DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 172

[Docket No. FDA–2012–F–0480]

Food Additives Permitted for Direct Addition to Food for Human Consumption; Folic Acid

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA or we) is amending the food additive regulations to provide for the safe use of folic acid in corn masa flour. We are taking this action in response to a food additive petition filed jointly by Gruma Corporation, Spina Bifida Association, March of Dimes Foundation, American Academy of Pediatrics, Royal DSM N.V., and National Council of La Raza.

DATES: This rule is effective April 15, 2016. See section VIII for further information on the filing of objections. Submit either electronic or written objections and requests for a hearing by May 16, 2016. The Director of the Federal Register approves the incorporation by reference of certain publications listed in the rule as of April 15, 2016.

ADDRESSES: You may submit objections and requests for a hearing as follows:

Electronic Submissions

Submit electronic objections in the following way:

- *Federal eRulemaking Portal: http://www.regulations.gov.* Follow the instructions for submitting comments. Objections submitted electronically, including attachments, to *http://www.regulations.gov* will be posted to the docket unchanged. Because your objection will be made public, you are solely responsible for ensuring that your objection does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your objection, that information will be posted on *http://www.regulations.gov.*
- If you want to submit an objection with confidential information that you do not wish to be made available to the public, submit the objection as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand delivery/Courier (for written/paper submissions):* Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper objections submitted to the Division of Dockets Management, FDA will post your objection, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–2012–F–0480 for ''Food Additives Permitted for Direct Addition to Food for Human Consumption; Folic Acid.'' Received objections will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *http://www.regulations.gov* or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions—To submit an objection with confidential information that you do not wish to be made publicly available, submit your objections only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *http://www.regulations.gov.* Submit both copies to the Division of Dockets Management. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *http://www.fda.gov/regulatoryinformation/dockets/default.htm.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *http://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Judith Kidwell, Center for Food Safety and Applied Nutrition (HFS–265), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740–3835, 240–402–1071.

SUPPLEMENTARY INFORMATION:

I. Background

In a document published in the **Federal Register** on June 13, 2012 (77 FR 35317), we announced that Gruma Corporation, Spina Bifida Association, March of Dimes Foundation, American Academy of Pediatrics, Royal DSM N.V., and National Council of La Raza (the petitioners), c/o Alston & Bird, LLP, 950 F Street NW., Washington, DC 20004–1404, had jointly filed a food additive petition (FAP 2A4796). Subsequently, the March of Dimes Foundation informed us that Alston & Bird, LLP, was no longer representing the petitioners and that the March of Dimes Foundation would be the main contact for the petition. The address of the March of Dimes Foundation is 1401 K. St. NW., Suite 900A, Washington, DC 20005. The March of Dimes Foundation also informed us that Royal DSM N.V. no longer was affiliated with this petition. The petition proposed that we amend the food additive regulations in *§ 172.345 Folic acid (folacin)* (21 CFR 172.345) to provide for the addition of folic acid to corn masa flour (CMF) at levels not to exceed 0.7 milligrams (mg) per pound (lb) (154 micrograms (µg) folic acid/100 grams (g) CMF). The petition requested this fortification to increase the folic acid intake for U.S. women of childbearing age who regularly consume products made from CMF as a staple in their diet, including, in particular, women of Latin American descent (for example, Mexican Americans), to help reduce the incidence of neural tube defects (NTDs), which are birth defects affecting the spine, brain, and spinal cord. This final rule is a complete response to the petition.

Folic acid is the synthetic form of folate, an important B vitamin essential to fetal development and other body functions. (Folate is the form of the vitamin found naturally in food.) It is

well recognized that pregnant women with folate deficiency have a higher risk of giving birth to infants affected with NTDs, specifically spina bifida and anencephaly. To reduce the incidence of NTDs, the U.S. Public Health Service (PHS) and Centers for Disease Control and Prevention (CDC) recommend that all women of childbearing age consume 0.4 mg (400 µg) of folic acid daily, in addition to the consumption of naturally occurring folate from the diet. In response to this recommendation, FDA began a mandatory folic acid fortification program in 1998, requiring folic acid to be added to enriched cereal grains and cereal grain products that have a standard of identity under 21 CFR parts 136, 137, and 139 at levels ranging from 0.43 mg to 1.4 mg/lb of the finished product (61 FR 8781, March 5, 1996) (1996 final rule).

Fortification with folic acid was required for enriched cereal-grain products that already had standards of identity at the time the 1996 final rule went into effect on January 1, 1998. (Standards of identity are FDA regulations that define a given food product, its name, and ingredients that must be used, or may be used, in the manufacture of the food. They were created to maintain the integrity of food products and to ensure that foods meet buyers' expectations.) Many foods do not have standards of identity, including CMF. The amounts of folic acid required in enriched cereal-grain products (bread, rolls, and buns; wheat flours; corn meals; farina; rice; and macaroni and noodle products) were specifically chosen to increase daily folic acid consumption for women of childbearing age without consumers in the general population exceeding established safe levels. In addition to mandatory fortification of these foods, folic acid may voluntarily be added at specified levels in breakfast cereal, corn grits, meal replacement products, infant formula, foods for special dietary uses, and medical foods (§ 172.345).

