishment of new standards for folate intakes and the interest in comparisons of total folate intakes, expressed as DFEs, with these values. We undertook this study with the assistance of the US Department of Agriculture (USDA) and the National Center for Health Statistics of the Centers for Disease Control and Prevention, the agencies that conducted the CSFII and NHANES III, respectively, used in this study.

METHODS

The key steps in updating estimated folate intakes were to *1*) modify available food-composition data to reflect fortification and bioavailability so that they could be used with the existing surveys to estimate current folate intakes by the population, and *2*) input information about folate intakes from dietary supplements as appropriate for persons in the surveys. This effort required both broad-based assumptions and detailed adjustments to food-composition data, sometimes on a food code–by–food code basis. The specific process is described in detail in the documentation for these analyses (9). The term "SFA" is used in this article to specify the synthetic form of the nutrient that is added to foods or found in dietary supplements; the term "folate" is used to refer to all forms of the nutrient, ie, SFA and NF.

Surveys used

The USDA's 1994–1996 CSFII and the Centers for Disease Control and Prevention's NHANES III (1988–1994) are the most current available national food consumption surveys. The CSFII was designed to obtain a nationally representative sample of non-institutionalized persons living in households in the United States and used a complex multistage sampling design and oversampled key population groups to ensure representation. Dietary intake data were obtained from selected individuals within each household and up to 2 nonconsecutive days of intake were obtained by using the 24-h dietary recall method. The survey contains information on ≈15 000 persons of all ages. NHANES III was a nationally representative survey of households in 81 counties across the United States. About 40 000 persons aged ≥2 mo were selected, including large samples of both young and old persons. All those selected were asked to participate in a detailed examination in a mobile examination center. Dietary intake data were collected for 1 d with an in-person 24-h dietary recall interview. A nonrandom subsample of ≈5% of the total sample received a second examination, including an in-person 24-h recall interview.

Each survey collects information on the amount of foods participants reported eating. These reports are linked to a food-composition database structured to provide information on the amount of nutrient per 100-g portion of food. In this way, estimated nutrient intakes for each individual can be derived.

Modification of food composition to reflect fortification

The food-composition databases for the 2 surveys were created before folate fortification requirements took effect; therefore, the data do not reflect the increase in folate intakes as a result of fortification. The first step was to modify the food-composition values so that they reflected the fortification of food with folate, as now required by a federal regulation (3). It was not possible to reanalyze the many products affected by the fortification regulation or to gather labeling information on all of these products. Therefore, the data were modified on the basis of regulatory requirements.

The USDA has developed a method for separating foods into their component ingredients (10). This method was used by the USDA to produce a file listing the weight of dry cereal-grain ingredients as a percentage of the total recipe weight for each survey food code (10). For example, this file contains the grams of cornmeal, sugar, shortening, and other ingredients in a cornmeal muffin. Because the amount of SFA that would have been added to an ingredient subject to fortification (eg, cornmeal) by the manufacturer is specified by regulation (3), the USDA was able to use the total amounts stipulated by the regulation along with estimated recipes to modify the folate values in the CSFII food-composition database (ie, the 1994–1996 Survey Nutrient Database, hereafter referred to as the 1996 database; 7) and, in turn, simulate the content of folate in today's food supply. The USDA used the values 1.54 μg folate/g for white flour and 0.95 μg folate/g for breads, rolls, and buns. For those products or ingredients for which the regulation gives a range for folate fortification levels, the USDA used the midpoint of the range. Specifically, 1.87, 1.87, 1.73, and 2.31 μg folate/g were used for corn grits, cornmeal, farina, and rice, respectively. For macaroni and noodle products, 2.31 μg folate/g was used. The use of midpoint values may have resulted in both underestimations and overestimations of the folate contents of foods, but other options, such as analytic data, were not practical. The updated amounts of added folate for each grain product were then used to update the existing folate intakes reported in the 1996 database and provided an estimation of the current folate value for each food. (Hereafter the updated database is referred to as the 1998 database.) The USDA shared this modified food-composition database with the FDA staff so that estimates of folate intake could be updated by the FDA.

At this time, the method used by the USDA to separate foods into their component ingredients cannot be applied to the NHANES III data and because no other method exists, a similar approach could not be used for the NHANES III data. However, because the food codes used for the food consumption data in the CSFII and NHANES III are very similar, we used the 1998 database for both surveys. The approach for combining the 1998 database within the NHANES III data is described in a separate section below.

Estimation of SFA in foods

The RDAs and EARs establish recommended intakes that account for the greater bioavailability of SFA when compared with that of NF. Moreover, both the ULs for folate for all age groups as well as the IOM recommendations for folate intakes for females of childbearing age are specified on the basis of SFA intakes. Thus, to estimate folate intakes that can be compared with these SFA-based standards, intakes attributable to SFA need to be partitioned from total folate intakes. Existing food-composition databases

provide total folate contents of foods, but do not distinguish between the content of NF and SFA.

