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Adding folic acid to corn Masa flour: Partnering to improve pregnancy outcomes and reduce health disparities[☆]

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Abstract

Although strides have been made in preventing neural tube defects (NTDs), Hispanic women remain more likely to have a baby born with an NTD and less likely to know the benefits of, or consume, folic acid than women of other race/ethnic groups. In 1998, the U.S. Food and Drug Administration (FDA) mandated that all enriched cereal grain products be fortified with folic acid; however, corn masa flour (CMF), used to make many corn products that are a diet staple of many Hispanic groups, was not included under this regulation. In 2006, a Working Group began a collaboration to address this disparity by pursuing a petition to FDA to allow folic acid to be added voluntarily to CMF. The petition process was a monumental effort that required collaboration and commitment by partners representing the affected population, manufacturers, scientists, and others. The petition was approved in 2016 and folic acid is now added to CMF products, with expected results of more women achieving the recommended daily folic acid intake, more infants born per year without an NTD, and millions of dollars in direct medical expenditures averted. This 10-year public-private partnership brought together diverse groups that traditionally have different goals. The Working Group continues to work toward ensuring that fortified CMF products are available to the consumer, with the end goal of achieving a reduction in NTD-affected pregnancies.

[☆]The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Keywords

Corn masa flour; Folic acid; Collaboration; Hispanics

1. Introduction

Daily consumption of 400 micrograms (mcg) of synthetic folic acid before and during early pregnancy has been shown to reduce the risk of serious birth defects of the brain and spine called neural tube defects (NTDs) (Blencowe et al., 2010), of which spina bifida and anencephaly are the most common. Approximately 1300 infants are born every year in the United States (U.S.) with an NTD (Williams et al., 2015).

Folic acid can be consumed in supplement form or in fortified foods. In 1998, legislation went into effect that mandated the addition of folic acid to enriched cereal grain products (ECGP) in the U.S. (CDC, 2010). Fortification in the U.S. has led to a significant decrease in the prevalence of folic acid-sensitive NTDs (CDC, 2010).

Although strides have been made in preventing neural tube defects, ethnic disparities remain. Hispanic women are more likely to have a baby born with an NTD (Williams et al., 2015), and less likely to know about the benefits of folic acid in the prevention of NTDs (deRosset et al., 2014). Post-fortification studies found that Hispanic women were less likely to consume folic acid from either fortified foods or supplements (Hamner et al., 2013a; Hamner et al., 2011; Yang et al., 2007) and had lower overall median serum folate concentrations (Pfeiffer et al., 2012) than non-Hispanic white women, indicating that this group of Hispanic women might not be benefitting from the success of wheat and other cereal grain fortification as much as their non-Hispanic counterparts.

Finally, disparities among Hispanic women exist by level of acculturation, with less acculturated women having lower folic acid intake levels (Hamner et al., 2013a; Hamner et al., 2011) and a higher likelihood for having a baby with an NTD than their more acculturated counterparts (Canfield et al., 2009). Certain groups of high-risk Hispanic women are not reached by the current folic acid fortification of wheat and other cereal grain products simply because it is not what they consume. With an estimated 56.6 million individuals identifying as Hispanic in the U.S. (Census, 2016), designing targeted interventions to meet the unique needs of the diverse segments of this population is critical to reducing overall NTD rates.

1.1. Corn masa flour fortification working group

In 1998, the U.S. Food and Drug Administration (FDA) mandated that all ECPG be fortified with folic acid. Corn masa flour (CMF), the nixtamalized (alkali-treated) flour used to make up to 70% of corn masa products (Kabani, 2016) such as tortillas, corn chips, and other corn products that are staple to the diets of many Hispanic groups, was not included under the 1998 FDA fortification regulation. As a result, these Hispanic groups lacked a culturally-appropriate avenue for obtaining folic acid in their diets through fortification. In 2006, a group of partners came together to discuss how they could collaborate to address this

disparity. These partners were interested in Hispanic health issues, and many had programs underway in their organizations that targeted this audience. The group, which later became known as the Corn Masa Flour Fortification Working Group (henceforth referred to as the Working Group and includes co-authors MAA, CP, RC, JE, SS), met with FDA to discuss options for how to include folic acid in CMF. Discussion ensued around whether CMF met the existing standards of identity for either white corn flour (21 CFR § 137.211) or yellow corn flour (21 CFR § 137.215). It was agreed that CMF did not fully fall under either existing regulation, and to develop a standard of identity for CMF would require time and expense that were beyond the scope and financial means of the Working Group. As an alternative, FDA suggested that the Working Group could achieve its goal through another regulatory mechanism -that of a food additive petition - which would allow CMF manufacturers to voluntarily add folic acid to products which they could then label as such. After much debate, the Working Group coalesced behind the choice to pursue a food additive petition to FDA. This petition would allow folic acid to be added voluntarily to CMF and CMF-based products.