To support the safety of the proposed uses of folic acid, the petitioners submitted dietary exposure estimates of folic acid from the proposed use in CMF, as well as all dietary sources from currently permitted uses of folic acid at levels reported in the U.S. Department of Agriculture's Food and Nutrient Database for Dietary Studies, which represents the most current database for nutrient composition in foods, including folic acid found in fortified foods. The petitioners included intake from dietary supplements reported in the National Health and Nutrition Examination Survey (NHANES) 2001–2008 datasets in their estimates. They reported exposure estimates at the median for several population groups stratified by gender, race/ethnicity, and age. The petitioners also reported estimates of the percentage of the different population groups whose intake estimates exceeded the Tolerable Upper Intake Levels (ULs) established by the Institute of Medicine (IOM) for folic acid. The IOM UL is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. Generally, the UL represents total intake from conventional food, water and dietary supplements.

Additionally, the petitioners included over 300 scientific literature reports on folic acid published through 2012. The majority of these references concern epidemiological studies that investigated associations between folate status or folic acid intake levels and health outcomes. The petitioners included some animal studies, most of which focused on the mechanisms of action of folic acid.

The petitioners also provided safety information from the 1998 IOM Dietary Reference Intake (DRI) report on folic acid (Ref. 1). In the 1998 report, the IOM established Recommended Dietary Allowances (RDA) for folate and ULs for folic acid. The petitioners also presented safety reviews and data evaluations on folic acid that were conducted by various national health agencies: United Kingdom (UK) Scientific Advisory Committee on Nutrition (Refs. 2 and 3); Food Standards Australia New Zealand (Refs. 4 and 5); Food Safety Authority Ireland (Refs. 6 and 7); and Health Council of the Netherlands (Refs. 8 and 9). These health agencies conducted thorough reviews of scientific papers, published through 2009, on the potential health outcomes of folic acid intake.

II. Evaluation of Safety

To establish with reasonable certainty that a food additive is not harmful under its intended conditions of use, we consider the projected human dietary exposure to the additive, toxicological data on the additive, and other relevant information (such as published literature) available to us. We compare an individual's estimated daily intake (EDI) of the additive from all food sources, including dietary supplements, to an acceptable intake level established by toxicological data. The EDI is determined by projections based on the amount of the additive proposed for use in particular foods and on data regarding the amount consumed from all food sources of the additive. We chose the 95th percentile of exposure as a conservative representation of habitual intake of folic acid by ''high'' consumers.

As part of our safety evaluation of folic acid fortification in CMF, we conducted an updated literature search for relevant scientific publications from 1998 through 2015. Results of our updated literature search confirmed that the petitioners adequately covered the available published relevant safety information on folic acid, and we found only a few additional relevant publications in our search.

A. Acceptable Daily Intake Level for Folic Acid

In the 1993 proposed rule (58 FR 53305, October 14, 1993) and the 1996 final rule for mandatory folic acid fortification in certain foods, we adopted a safe upper limit of 1 mg per day (d) of total folate intake for the general population. This decision was based on the recommendation of the PHS that all women of childbearing age consume 0.4 mg (400 µg) of folic acid daily to reduce the risk of NTDs. The PHS further reported that total folate and folic acid consumption should be maintained at levels under 1 mg/d because high folic acid intakes could mask the signs of pernicious anemia thereby complicating the diagnosis of vitamin B_{12} deficiency (Ref. 10).

In its 1998 safety assessment, the IOM concluded that, based on the weight of the limited but suggestive evidence, excessive folic acid intake may precipitate or exacerbate neuropathy in vitamin B_{12}-deficient individuals and justifies the selection of this endpoint as the critical endpoint for the development of a UL (Ref. 1). In its dose-response analysis, the IOM evaluated case reports of patients with vitamin B_{12} deficiency who developed or demonstrated a progression of neurological complications and who had been treated with oral administrations of folic acid. The data from this analysis did not provide a no-observed-adverse-effect level. Instead, the IOM established a lowest-observed-adverse-effect level (LOAEL) at the 5 mg/d dose based on the number of reported cases of neurological deterioration at certain doses of folic acid.

An uncertainty factor of 5 was applied to the LOAEL, establishing a UL of 1 mg/d for adults 19 years and older. This UL was adjusted for children and adolescents on the basis of relative metabolic body weights and the resulting values were rounded down. For children 1 to 3 years of age, the IOM established a UL of 300 µg/p/d; for

children 4 to 8 years of age, the IOM established a UL of 400 μg/p/d; for children 9 to 13 years of age, the IOM established a UL of 600 μg/p/d; for children 14 to 18 years of age; the IOM established a UL of 800 μg/p/d. The IOM determined that a UL for infants could not be established because of a lack of data on adverse effects in this age group and concerns about the infant's ability to handle excess amounts of folic acid (Ref. 1).

Folic acid intake of 1 mg/d is widely recognized by different international bodies as the safe or tolerable UL for adults. This UL has been used by different countries in the evaluation of their fortification policies, including Australia and New Zealand, the UK, Ireland, and the Netherlands. In a reevaluation in 2008, the European Food Safety Authority (EFSA) concluded that the evidence and dose-response information on other health endpoints were not sufficient to support establishing a different UL (Ref. 11). We reviewed available updated safety and epidemiological studies published after the publication of the 1998 IOM report and found no scientific concerns that would justify revision of the current IOM ULs (Ref. 12).