Assumptions were necessary to estimate the amount of SFA in foods in the 1998 database. First, because folate is regulated as a food additive and therefore had not been widely added to foods before 1998 (with 3 exceptions described below), the assumption was made that the folate in foods before fortification was NF. Because fortification became effective in January 1998, the difference between folate intakes reported in the 1996 database and those reported in the 1998 database provides an estimation of the SFA content in foods, for most foods. We used this subtraction approach to estimate the amount of SFA in foods for all but 3 categories of foods. On the basis of this approach, products or foods with ingredients not subject to fortification would result in a subtraction outcome of zero (ie, no SFA added) and thus any folate in these products was considered to be NF. It was noted that total folate was lower in the 1998 database than in the 1996 database for a few foods (9). For these foods, it was assumed that no SFA had been added and the total folate and NF content of the food was set to equal the value in the 1998 database.

The subtraction approach could not be used for breakfast cereals, meal-replacement products (eg, instant breakfast drinks), and infant formula because, historically, folate has been added to these foods. Thus, folate intakes from these foods in the 1996 database could not be assumed to come entirely from NF. Despite the variation in the amount of SFA added to these foods as well as in the types and amounts of other ingredients in the products, the amount of SFA added to these foods needed to be accounted for in the present study. Breakfast cereals are frequently consumed and contribute significant amounts of folate in the diet. Meal-replacement products are much less frequently consumed, but could not be overlooked. It was important to estimate the intake of SFA from infant formula because of the interest in comparing the intake of the children aged 1–3 y with that of the UL for this group.

We divided breakfast cereals into ready-to-eat (RTE) and cooked or prepared cereals because the amount of folate per gram of product varies depending on whether the 100-g weight is based on the dry weight of the product or on the "as consumed" weight (eg, farina with water added). Folate values for breakfast cereals were based on data from both the *USDA Nutrient Data Base for Standard Reference* (11), a food-composition database more comprehensive than the 1996 database, and FDA-developed databases that express nutrient values from this USDA database in terms of regulatory "reference amounts customarily consumed" (ie, serving sizes) instead of 100-g portions (9).

Details of the approach used to estimate folate in breakfast cereals has been documented by the FDA (9). The overall approach used to estimate folate in RTE cereals required a review of the amounts of folate per serving of cereal to characterize the current fortification practices, to determine a cutoff point to identify cereals likely to be fortified, and to review the amounts of folate in unfortified cereals to obtain an estimate of NF in cereals. The review and the assumptions used suggested that about two-thirds of the RTE cereals were fortified and that the fortification practices were generally consistent, providing 25% of the daily value (ie, 100 μg) per serving (12). RTE cereals containing ≥0.9 μg folate/g (90 μg folate/100 g) were assumed to be fortified. The folate content of nonfortified RTE cereals ranged from 0.07 to 0.71 μg/g (7 to 71 μg/100 g) and the folate was assumed to be NF. Overall, on the basis of the range of NF compared with total folate contents reported for these breakfast cereals (9), it appeared that 2–40% of the folate from RTE cereals was NF. We chose the approximate midpoint of this range, 20%, as the proportion of folate in RTE cereals assumed to be NF. The remainder was attributed to SFA, ie, 80% of the folate in RTE cereals was assumed to have been added. A similar approach was used to estimate folate contents in cooked or prepared cereals (9). Briefly, for cooked or prepared cereals, if the total folate content was <0.15 μg/g (<15 μg/100 g) then all folate was assumed to be NF; if the total folate content was ≥0.15 μg/g, then 90% of total folate was assumed to be SFA.

Meal-replacement products were divided on the basis of liquid and powder forms, whereas infant formulas were divided on the basis of milk- or soy-based formulations. The specific approach used for these products is described in detail in the documentation (9). For liquid meal-replacement products, 80% of total folate was assumed to be SFA; for powdered meal-replacement products, 90% was assumed to be SFA. For milk-based infant formulas, 95% of total folate was assumed to be SFA; for soy-based formulas, 85% was assumed to be SFA.

Correction for the bioavailability of SFA from food

According to the IOM report (6), SFA is considered to be more bioavailable than is NF. Food-composition values had to be adjusted so that the greater bioavailability of SFA than of NF was reflected in the total folate value for the food, which was then expressed as DFEs. The 1998 database, as described above, was adjusted so that the amount of estimated SFA in each food reported in the 1994–1996 CSFII could be listed separately. Therefore, the estimated SFA contents of each food were multiplied by 1.7, the bioavailability correction factor provided by the IOM. This amount was added to the amount of NF in the food and the result was a DFE value for each food. For foods containing only NF, the DFE value was equal to the amount of NF.

Coupling data from the 1998 database with NHANES III data

Most NHANES III food codes can be linked with CSFII food codes because both surveys rely on the USDA Survey Nutrient Database as their basis and thus use virtually the same food codes. For the >7000 food codes in the CSFII database, the FDA found that most matched one-to-one with NHANES III food codes. Thus, the modified folate values in the 1998 database could be substituted for NHANES III food folate values. For ≈200 food codes, there were several CSFII food codes that could be linked to only one NHANES III food code. For these, we used an average of the folate values for the food codes, weighted by the number of times each food was reported to have been consumed in the CSFII. For 105 food codes, no match between the CSFII and NHANES III data could be determined. For about two-thirds of the 105 food codes, there were fewer than 5 reported eatings for the associated foods during the survey period. Nonetheless, as described in the documentation (9), the FDA estimated modified folate values for the unmatched food codes on the basis of reviews of other data sources. The amounts of SFA and NF in these foods were estimated in the same way as described above.