The food additive petition process is a very detailed and complex undertaking with requirements set forth in 21 CFR, part 17 (FDA, 2016). Among other requirements, the petition must include information relating to 1) the physical, chemical, and biological properties of the additive, including reaction by-products; 2) shelf-stability data for the isolated ingredient additive, as well as stability data collected in the food vehicle (in this case CMF), and during its conversion to finished products, an evaluation of losses occurring over the typical shelf-lives of common finished products; 3) a description of typical analytical methods for detection of the additive in raw, processed, and/or finished foods; and 4) full reports of investigations made with respect to the safety of the food additive for its intended use, taking into consideration expected consumption data for the additive based on current daily intakes and expected increases due to the proposed regulation.

As indicated earlier, a diverse group of participants from industry and the non-profit sector formed the Working Group that would submit the food additive petition to FDA. As part of the process, a partner was chosen to be the primary petitioner. This role is generally designated to the partner likely to be most impacted economically by the petition. Gruma Corporation (Gruma), the global leading manufacturer of CMF, agreed to serve as the primary petitioner. Gruma, the parent company of U.S. Azteca Milling LP, began its operations in 1949 and has long been involved with micronutrient fortification initiatives for countries where corn masa products are staple foods.

The other partners of the Working Group - March of Dimes, Spina Bifida Association, American Academy of Pediatrics, Walmart, Royal DSM, and UnidosUS – provided instrumental informational and programmatic support throughout the process. Later in the process, March of Dimes took over as the lead petitioner. A second group of experts from academia and government, not formally engaged as petitioners nor as part of the Working Group (includes co-authors ALF, AMC, JES, MD, KSC, ST, CB), provided scientific technical expertise to the Working Group. In addition, Dr. Lynn Bailey, a nutritionist who was with the University of Florida at the time the petition process began, and various experts

from the U.S. Centers for Disease Control and Prevention (CDC) provided scientific support and technical expertise throughout the petition process.

2. Methods

2.1. Collecting the scientific evidence

In February 2010, researchers from the CDC, University of Colorado School of Medicine, and FDA presented a CDC Public Health Grand Rounds that focused on folic acid and NTD prevention. This provided the opportunity to collate, examine, and present the existing evidence related to folic acid and NTD prevention and highlight gaps that remained. Subsequently, in August 2010 CDC and the Working Group met with FDA to discuss the food additive petition process and plans for submitting the folic acid petition. The main concerns raised by FDA were related to 1) folic acid intake by certain sub-population groups (e.g., children, older adults), 2) the potential for exceeding the Tolerable Upper Intake Level (UL) via supplements and consumption of fortified foods, 3) safety (e.g., “masking” of pernicious anemia, cognitive impairment, and cancer risk), 4) measurement of impact (i.e., limitations of systems that monitor the occurrence of NTDs), and 5) stability of folic acid in nixtamalized flour. Following the meeting with FDA, the Working Group asked scientists from CDC's National Center on Birth Defects and Developmental Disabilities (NCBDDD) to lead the development of a technical assistance package that would address FDA's scientific questions and concerns. NCBDDD not only had expertise in folic acid and fortification, but also had significant programmatic activities targeting the Hispanic population. A team of about 10 scientists from across NCBDDD's Division of Congenital and Developmental Disorders (DCDD) came together to develop a technical assistance package to be included in the Working Group's petition submission. This package was submitted to the Working Group in October 2011.