B. Estimated Daily Intake for Folic Acid

The petitioners provided dietary intake estimates for folic acid from the proposed use in CMF and from all current dietary sources, including dietary supplements. In calculating exposure to folic acid from foods, the petitioners used food consumption data from the NHANES 2001–2002 dataset, which is based on one 24-hour dietary recall survey, and from the NHANES 2003–2008 dataset, which is based on two 24-hour dietary recall surveys. We note that estimates of nutrient exposure based on a single day of consumption do not adequately account for within-person variation in intake and can lead to underestimation of population variance, thereby underestimating the exposure (Ref. 13).

In modeling folic acid exposure from fortified CMF, the petitioners identified 103 foods as containing CMF. The petitioners considered CMF as a non-whole grain and used a proxy of non-whole grains to estimate the amount of CMF in each identified food item based on the number of ''ounce equivalents'' of non-whole grains present in each food item. The petitioners' estimate indirectly determined the proportion of CMF present in a grain product; however, we typically use the weight (*e.g.,* gram, milligram) percentage of CMF in each food item for dietary exposure assessments. Based on our review, we identified 118 foods currently available on the market that contain CMF as an ingredient. For these reasons, we conducted our own exposure estimate to folic acid for the overall U.S. population 1 year of age and older, excluding pregnant women, and various population subgroups stratified by age, gender, and race/ethnicity, and for various percentiles of intake.

Specifically, we calculated total dietary exposure estimates for folic acid that included exposure to folic acid from currently fortified foods, dietary supplements, and the proposed fortification in CMF. We used consumption data from the NHANES 2003–2008 database and a method for estimating usual dietary intakes of foods and nutrients developed by the National Cancer Institute (*http://appliedresearch.cancer.gov/diet/usualintakes/method.html.*). Naturally occurring food folate was not included in the total folic acid exposure estimates because the IOM ULs were established for synthetic folic acid only.

The NHANES survey has five race/ethnicity codes in its demographic data file. According to NHANES, this race/ethnicity variable was derived from responses to the survey questions on race and Hispanic origin. Respondents who self-identified as ''Mexican American'' were coded as such (Mexican American) regardless of their other race-ethnicity identities. For respondents who self-identified as ''Hispanic'' but not as ''Mexican American'' the race/ethnicity was categorized as ''Other Hispanic.'' Non-Hispanic respondents were categorized based on their self-reported races: Non-Hispanic White, non-Hispanic Black, and other non-Hispanic races including non-Hispanic multiracial (Ref. 14).

Using a statistical analysis software program (SAS®), we calculated exposure to folic acid from the proposed use in CMF by adding the daily exposure to folic acid from conventional foods to the average daily exposure of folic acid from dietary supplements. We used this software program to determine distributions of exposure (*i.e.,* means, medians, percentiles) and the percentage of individuals with usual daily total folic acid whose exposure exceeded the UL (1,000 μg or other age-specific ULs). We estimated exposure for the same population subgroups for which the petitioners reported exposure in their submission in 8 age groups (1 to 3 years, 4 to 8 years, 9 to 13 years, 14 to 18 years, 19 to 30 years, 31 to 50 years, 51 to 70 years, and 71+ years), 2 gender groups (male and female), and 3 race/ethnicity subgroups (Non-Hispanic (NH) White, NH Black, and Mexican American).

We estimated exposure for two scenarios. The first estimate represented a background (current) cumulative exposure of folic acid that included currently permitted uses of folic acid in conventional foods and dietary supplement use. The second estimate represented a modeled cumulative exposure of folic acid that included currently permitted uses of folic acid in conventional food, dietary supplement use, and the proposed use in CMF and products made from CMF, such as tortillas and tortilla chips (modeled). For the second scenario, we assumed a fortification level of 140 μg folic acid/100 g CMF. This fortification level was chosen to account for the petitioners' estimates of loss of folic acid during processing and storage (Ref. 13). Exposure estimates at the 95th percentile represent ''high'' consumers of folic acid and provide a conservative estimate of exposure.

Table 1 summarizes our exposure estimates for the overall U.S. population for each of the scenarios at the median and 95th percentile of intake with the number of people represented in each age group in the NHANES survey indicated in the table:

TABLE 1—ESTIMATED CUMULATIVE FOLIC ACID INTAKE FOR THE U.S. POPULATION

Age (years)	NHANES (n)	IOM UL (μg/d)	Median intake (μg/d)		95th percentile intake (μg/d)	
			Current	Modeled	Current	Modeled
All (1+ years)	22717	.....	231	244	765	775
1–3	1911	300	156	160	493	504
4–8	2071	400	255	267	618	633
9–13	2608	600	240	257	622	628

TABLE 1—ESTIMATED CUMULATIVE FOLIC ACID INTAKE FOR THE U.S. POPULATION—Continued

Age (years)	NHANES (n)	IOM UL (μg/d)	Median intake (μg/d)		95th percentile intake (μg/d)	
			Current	Modeled	Current	Modeled
14–18	3038	800	239	252	646	658
19–30	2608	1000	229	247	744	758
31–50	4118	1000	219	237	769	783
51–70	3861	1000	266	271	919	927
71+	2302	1000	255	258	836	840

The median intakes for all age groups are well below the respective ULs. For children (1 to 13 years of age), the current 95th percentile folic acid intake estimates exceed their respective age-corresponding IOM ULs. We estimate that the addition of folic acid in CMF at the proposed level would result in a small additional increase of up to 15 μg/d of folic acid intake for this population group. Our exposure estimates at the 95th percentile for the adult population 19 years of age and older and for children 14 to 18 years of age did not exceed the IOM UL for either exposure scenario.