Estimated SFA from dietary supplements

During the household interview conducted as part of NHANES III, respondents were asked a series of questions about vitamin or mineral supplements used during the previous month. A proxy, usually a child's parent or guardian, provided this information for

children aged 2 mo to 16 y. If the respondents or proxies reported that supplements were consumed, they were asked to indicate the number of supplements consumed. For each supplement reported, the interviewer asked to see the supplement container to record the name of the product and the manufacturer. If the container was not available, the interviewer probed for this information. Respondents or proxies were also asked for the monthly frequency, dose, and duration of use of the supplement. After the survey was completed, NHANES III staff researched information about the supplements that were reported and then constructed a database of the nutrients and ingredients for these products. An estimate of daily folate intakes from supplements was based on the folate content in one dose of the product, the dosage reported, and the frequency reported over the previous month (calculated as frequency per day). The daily folate intake for each product was then summed for all products reported by each respondent to yield the daily folate intake from all supplements for each respondent. This estimate was then coupled with the 24-h dietary-recall data to estimate the total folate intake from all sources. Because the FDA analysis began before the NHANES III staff had input the dietary supplement data into the released survey data, NHANES III staff provided the quantitative information on folate intakes from dietary supplements for participants in the survey.

The approach for estimating dietary supplement intakes for CSFII participants was used previously (13). The 1994–1996 CSFII included several questions on the frequency of dietary supplement use and type of supplements used, but did not quantify intakes of nutrients from supplements. CSFII participants were first asked, "How often, if at all, do you take any vitamin or mineral supplement in pill or liquid form?" and "Would you say every day or almost every day, every so often, or not at all?" They were then asked, "Which of these types of supplements do you usually take: multivitamin, multivitamin with iron or other minerals, combination of vitamin C and iron, or single vitamins/minerals?" They were also asked, "Which of these single vitamins and minerals do you usually take?"; the supplement folacin was listed as a choice for the participants. We assumed that a positive response about the use of a multivitamin or multivitamin with iron or other minerals was likely to indicate SFA intake because these products typically contain folate (14). Participants who reported taking such a supplement or who reported taking a single folacin supplement were assigned an intake value based on their reported frequency of use. Persons aged ≥4 y were assigned a daily intake of 400 μg SFA from supplements if they reported taking a vitamin or mineral supplement "every day or almost every day." This estimated amount was used because supplements marketed without reference to age or physiologic state generally contain 400 μg SFA per unit (14). Persons aged ≥4 y who reported taking a supplement "every so often" were assigned a daily intake of 200 μg SFA from supplements. Persons aged 1–3 y were assigned a daily intake of 200 μg SFA from supplements if they were reported to be taking a supplement "every day" or "almost every day." This intake was based on results of a survey of dietary supplement products that showed supplements marketed for this age group contained 0–300 μg SFA (13); 200 μg is also the reference value used informally in labeling of products for children aged <4 y (15). Children aged 1–3 y who were reported to be taking a supplement "every so often" were assigned a daily intake of 100 μg SFA. In estimating participants' intakes as DFEs, the contribution of SFA from dietary supplements was multiplied by 1.7 to account for its greater bioavailability than that of NF.

Data analysis

We calculated means, medians, and distributions using SAS software (release 6.12; SAS Institute Inc, Cary, NC). We weighted the results using factors supplied with the data sets that were designed to provide results representative of the US population. Because of the day-to-day variation in an individual's intake, estimates of the distribution of intakes for a population based on one 24-h dietary recall are considered less desirable than estimates based on more than 1 d of data. Because the NHANES III data included a subsample of second dietary recalls, it was possible to adjust for this within-person variability by using statistical procedures (6). We made these adjustments using the equations provided by NHANES III staff. Adjusted estimates were made only for persons aged >6 y because the sample of second dietary recalls for children aged <6 y was too small. For the CSFII data, no correction factor was available, but only persons with 2 d of data recorded were included in our analyses to reduce the within-person variability for this survey. The sex and age groups with the greatest importance for regulatory monitoring purposes were selected for analysis: children aged 1–5 y, females of childbearing age (ie, ages 11–19 and 20–49 y), men aged 45–65 y, and elderly men and women aged >70 y.