The package contained three sections. The first section modeled usual total folic acid intake among the U.S. population with folic acid fortification of CMF using data from the National Health and Nutrition Examination Survey (NHANES), a cross-sectional nationally-representative survey of health and nutrition status in the United States. The usual folic acid intakes of different population subgroups were estimated based on the existing fortification policy, and these values were compared with the estimated usual folic acid intakes expected if foods with CMF were fortified with folic acid at 140 mcg/100 g, the level added to other cereal grain products. These simulations demonstrated that CMF fortification would be expected to have the largest impact on less acculturated Hispanic women (Hamner et al., 2013a), the target population for this intervention, while having minimal impact on the proportion of the population having intake over the UL in any population subgroup (Hamner et al., 2013b).

Using estimated increases in folic acid intake - were CMF to be fortified with folic acid at the proposed level - the second section of the package provided an estimate of the number of NTDs that could be prevented with the addition of folic acid to CMF. The estimated increase in folic acid intake and resulting reduction in NTD prevalence observed when ECGP fortification was implemented were extrapolated and applied to CMF fortification (Tinker et al., 2013).

Finally, the third section was a discussion related to folic acid safety. Acknowledging the inability to scientifically prove the absolute absence of harm of any substance, FDA's Code of Federal Regulations defines "safe" or "safety" as meaning "that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use" (FDA, 2016). At the time this petition was developed, six governmental and independent advisory agencies, both in the U.S. and internationally, had conducted evidence-based reviews on the safety of mandatory folic acid fortification (Food and Drug Administration (FDA), 1993a, 1993b, 1993c, 1993d, 1996a, 1996b, 1996c; IOM, 1998; SACN, 2009, 2006; FSANZ, 2016, 2009, 2006; FSAI, 2008, 2006; HCN, 2008). All six agencies concluded that mandatory fortification of staple foods was safe and effective, and recommended that their respective countries implement a plan to fortify food with folic acid. To meet FDA's requirement that a food additive be shown safe for its intended use, CDC scientists summarized the findings of these evidence-based reviews, along with additional scientific literature published after these reviews were conducted (January 2007 – March 2011). Further, CDC scientists conducted systematic reviews as appropriate, while also summarizing scientific literature and providing tabular results of relevant studies published prior to 2007 for five potential adverse mechanisms and outcomes that were not thoroughly considered previously by the advisory agencies' reviews. These mechanisms and outcomes were: 1) recommended dietary allowances, 2) UL for adults and children, 3) potential mechanisms by which folic acid intake might cause adverse effects, 4) issues related to folic acid intake and vitamin B12 status, and 5) potential adverse outcomes of folic acid intake.

This extensive review and compilation of the evidence related to folic acid safety was incorporated into the food additive petition developed under the leadership of the Working Group. Other sections of the petition, including the biological properties and activity of folic acid, manufacturing information about folic acid and fortified CMF, evidence of stability of folic acid in foods, review of regulatory status of other folic acid-fortified foods, and proposed conditions of use (including the proposed amount of folic acid per pound of CMF) were written by other members of the Working Group. The March of Dimes provided technical assistance in preparing the final version of the document, references and accompanying appendices. The petition was submitted to FDA in April 2012, initiating the agency's review process.

In December 2012, FDA issued a formal notice asking for further clarification on the stability of folic acid in CMF during both storage and the process of making the flour into finished products, particularly the frying or baking of products like tortillas and chips. Years earlier, as part of an unrelated research effort, Royal DSM had collaborated with Dr. Michael Dunn from Brigham Young University and the Monterrey Institute of Technology (ITESM) on a multi-year project. The aim of this project, funded by a Gates Foundation grant to Sharing United States Technology to Aid in the Improvement of Nutrition (SUSTAIN), was to incorporate a vitamin-mineral premix containing folic acid into products made from fresh corn masa (rather than flour) in Mexico. At that time (2003–2008) fresh masa products represented over half of the total masa product market share in Mexico (Condesa Consulting Group, 2015). Historically, thousands of small neighborhood mills throughout Mexico have prepared fresh nixtamal (alkali-steeped corn) using a traditional process, and

ground it directly into corn masa before converting it into tortillas, chips, and tamales. Following several years of research and trials with these small mills and tortillerias, this group was able to develop a commercially viable fortification process. While five of the six micronutrients included in the premix proved to be extremely stable through the milling and tortilla baking process, only 20% of added folic acid remained (Dunn et al., 2008). Despite the fact that these results pertained to fortification of fresh masa during a wet milling process in small neighborhood mills, FDA's awareness of the significant folic acid losses reported in this study raised concerns with respect to folic acid fortification in CMF. As a result, FDA requested additional studies. In 2013, the Working Group, led by the March of Dimes, explored various avenues for obtaining the stability data sought by FDA from either domestic or international sources. Ultimately, the Working Group decided that a new, original study would have to be performed to generate these data.