Results from our exposure assessment demonstrate that CMF fortification would result in a slight increase in total folic acid exposure among the U.S. population. Further, as shown in Table 2, the proposed CMF fortification would result in a greater proportional increase in the median usual total folic acid exposure among Mexican Americans than among the NH White and NH Black populations. The estimated current median usual total folic acid intake of Mexican Americans is lower than that of the NH White population. Intake estimates that include the proposed CMF fortification show a larger increase for the median usual total folic acid exposure of Mexican Americans compared to the other groups, but the median intake estimate for Mexican Americans remains lower than that of NH Whites.

TABLE 2—USUAL TOTAL FOLIC ACID INTAKE ESTIMATES FOR THE U.S. POPULATION BY RACE/ETHNICITY

Race/Ethnicity	Exposure (median/95th percentile)	
	Current (μg/d)	Modeled (μg/d)
All	231/765	244/775
Non-Hispanic White	253/820	261/834
Non-Hispanic Black	181/597	191/608
Mexican American	187/588	228/622

In addition, for non-pregnant women of childbearing age (15 to 44 years), our exposure estimates show an increase in the median usual total folic acid intake of Mexican American women from 164 μg/d to 206 μg/d when intake from fortified CMF was included in the analysis. Our exposure estimates also show an increase in folic acid intake among NH White women (214 μg/d to 221 μg/d) and NH Black women (168 μg/d to 179 μg/d) from the petitioned use of folic acid in CMF (Ref. 13).

Dietary Supplements

Because the use of supplements containing folic acid is a contributing factor to total exposure, we calculated usual folic acid intake for supplement non-users (*i.e.,* those who did not report consuming supplements containing folic acid in the NHANES Dietary Supplement Questionnaire) and supplement users (*i.e.,* those who reported consuming supplements containing folic acid).

As shown in Table 3, among dietary supplement users who consume CMF products, the 95th percentile total folic acid intake estimates for all age groups exceeded the respective age-corresponding ULs, except for the population 71 years of age and older.

TABLE 3—ESTIMATED TOTAL FOLIC ACID INTAKE AMONG CORN MASA CONSUMERS WHO ARE DIETARY SUPPLEMENT USERS AND NON-USERS

Dietary supplement usage	Age (years)	NHANES (n)	IOM UL (μg/d)	95th percentile intake (μg/d)		Amount of folic acid intake exceeding the UL (95th percentile minus UL) (μg/d)	
				Current	Modeled	Current	Modeled
Users	1–3	362	300	552	575	252	275
	4–8	626	400	774	811	374	411
	9–13	444	600	699	724	99	124
	14–18	361	800	998	1051	198	251
	19–30	536	1000	1091	1135	91	135
	31–50	1161	1000	1107	1130	107	130
	51–70	1482	1000	1133	1148	133	148
	71+	947	1000	889	866	0	0
Non-users	1–3	655	300	259	287	0	0

TABLE 3—ESTIMATED TOTAL FOLIC ACID INTAKE AMONG CORN MASA CONSUMERS WHO ARE DIETARY SUPPLEMENT USERS AND NON-USERS—Continued

Dietary supplement usage	Age (years)	NHANES (n)	IOM UL (μg/d)	95th percentile intake (μg/d)		Amount of folic acid intake exceeding the UL (95th percentile minus UL) (μg/d)	
				Current	Modeled	Current	Modeled
	4–8	830	400	357	388	0	0
	9–13	1086	600	450	489	0	0
	14–18	1239	800	457	510	0	0
	19–30	862	1000	344	400	0	0
	31–50	1122	1000	329	389	0	0
	51–70	675	1000	312	354	0	0
	71+	258	1000	413	419	0	0

For the 51 to 70 year age group, exposure at the 95th percentile was estimated to be 1133 μg/d, representing 113 μg/d more than the adult UL of 1 mg/d (1000 μg/d). CMF fortification would further increase the 95th percentile intake by 15 μg/d, resulting in an intake estimated to be 1148 μg/d, which is 148 μg/d more than the UL.

In contrast, CMF consumers who are not dietary supplement users had considerably lower folic acid exposure estimates compared to the supplement users. The 95th percentile folic acid intakes for all dietary supplement non-user age groups did not exceed their respective age-corresponding IOM ULs. While the proposed folic acid CMF fortification will increase folic acid intakes in these individuals, their modeled 95th percentile folic acid intakes remain below their respective age-corresponding ULs.