RESULTS

Folate fortification is often misconstrued to involve primarily enriched breads, when in fact a wide range of cereal-grain products are fortified with SFA. Foods required to be fortified include rice and pasta as well as many commonly used food ingredients such as flour and cornmeal. A review of the updated listing of folate composition for the >7000 foods represented in the CSFII indicated that many different foods, often foods commonly eaten, had the potential to contribute an increased amount of folate to the diet when fortification requirements for the product were taken into account. More than one-third of the foods in the database were found to have a higher folate content after the fortification update was completed. Because many foods were low in folate before fortification, the increase in the folate content of foods after fortification was considerable in relation to the amount of NF. Examples of changes in the folate content of several foods are listed in **Table 1**. As shown, a range of food types that are commonly eaten were affected by the fortification, suggesting that even persons with unusual eating patterns are likely to increase their folate consumption. Additionally, as shown in Tables 8–10 of the IOM report (6), breakfast cereals can be a major and frequent contributor to folate intake. Many cereals provide 25% of the daily value of folate (ie, 100 μg) per serving. Supplement use was prevalent in both surveys, with 28% of persons in NHANES III and 37% in the CSFII reporting use of a supplement containing SFA or assumed to contain SFA. This finding is consistent with other reports of dietary supplement use (14, 16), which emphasize the importance of determining folate intakes from all sources. For persons who reported supplement use, the percentage of SFA contributed by supplements was 68% for NHANES III participants and 70% for CSFII participants. For all survey participants, SFA from supplements accounted for 15% of SFA for NHANES III participants and 26% for CSFII participants.

TABLE 1
Comparison between folate contents prefortification (1996) and postfortification (1998) for selected foods reported in the Continuing Survey of Food Intakes by Individuals (CSFII)[1]

Food and CSFII food code	1996	1998
	μg/100 g	
Chicken nuggets, 24198740	11.0	29
Cheese pizza (thick crust), 58106230	18.8	60.2
Beef goulash with noodles, 27212150	8.5	27.2
Spaghetti with tomato sauce, 58132110	8.4	35.1
Cheeseburger on bun (plain), 27510210	17.9	52.5
Fried rice with shrimp, 58150510	11.8	47.5
Chocolate cupcake, 53108200	7.0	36.2
TWIX cookie bar, 91703200[2]	7.0	39.0

[1] Prefortification (1996) values reflect contents in the existing CSFII database (7); postfortification (1998) contents reflect modifications to the database based on recipe calculations and the amounts of folate required to be added to foods and ingredients per federal regulations.

[2] M&M/Mars, Maple Plains, MN.

In all cases, modifications made to the data used in this study resulted in estimated folate intakes that were considerably higher than intakes indicated by the data that was not modified. For comparison, the IOM report provided information on folate intakes without benefit of the modifications conducted here and listed a median intake of 297 μg for men aged 19–30 y in the CSFII (5th–95th percentiles: 148–584 μg) and 277 μg for men aged 19–30 y in NHANES III (5th–95th percentiles: 163–564 μg). These values were not DFEs and therefore could not be compared with the EAR of 320 μg DFE. The analyses using the modified data estimated a median intake of 546 μg (5th–95th percentiles: 299–1388 μg) for the same group in NHANES III and 615 μg (5th–95th percentiles: 226–1885 μg) for the same group in the CSFII. These folate intakes were estimated by using the SFA content multiplied by 1.7 (the bioavailability correction factor) and thus reflect DFEs. Although median intakes increased, ranges increased notably, in some cases 5-fold. The effect of data modification on intake distribution relative to the EAR is shown in **Figure 1**. Intake distributions on the basis of modified and unmodified data for men and women aged >19 y in NHANES III are compared. The IOM selected to feature these sex and age groups in their report (6), but modified data could not be provided. As a result of FDA data modification, the distribution shifted to the right and there is evidence of long "tails," suggesting that some persons had very high intakes of folate once the factors of fortification and bioavailability were accounted for. This distribution pattern on the basis of the modified CSFII data is similar to that on the basis of NHANES III data: 16% of men and 27% of women had an intake below the EAR and a "tail" extending to >3000 μg.

Means, medians, and ranges of intakes on the basis of modified data for the 6 sex and age groups are shown in **Table 2**. Both mean and median values exceeded the EAR and the RDA for each age group in each survey. Although the incorporation of intakes attributed to dietary supplement use and food fortification into the database was in part responsible for these higher intake estimates, the contribution of the bioavailability factor cannot be overlooked. The contribution of SFA to total folate intake, when calculated without use of the bioavailability correction factor for SFA, ranged from 45% to 58% of total folate intake in all groups in both surveys. When intakes were multiplied by the bioavailability correction factor of 1.7, SFA made a significant contribution to the overall estimates of intake. The percentage of children aged 1–5 y, females aged 11–19 y, women aged 20–49 y, men aged 45–69 y, women aged >70 y, and men aged >70 y meeting or surpassing the EAR were as follows: 95%, 88%, 85%, 92%, 82%, and 90%, respectively, in NHANES III and 97%, 77%, 75%, 83%, 67%, and 77%, respectively, in the CSFII.

The IOM report (6) recommends that women capable of becoming pregnant consume 400 μg SFA/d from foods and dietary supplements in addition to NF from foods. This was a special recommendation for this group and was established separately from the EAR and RDA for this same population. The partitioning of SFA intakes from total folate intakes in this study allowed us to estimate the extent to which this recommended intake was being met. Because the recommendation reflects SFA intakes and not DFEs, which account for the bioavailability correction and the contribution of NF, these intakes are lower than would be suggested by Table 2, which lists estimates of DFE intakes. In NHANES III, slightly >25% of women aged 20–49 y achieved this goal, and the percentage was lower in younger females (**Table 3**). The CSFII data showed the same pattern but a greater percentage of women aged 20–49 y consumed ≥400 μg SFA/d.