The population group of users of dietary supplements with the highest percentile exceeding the UL for folic acid was children 1 to 8 years of age. For this population, exposure estimates exceed the age-specific ULs whether consumption of fortified CMF was included in the estimate or not (Ref. 13). Children are more likely than adults to exceed their age-specific UL because of their higher consumption of food and drink on a body weight basis as compared to adults. Another reason is the lower UL values established for children. We note that the ULs for children were not based on adverse effects, but extrapolated from the adult UL.

C. Safety of the Petitioned Uses of Folic Acid

In our safety review, we considered several potential health effects of folic acid intake that the petitioners reported in their submission. Specifically, these health effects include:

- Masking vitamin B_{12} deficiency;
- Direct effects on vitamin B_{12} deficiency-related neurological complications and cognitive decline;
- Cancer;
- Effects of prenatal exposure on childhood health outcomes;
- Hypersensitivity;
- Reproductive effects; and
- Folic acid-drug interaction.

Of these health effects, our review found suggestive evidence for masking of vitamin B_{12} deficiency and exacerbation of vitamin B_{12} deficiency-related neurological complications and cognitive decline. The most at-risk population for both of these potential health effects is the population 50 years of age and older. For the other health effects, the overall evidence is unclear and could not be substantiated based on the available evidence (Ref. 12).

1. Masking Effect of Folic Acid on Vitamin B_{12} Deficiency

We reviewed data from clinical case reports from vitamin B_{12} deficient patients and found that masking cases were mostly associated with pharmacological doses of folic acid (greater than 5 mg/d). There was no information in the reports to identify the lowest level of folic acid associated with the masking effect. For populations with dietary exposure to folic acid, epidemiological studies have shown mixed results and study design limitations. In a recent study in which data from the NHANES 1991–1994 (pre-mandatory fortification in the United States) and 2001–2006 (post-mandatory fortification) surveys were compared, the prevalence of low vitamin B_{12} status in the absence of megaloblastic anemia or macrocytosis among adults 50 years of age and older did not increase after fortification (Ref. 15). The masking effect of folic acid has been reviewed by other regulatory authorities (Refs. 2 to 9). We agree with their conclusions that folic acid intake up to the UL of 1 mg/d is not likely to mask vitamin B_{12} deficiency. Additionally, current medical practice does not rely primarily on the hematological index to screen for vitamin B_{12} deficiency (Refs. 16 to 18). Currently, the recommended testing for vitamin B_{12} deficiency includes analyzing for serum levels of vitamin B_{12} and of the metabolites, methylmalonic acid and homocysteine. Based on our exposure estimates and the incremental increase in estimated exposure from the proposed use of folic acid in CMF, we conclude that the CMF fortification at the proposed level is not likely to increase the risk of masking vitamin B_{12} deficiency, and that the risk of the masking effect from current and proposed levels of dietary folic acid intake is low (Ref. 12).

2. Direct Effects of Folic Acid on Vitamin B_{12} Deficiency-Related Neurological Complications and Cognitive Decline

a. *Accelerating or exacerbating neurological complications.* In addition to the indirect masking effect of folic acid, there have been concerns that excess folic acid also may directly accelerate or exacerbate B_{12} deficiency-related neurological complications such as neuropathy. These endpoints were evaluated by IOM to determine the folic acid UL. In reviewing the historical clinical cases of neuropathy related to vitamin B_{12} deficiency, we noted that the rate of disease progression varied significantly among vitamin B_{12}-deficient patients, regardless of folic acid treatment. Because of the limited number of recorded cases, the large variability among patients at clinical presentation, and no new evidence presented after the IOM evaluation, the evidence remains suggestive as IOM stated in 1998. A definitive conclusion cannot be determined in this review whether folic acid directly enhances or worsens B_{12} deficiency-related neuropathy.

The potential neurological effects of high folic acid intake in children and women of childbearing age have not been thoroughly studied. However, because vitamin B_{12} deficiency is rare in these two populations in the United States (Ref. 19), the public health risk of this effect associated with increased exposure from folic acid fortification of CMF is likely to be insignificant.

b. *Cognitive decline among the population group ages 50 years and older.* Acceleration of cognitive decline among individuals who are vitamin B_{12}-deficient is a potential adverse health effect if undetected because of high folic acid intake. The most at-risk population for this adverse effect are consumers 50 years and older who have total folic acid intake higher than the UL. As described previously, people 50 years of age and older are unlikely to have total folic acid intake higher than the UL unless they use dietary supplements. According to an analysis in 2007, most multivitamins for seniors that contain folic acid also contain vitamin B_{12} (Ref. 20). Therefore, unless their vitamin B_{12} absorption is severely impaired due to certain diseases, individuals in this age group who have total folic acid higher than the UL are unlikely to have vitamin B_{12} deficiency, and thus are not at risk for this effect. Therefore, we conclude that cognitive health risks are not likely to be an issue for this sensitive population as a result of the petitioned use of folic acid in CMF (Ref. 12).

3. Metabolic Fate of Folic Acid

Folic acid is a water soluble vitamin that is quickly absorbed by the body. In humans, the bioavailability of folic acid is about 85 percent in fortified foods (Ref. 1). To be used as a methyl group donor, it must first be converted to dihydrofolate (DHF) and then tetrahydrofolate (THF) by the liver enzyme dihydrofolate reductase (DHFR). Evidence has shown that the activity of DHFR in humans is extremely low in comparison to that in rats; highly variable due to genetic polymorphism; and may become saturated when folic acid is consumed at levels higher than the 1 mg/d (Ref. 21). In addition, unlike DHF, folic acid is a poor substrate of DHFR, making the first step of metabolism rate-limiting (Ref. 22).