The IOM also established ULs for 5 age groups based on SFA intakes (6). SFA intakes from NHANES III and the CSFII compared with ULs for the 2 youngest age groups for which ULs were established are shown in **Figure 2**. These 2 groups had the most persons exceeding the UL for folate. The ULs for young children were established on the basis of body size and extrapolated from the estimates for adults; therefore, it was not surprising that the SFA intake of young children, who characteristically consume breakfast cereals, dietary supplements, and fortified foods such as noodles and pasta, exceeded the UL by the highest percentage. As established by the IOM, the ULs for persons aged 9–13 y, 14–18 y, and ≥19 y are 600, 800, and 1000 μg SFA/d, respectively. The analyses based on NHANES III data showed that for these same sex and age groups, ≈3%, 1%, and 3%, respectively, intakes exceeded the ULs. The percentages of children aged 1–5 y, females aged 11–19 y, women aged 20–49 y, men aged 45–69 y, women aged >70 y, and men aged >70 y exceeding the ULs in NHANES III were 26%, 3%, 5%, 1%, 0.5%, and 0.5%, respectively. The results were similar on the basis of CSFII data (not reported).

Before interpreting the results of these findings, we considered the potential sources of error in our study. Methods for determining the folate content of foods are problematic and generally tend to underestimate the amount of folate in food (17, 18). Recently, the importance of extensive digestion of food samples with enzymes capable of breaking down complex food matrixes has been recognized (19–22), but the development of a food folate database that relies on these or other optimized extraction techniques will require many years of work. Additionally, a recent study indicated that the analyzed content of folate in many foods was higher than indicated on food labels (22), probably because manufacturers want to ensure that their products are in compliance with regulations if singled out for review. Additionally, overages of folate are allowed, consistent with good manufacturing practices. Thus, if databases rely, even in part, on labeled values to estimate the folate content of foods, errors may be introduced. Moreover, it is likely that errors were introduced when the USDA modified the 1996 database to reflect the folate content of
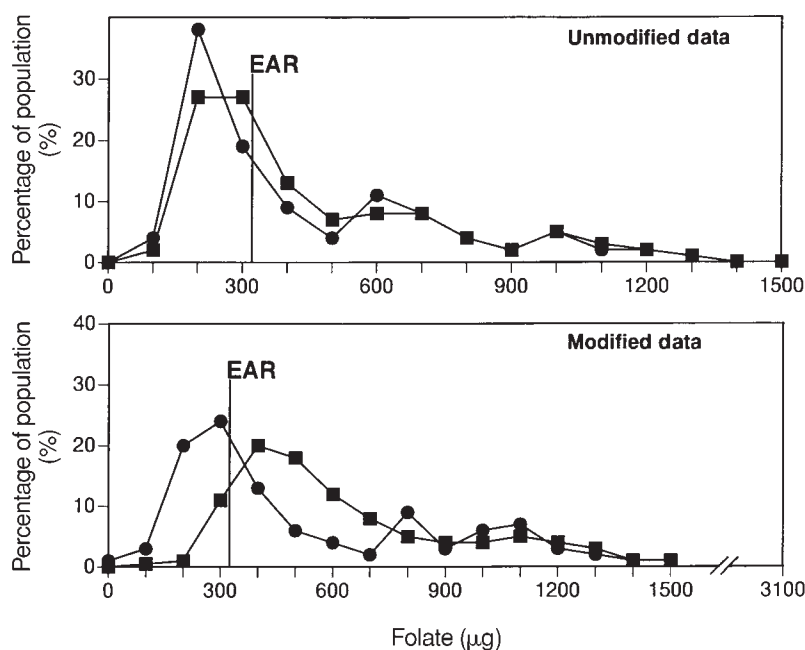
FIGURE 1. Comparison of the distribution of estimated folate intakes on the basis of modified and unmodified data relative to the estimated average requirement (EAR) in men (■) and women (●) aged 19–30 y represented in the third National Health and Nutrition Examination Survey (1988–1994; 8). Both the unmodified and modified data are expressed as micrograms; however, the modified data reflect micrograms expressed as dietary folate equivalents and reflect food fortification with folate, folate supplement use, as well as the bioavailability of synthetic folic acid.

foods because they added an amount of folate for each product that took into account the amount of NF in the food when estimating the amount that would be needed to meet specifications. The usual manufacturing practice, however, is to add the specified amount of SFA to the product regardless of the amount of NF in the product. Thus, it is likely that there are inaccuracies in the existing databases and, of course, these databases were the starting point for our study. However, these were the best data available at the time.

It is also well known that food consumption surveys typically underreport the amount of food consumed (23), which, in turn, contributes to an underestimation of nutrient intakes. Relative to intakes from dietary supplements, neither survey could provide the amount of folate actually consumed on the days of the survey, and broad assumptions were made for the CSFII. Additionally, data obtained in the 1986 National Health Interview Survey indicate that most, but not all, multivitamin supplements contain folate (14). Whether these estimates are biased toward an underestimation or overestimation of intakes from supplements is unknown.

Furthermore, the update procedure itself undoubtedly introduced some errors because we could not conduct a food-by-food analysis to determine folate contents in foods after fortification began; therefore, many assumptions were made. For example, the midpoint of the specified fortification ranges for regulated foods was input into the database when in fact the provisions allow both higher and lower values to be used. In addition, except for breakfast cereals, meal-replacement products, and infant formulas, we assumed that foods in the original 1996 database (ie, before fortification began) contained only NF. To the extent that manufacturers fortify foods other than those provided for by regulation, eg, peanut butter, this assumption would result in an underestimate of the contribution of SFA to the total diet.

We assumed that products such as breakfast cereals and infant formulas are more uniform in composition than they are likely to be, which may have led to both underestimations and overestimations of folate contents. Other sources of error may have arisen from the use of standard food recipes to estimate amounts of ingredients consumed. Moreover, there is uncertainty concerning the appropriateness and precise magnitude of the correction factor for the bioavailability of folate. The magnitude and direction of error that might result from these assumptions is difficult to assess. However, if all of the potential sources of error discussed above are considered, it is likely that we underestimated rather than overestimated folate intakes.

DISCUSSION

The potential sources of error in this study warrant caution relative to specific estimated folate intakes; however, the outcomes of our study are meaningful in several aspects.

First, the data strongly underscore the importance of accounting for the bioavailability factor, for food fortification, and for supplement use when estimating intakes. Although the specific effect on estimated intakes of NF in food compared with that of SFA added to foods or from dietary supplements is of interest, it was outside the scope of our study. Rather, the findings we report are for the purposes of monitoring total folate intakes to ensure a safe and adequate food supply. Furthermore, the extent to which updating the data changed the estimates of folate intake was important. The changes were striking, as confirmed by differences between estimated intakes in the IOM report and those resulting from the use of the same database after it was modified. The absolute nature of these differences cannot be known; however, the magnitude of the differences seen in this study points to

TABLE 2
Estimated folate intakes on the basis of NHANES III and CSFII data derived from food-consumption and food-composition data modified to reflect food fortification requirements, correction for bioavailablity of synthetic folic acid, and supplement use[1]

Age and sex group	EAR	RDA	NHANES III			CSFII		
			Mean	Median	Range[2]	Mean	Median	Range[2]
	μg DFE	μg DFE	μg DFE			μg DFE		
Children 1–5 y	120160	150200	548	400	117–1553	553	479	157–1364
Females 11–19 y	250330	300400	570	448	279–2170	574	437	169–1483
Women 20–49 y	320	400	718	455	262–2807	644	537	154–1565
Men 45–69 y	320	400	708	504	281–2118	718	588	202–1836
Women >70 y	320	400	638	441	259–1800	600	452	145–1498
Men >70 y	320	400	649	470	276–1765	644	519	176–1632

[1] NHANES III, third National Health and Nutrition Examination Survey (1988–1994; 8); CSFII, Continuing Survey of Food Intake by Individuals (1994–1996; 7); EAR, estimated average requirement; RDA, recommended dietary allowance (6); DFE, dietary folate equivalent.
[2] 5th–99th percentiles.

the urgent need to incorporate these components (ie, the higher bioavailability of SFA than of NF, the SFA content of foods resulting from fortification, and SFA intakes from dietary supplements) of folate intake estimation into available databases. Although the consistency of the findings between the 2 surveys used in our study is reassuring, there were differences in estimated intakes. The 1994–1996 CSFII and NHANES III were designed to allow compatibility and close comparison, but are nonetheless 2 separate surveys and were conducted by using somewhat different methods. It is possible, for example, that the difference in approaches for collecting data on dietary supplements may have accounted for some of the differences in total intake estimates when the 2 surveys were compared. In any case, current emphasis on folate intakes warrants efforts to better quantify folate intakes from all sources.

Second, within the limitations of the data, but given the overall likelihood that the data underestimated intakes, the outcomes suggest that total folate intakes of the US population, with some notable exceptions, compare favorably with the new IOM standards. On the other hand, the folate intakes of toddlers and young children may warrant close monitoring relative to the ULs. Conclusions about these folate intake estimates are tentative and require confirmation by using clinical measures and other more specific research. Furthermore, whereas a sizable proportion of the overall population appears to have adequate total folate intakes relative to the IOM standards, there was a subgroup for whom estimated intakes did not meet the EARs. For example, the percentage of persons in the 6 monitoring groups with intakes below the EARs ranged from 5% to 33% in the surveys used. Given the IOM definition of the EAR, the value estimated to meet the requirements of half the healthy individuals in a group, this is cause for further study.