Upon conversion, THF is distributed in all body tissues. Excretion is the main elimination route of folic acid. In response to normal intake from food, the majority of folate is effectively reabsorbed in the kidney proximal tubules and little or no folate is lost in the urine (Ref. 22). Following oral administration of single 0.1 mg to 0.2 mg doses of folic acid in healthy adults, only a trace amount appears in urine. However, after doses of about 2.5 mg to 5 mg folic acid, about 50 percent is excreted in urine as a result of exceeded renal capacity for reabsorption (Refs. 22 and 23). Therefore, a significant amount of folic acid can be excreted from urine when the renal capacity for reabsorption is saturated by high intake, eliminating excess folic acid (Refs. 22 and 24).

4. Conclusions on the Potential Adverse Health Outcomes From High Intakes of Folic Acid

There is some evidence linking two potential adverse health outcomes with high folic acid intake in adults: (1) Masking vitamin B_{12} deficiency and (2) accelerating or exacerbating neurological complications and cognitive decline among those who are vitamin B_{12} deficient.

For both of these adverse health outcomes, the most at-risk population is individuals 50 years of age and older who have total folic acid intake higher than the UL. According to the results from our exposure assessment, these individuals primarily are dietary supplement users. The NHANES 1999–2002 data have established that, among the 60 years of age and older population in the United States, about 25 percent have low vitamin B_{12} status. Because about 10 to 30 percent of the population 50 years and older have decreased absorption of food-bound vitamin B_{12}, the IOM DRI report recommends that individuals 50 years of age and older obtain most of their vitamin B_{12} RDA, (2.4 µg/d) from vitamin B_{12}-fortified foods or supplements (Ref. 1). Since most multivitamins for seniors contain both folic acid and vitamin B_{12} (Ref. 20), their risk for vitamin B_{12} deficiency should be low, unless their vitamin B_{12} absorption is severely impaired due to certain diseases. In addition, because the currently recommended medical practice in the United States does not rely primarily on the hematological index to screen for vitamin B_{12} deficiency but rather serum B_{12} metabolites, the masking effect is less likely. Therefore, we conclude that these health risks (vitamin B_{12} masking and exacerbating neurological deterioration) are not likely to be an issue for this population as a result of the petitioned use of folic acid in CMF.

For other potential health outcomes, such as promoting the progression of established neoplasms, childhood hypersensitivity and reproductive outcomes, the evidence is not clear but suggests further study. There may be other, as-yet unidentified potential adverse effects of high folic acid intake in children and further study is warranted. However, as previously discussed, allowing folic acid in CMF is only projected to result in a slight increase for children 1 to 13 years and 14 to 18 years of age at the 95th percentile of folic acid intake, such that there is only a marginal increase in exposure beyond the current intake levels for children.

5. Safety and Risk Characterization for Folic Acid

Based on the data reviewed in this safety and risk assessment on folic acid, there was no definitive association of adverse effects of folic acid at the noted levels of folic acid exposure. We do not consider that any of the intake estimates in excess of the UL in this evaluation would cause an adverse health impact on any of the population subgroups because of the following reasons:

- The increase in exposure to folic acid for the studied populations from CMF fortification is small other than for Mexican Americans. For Mexican Americans, the increase in exposure is significantly larger but the resultant exposure levels are still below the levels for the general population.
- The ULs were calculated using a five-fold uncertainty factor, which is approximately twice that used for other B vitamins, providing an additional margin of safety (Ref. 12).
- The risk of masking vitamin B_{12} deficiency and related neurological complications from the estimated intake levels of folic acid is low because the most at-risk population to these health outcomes are individuals 50 years of age and older and most multivitamins for seniors that contain folic acid also contain vitamin B_{12}. Additionally, current medical practice does not rely primarily on the hematological index to screen for vitamin B_{12} deficiency but rather serum testing for vitamin B_{12} and its metabolites, making the masking effect less likely.
- The metabolic activation of folic acid by the enzyme DHFR is slow in humans and may be saturated at doses higher than 1 mg/d.
- Unmetabolized folic acid (UMFA) has no known biological function as a methyl group donor in DNA synthesis and methylation. To become active, folic acid must be reduced to THF. Excess levels of folic acid are unable to completely convert to its active form resulting in circulating UMFA. Currently there is no consistent evidence of adverse health effects causatively associated with circulating UMFA.
- Folic acid is a water-soluble vitamin. A significant amount of folic

acid is excreted from urine when the renal capacity for reabsorption is saturated by high intake, eliminating excess folic acid.

- FDA's modeled intake estimates for folic acid in CMF are conservative in that they assume all CMF will be fortified with folic acid at the maximum permitted level and that manufacturing and storage losses would result in folic acid levels of 140 µg/100 g in CMF as consumed.