Third, the considerable effort expended to distinguish between NF and SFA in the food-composition database was worthwhile, not only because it allowed for calculations of intakes as DFEs, but also because it provided, for the first time, an estimate of the extent to which the IOM recommendation of 400 μg SFA/d for females of childbearing age was being met. Our findings suggest that a considerable percentage of this population did not achieve this goal. This recommendation clearly constitutes a special challenge for health professionals and nutrition educators. Our findings, however, need to be assessed in the context of the IOM discussions concerning this recommendation.

The IOM report indicates that although the evidence is strong that the risk of having a fetus with an NTD decreases with increasing intakes of folate during the periconceptional period, this type of risk reduction was judged inappropriate for use as an indicator for setting the EAR for folate for females of childbearing age (6). As discussed in this report, the population at risk is females capable of becoming pregnant, but only those females who become pregnant benefit from an intervention aimed at reducing the risk of NTDs. According to the review of available data conducted by the IOM, the risk of NTDs in the US population is ≈1/1000 pregnancies. Furthermore, the critical period for prevention is very short. Thus, the IOM concluded that the definition of the EAR does not accommodate NTD prevention as an appropriate criterion for the EAR and RDA. Whereas the IOM did address this issue by recommending an intake of 400 μg SFA/d for females of childbearing age, they pointed out that there are still uncertainties about the relations among folate intakes, red blood cell folate concentrations, and NTD risk. Moreover, they noted uncertainty about the extent to which the effect of NF intakes on NTD risk varies from the effect of SFA intakes. The recommendation of 400 μg SFA/d from fortified foods, dietary supplements, or both for females of childbearing age is based on evidence that SFA offers a more protective effect against NTDs than does NF (6). However, the IOM suggested that it is conceivable that, if consumed in adequate quantities, NF can be as effective in reducing the risk of NTDs as is SFA. This issue is particularly intriguing given that we found a considerable number of females

TABLE 3
Percentage of females of childbearing age consuming specified amounts of synthetic folic acid[1]

Intake	NHANES III		CSFII	
	11–19 y	20–49 y	11–19 y	20–49 y
	%			
<100 μg/d	11	24	27	28
100–199 μg/d	55	37	16	20
200–299 μg/d	15	9	29	14
300–399 μg/d	5	4	7	7
≥400 μg/d	13	27	21	32

[1] Values may not add up to 100 because of rounding. NHANES III, third National Health and Nutrition Examination Survey (1988–1994; 8); CSFII, Continuing Survey of Food Intake by Individuals (1994–1996; 7).
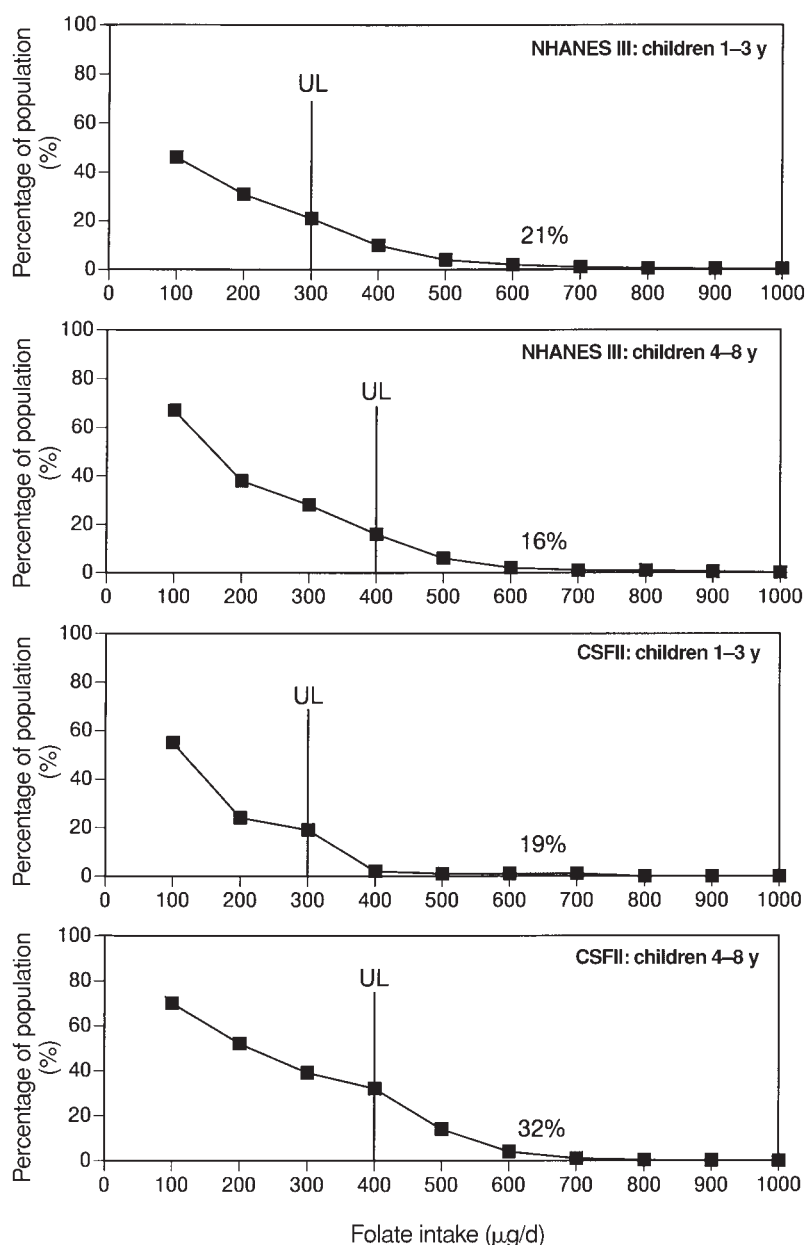
FIGURE 2. Comparisons of synthetic folic acid (SFA) intakes versus tolerable upper intake levels (ULs) for children aged 1–3 and 4–8 y represented in the third National Health and Nutrition Examination Survey (1988–1994; NHANES III; 8) and the Continuing Survey of Food Intakes by Individuals (1994–1996; CSFII; 7). Data are expressed as cumulative percentages and were modified to account for SFA intakes from food fortification and dietary supplements. The percentage shown within each panel is the percentage of the group exceeding the UL.