III. Incorporation by Reference

FDA is incorporating by reference the Food Chemicals Codex (FCC), 9th ed. (updated through Third Supplement, effective December 1, 2015), pp. 495–496 (the most current edition), which was approved by the Office of the **Federal Register**. You may obtain a copy of the material from the United States Pharmacopeial Convention, 12601 Twinbrook Pkwy., Rockville, MD 20852, 1–800–227–8772, *http://www.usp.org/.*

The FCC is a compendium of internationally recognized standards for the purity and identity of food ingredients. Because the current regulation for the use of folic acid in food (§ 172.345) indicates that the additive must meet the specifications in the FCC, we are amending the regulation to provide for the most current edition.

IV. Conclusion

Based on all data relevant to folic acid that we reviewed, we conclude that the petitioned use of folic acid in CMF at a level not to exceed 0.7 mg folic acid per lb. CMF is safe. Consequently, we are amending the food additive regulations as set forth in this document. Additionally, the current regulation for the use of folic acid in food (§ 172.345) indicates that the additive must meet the specifications in the FCC, 7th Edition (FCC 7). The more current FCC is the 9th Edition (FCC 9). Because the specifications for folic acid in FCC 9 are identical to those in FCC 7, we are amending § 172.345 by adopting the specifications for folic acid in FCC 9 in place of FCC 7.

V. Public Disclosure

In accordance with § 171.1(h) (21 CFR 171.1(h)), the petition and the documents that we considered and relied upon in reaching our decision to approve the petition will be made available for public disclosure (see **FOR FURTHER INFORMATION CONTACT**). As provided in § 171.1(h), we will delete from the documents any materials that are not available for public disclosure.

VI. Analysis of Environmental Impacts

We previously considered the environmental effects of this rule, as stated in the June 13, 2012, **Federal Register** notice of petition for FAP 2A4796 (77 FR 35317). We stated that we had determined, under 21 CFR 25.32(k), that this action ''is of a type that does not individually or cumulatively have a significant effect on the human environment'' such that neither an environmental assessment nor an environmental impact statement is required. We have not received any new information or comments that would affect our previous determination.

VII. Paperwork Reduction Act of 1995

This final rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VIII. Objections

If you will be adversely affected by one or more provisions of this regulation, you may file with the Division of Dockets Management (see **ADDRESSES**) either electronic or written objections. You must separately number each objection, and within each numbered objection you must specify with particularity the provision(s) to which you object, and the grounds for your objection. Within each numbered objection, you must specifically state whether you are requesting a hearing on the particular provision that you specify in that numbered objection. If you do not request a hearing for any particular objection, you waive the right to a hearing on that objection. If you request a hearing, your objection must include a detailed description and analysis of the specific factual information you intend to present in support of the objection in the event that a hearing is held. If you do not include such a description and analysis for any particular objection, you waive the right to a hearing on the objection.

Any objections received in response to the regulation may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at *http://www.regulations.gov.*

IX. Section 301(*ll*) of the Federal Food, Drug, and Cosmetic Act

Our review of this petition was limited to section 409 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 348). This final rule is not a statement regarding compliance with other sections of the FD&C Act. For example, section 301(*ll*) of the FD&C Act (21 U.S.C. 331(*ll*)) prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FD&C Act (21 U.S.C. 355), a biological product licensed under section 351 of the Public Health Service Act (42 U.S.C. 262), or a drug or biological product for which substantial clinical investigations have been instituted and their existence has been made public, unless one of the exemptions in section 301(*ll*)(1) to (*ll*)(4) of the FD&C Act applies. In our review of this petition, FDA did not consider whether section 301(*ll*) of the FD&C Act or any of its exemptions apply to food containing this additive. Accordingly, this final rule should not be construed to be a statement that a food containing this additive, if introduced or delivered for introduction into interstate commerce, would not violate section 301(*ll*) of the FD&C Act. Furthermore, this language is included in all food additive final rules and therefore should not be construed to be a statement of the likelihood that section 301(*ll*) of the FD&C Act applies.

X. References

The following references marked with an asterisk (*) are on display at the Division of Dockets Management (see **ADDRESSES**), under Docket No. FDA–2012–F–0480, and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday, they also are available electronically at *http://www.regulations.gov.* References without asterisks are not on display; they are available as published articles and books.

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*2. Scientific Advisory Committee on Nutrition (SACN), 2006. ''Folate and Disease Prevention,'' London.
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*5. FSANZ, 2009. ''Mandatory Folic Acid Fortification and Health Outcomes.''
*6. Food Safety Authority of Ireland (FSAI), 2006. ''Report of the National Committee on Folic Acid Food Fortification.''
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Food Fortification to the Department of Health and Children.''
*8. GR Health Council of the Netherlands (HCN), 2000. ''Risks of Folic Acid Fortification.'' The Hague, Health Council of the Netherlands 2000/21.
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*11. EFSA, 2009. Report prepared by the EFSA Scientific Cooperation Working Group on ''Analysis of Risks and Benefits of Fortification of Food with Folic A.''
*12. Memorandum from J. Zang, Toxicology Team, Division of Petition Review, to J. Kidwell, Division of Petition Review, March 23, 2016.
*13. Memorandum from H. Lee, Chemistry Review Group, Division of Petition Review, to J. Kidwell, Regulatory Group I, Division of Petition Review, April 2, 2014.
14. National Health and Nutrition Examination Survey 2007–2008 Data Documentation, Codebook, and Frequencies, CDC, 2009. Available at: *http://wwwn.cdc.gov/nchs/nhanes/search/nhanes07_08.aspx* (accessed April 1, 2016).
15. Qi, Y.P., A.N. Do, H.C. Hamner, C.M. Pfeiffer, et al., 2014. ''The Prevalence of Low Serum Vitamin B-12 Status in the Absence of Anemia or Macrocytosis Did Not Increase Among Older U.S. Adults after Mandatory Folic Acid Fortification.'' *The Journal of Nutrition* 144, 170–176.
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17. Stabler, S.P., 2013. ''Clinical Practice. Vitamin B_{12} Deficiency.'' *New England Journal of Medicine* 368(2): 149–160.
18. Hunt A., D. Harrington, and S. Robinson, 2014. ''Vitamin B_{12} Deficiency.'' *British Medical Journal* 349: g5226.
19. Wright J.D., K. Bialostosky, E.W. Gunter, M.D. Carroll, et al., 1998. ''Blood Folate and Vitamin B_{12}: United States, 1988–94.'' *Vital Health and Statistics* 11:1–78.
20. Berry, R.J., H.K. Carter, and Q. Yang, 2007. ''Cognitive Impairment in Older Americans in the Age of Folic Acid Fortification.'' *American Journal of Clinical Nutrition* 86, 265–267; author reply 267–269.
21. Bailey, S.W. and J.E. Ayling, 2009. ''The Extremely Slow and Variable Activity of Dihydrofolate Reductase in Human Liver and its Implications for High Folic Acid Intake.'' *Proceedings of the National Academy of Sciences of the United States of America* 106 (36), 15424–15429.
22. Shane, B., ''Folate Chemistry and Metabolism,'' in *Folate in Health and Disease,* L. B. Bailey, Ed. Marcel Dekker, Boca Raton, FL, USA, 2nd edition, 2009.
23. McEvoy, G.K. (ed.). ''American Hospital Formulary Service—Drug Information 2005.'' Bethesda, MD: *American Society of Health-System Pharmacists, Inc.* 2005 (Plus Supplements).
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List of Subjects in 21 CFR Part 172

Food additives, Incorporation by reference, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs and redelegated to the Director, Center for Food Safety and Applied Nutrition, 21 CFR part 172 is amended as follows:

PART 172—FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION

■ 1. The authority citation for 21 CFR part 172 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 342, 348, 371, 379e.

■ 2. Amend § 172.345 by revising the first sentence of paragraph (b) and adding paragraph (i) to read as follows:

§ 172.345 Folic acid (folacin).

* * * * *

(b) Folic acid meets the specifications of the Food Chemicals Codex, 9th ed., updated through Third Supplement, effective December 1, 2015, pp. 495–496, which is incorporated by reference. * * *

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(i) Folic acid may be added to corn masa flour at a level not to exceed 0.7 milligrams of folic acid per pound of corn masa flour.

Dated: April 12, 2016.

Susan Bernard,

Director, Office of Regulations, Policy and Social Sciences, Center for Food Safety and Applied Nutrition.

[FR Doc. 2016–08792 Filed 4–14–16; 8:45 am]

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DEPARTMENT OF THE INTERIOR

Bureau of Indian Affairs

[167A2100DD/AAKC001030/A0A501010.999900 253G]

25 CFR Part 151

RIN 1076–AF28

Title Evidence for Trust Land Acquisitions

AGENCY: Bureau of Indian Affairs, Interior.

ACTION: Interim final rule; delay of effective date.

SUMMARY: The Bureau of Indian Affairs (BIA) published an interim final rule on title evidence for trust land acquisitions and received comments during the public comment period. The BIA anticipates making technical revisions to the rule in response to those comments. This notice delays the effective date of the interim final rule for 30 days, during which time BIA plans to publish a final rule with technical revisions.

DATES: The effective date of the interim final rule published March 1, 2016 (81 FR 10477) is delayed from April 15, 2016 to May 16, 2016.

FOR FURTHER INFORMATION CONTACT: Ms. Elizabeth Appel, Director, Office of Regulatory Affairs and Collaborative Action, Office of the Assistant Secretary—Indian Affairs; telephone (202) 273–4680, *elizabeth.appel@bia.gov*.

SUPPLEMENTARY INFORMATION: On March 1, 2016, BIA published an interim final rule with an effective date of April 15, 2016. 81 FR 10477. The interim final rule deletes the requirement for fee-to-trust applicants to furnish title evidence that meets the ''Standards for the Preparation of Title Evidence in Land Acquisitions by the United States'' issued by the U.S. Department of Justice (DOJ), and replaces the requirement with a more targeted requirement for title evidence, because adherence to the DOJ standards is not required for acquisitions of land in trust for individual Indians or Indian tribes. The BIA received 13 comments during the public comment period and anticipates making technical changes in response to those comments. The interim final rule stated that BIA may withdraw, initiate a proposed rulemaking, or revise the rule in response to comments. The BIA has determined that technical revisions to the rule may be appropriate and is therefore delaying the effective date of the rule for 30 days, during which time