of childbearing age to have estimated intakes of SFA below the recommended intake of 400 μg/d, but also found that many were meeting or surpassing the EAR when estimated intakes were considered on the basis of DFEs.

We are aware of the interest in researching the relation between folate and homocysteine intakes and the risk of cardiovascular disease. However, the relevance of our data to this relation is unclear. Whereas the link between low blood homocysteine concentrations and adequate folate intakes is well established (24–26), the relation between low homocysteine intakes and the onset of cardiovascular disease is not known. The IOM reviewed the available findings on the relation between folate intakes and

risk of vascular disease and found them conflicting (10). The IOM report suggests that ongoing, prospective controlled intervention trails may help to elucidate the nature of this relation. There is evidence that the relation between dietary folate intakes and mean blood homocysteine concentrations is not linear, but apparently reaches a plateau at total folate intakes of >300 μg/d on the basis of data from several studies (6). A study on the incidence of myocardial infarction and cardiovascular disease in women that used prospective observational data suggested that risk reduction was greatest at median intakes between 158 and 217 μg/d, when adjusted to consider the intake of folate separately (27). These folate intakes, as well as the 300 μg value men-

tioned above, were not corrected for bioavailability and are thus not expressed as DFEs. For men aged 45–69 y in our study, the uncorrected median folate intake was 402 µg in NHANES III and 452 µg/d in the CSFII. For women aged 45–69 y, uncorrected median intakes were 352 µg in NHANES III and 377 µg/d in the CSFII. However, in the absence of more research, such comparisons cannot be interpreted reliably. Moreover, it must be recognized that the primary endpoint measure used by the IOM to establish the EAR for folate and, in turn, the RDA for folate, was red blood cell folate; plasma homocysteine was used as an ancillary indicator (6). In brief, the endpoint was not the risk of cardiovascular disease because available evidence was insufficient to allow the use of such a measure. Thus, a comparison of our estimated folate intakes with the EAR or RDA for folate to indicate the risk of cardiovascular disease is inappropriate.

Our estimated folate intakes offer some insight about safety. After considering general toxicity, reproductive and developmental effects, carcinogenicity, hypersensitivity, and interference with intestinal zinc absorption, the IOM concluded, in part due to lack of data, that the relation between folate and vitamin B-12 was the best criterion to use in establishing a UL for folate (6). It is well recognized that excessive intakes of folate may mask vitamin B-12 deficiency and perhaps delay its diagnosis; a delay in diagnosis could result in neurologic damage. It was for this reason that, historically, the addition of folate to the food supply was limited and the subject of considerable debate during the development of regulations to allow for folate fortification of foods (3, 4). In an earlier study focusing on folate fortification, the FDA highlighted the importance of implementing fortification in such a way as to ensure safe intakes for all age and sex groups at the high end of intake distribution curves, while at the same time increasing the intakes of target populations, such as females of childbearing age, at the low end of their intake distributions (13).

In our analyses, several very high folate intakes were reported, but only a small percentage of the population in the various age and sex groups exceeded the ULs. The exceptions were the groups consisting of children aged 1–3 y and 4–8 y. Although these high intakes should be considered in future monitoring efforts, vitamin B-12 deficiency is extremely rare in these young age groups. Nonetheless, although this fact might suggest that high folate intakes in children are not a major concern, relatively little is known about dietary imbalances or other adverse effects that may occur when folate intakes are excessively high. Thus, our findings may have significance in clinical settings. On the other hand, the elderly are at risk for vitamin B-12 deficiency. Although the analyses in our study suggest that folate intakes in this age group did not greatly exceed the ULs, monitoring should continue and observations should be interpreted in light of relevant clinical measures.

Finally, an increase in folate intakes among the target population of females of childbearing age while ensuring safe intakes for other populations is of concern. Although all folate intakes increased when the 1996 database was modified, the intakes of many women remained at the low end of the distribution range, whereas the high end of the distribution range increased considerably, especially among males. Further studies are needed to characterize the dietary practices of females of childbearing age who have low folate intakes to determine the most prudent options for improving their folate intakes without putting other groups within the population at risk of excessive folate intakes.

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