Dr. Michael Dunn led these additional studies, funded by March of Dimes, to strengthen the understanding of folic acid stability during extended storage of fortified CMF, as well as during subsequent baking and frying processes used during the manufacture of tortillas and chips – the two principal finished products derived from CMF. Stability of folic acid over the shelf-life of these finished products was also evaluated to allow accurate estimates of potential consumer intakes and to confirm that the proposed addition level would result in the intended nutritional effect in the target population. Findings of a parallel study indicated that the folic acid losses in fresh masa resulted from thermo-chemical degradation during extended holding of fortified wet masa at high temperatures prior to conversion to tortillas or other finished products (Adolphson et al., 2016). Such practices and conditions would not be typical during manufacture with dry CMF. The final data for the new March of Dimes funded study were submitted to FDA in October 2015.

3. Results and discussion

In April 2016, the Working Group received notification from FDA that the petition had been approved. Following the petition's approval, Gruma quickly began the process of adding folic acid to its CMF products. As the world's leader in corn flour, tortilla, and wrap production (Gruma, 2017), Gruma's products have the potential to reach millions of individuals, especially Hispanic populations. With an estimated 11 million Hispanic women aged 18–44 in the United States (Census, 2015a), the number of women potentially consuming folic acid through CMF products is significant.

The benefits of the addition of folic acid to CMF for women of childbearing age are numerous, in particular for Mexican-Americans as the largest sub-group of Hispanics in the U.S. (López and Patten, 2015), and among the primary consumers of corn masa flour products (Bressani et al., 1997). First, given that there are approximately 7.5 million Mexican-American women of childbearing age in the U.S. (Census, 2015b), with folic acid being added to CMF, it is estimated that close to 450,000 additional Mexican-American women would achieve the daily recommended folic acid intake of 400 mcg.

Second, the addition of folic acid to CMF is predicted to increase the average daily folic acid consumption among Mexican-American women by 21%, and for Mexican-American

women who do not take vitamin supplements or eat fortified cereals by 42.9% (Hamner and Tinker, 2014). While these estimates were based on an assumption that folic acid would be added to all CMF products, because of Gruma's large presence in the industry, their products have the potential to reach a large segment of the Hispanic population that consumes CMF products. Further, since the approved petition now allows direct addition of folic acid to CMF, it eliminates the need for women to make a behavior change. They can continue to eat the foods they usually eat, but now with the added benefit of increasing their daily consumption of folic acid.

The third benefit of the addition of folic acid to CMF is that an estimated 40 additional Hispanic infants per year (range: 0–120) will be born without an NTD (Tinker et al., 2013). Finally, the financial burden associated with caring for an infant born with a neural tube defect, such as spina bifida, can be very high. A recent publication estimated the average lifetime direct cost of caring for an infant with spina bifida to be \$791,000 (Grosse et al., 2016). Averting these costs can reduce the significant financial impact of these birth defects on families, the overall economy, and society.

4. Conclusion

4.1. A true collaboration to address a significant disparity

The petition process to allow the addition of folic acid to CMF was a major effort that required intense collaboration and commitment from the partners involved. This process, however, was not without its challenges. Motivating a partnership of diverse organizations, communicating and maintaining clear roles, and keeping individuals and organizations focused and engaged over ten years is a formidable task. As would be expected to happen over a decade, there was some staff turnover in the organizations and - due to the technical nature of this petition - the Working Group had to identify and engage additional consultants who had specific subject matter expertise. Further, this petition process required that some of the Working Group partner organizations provide funding for additional studies. Challenges notwithstanding, the fact that the Working Group was composed of diverse organizations that all had a keen interest in promoting health of Hispanic women and their infants, allowed the group to persevere for 10 years on this effort. This public-private partnership represented a full complement of viewpoints on the issue, and partners with the resolve and credibility to keep the process moving forward.

Each partner organization belonging to the Working Group had a critical role to play in the success of this collaboration. The Working Group reached out to key members of Congress in the Women's and Hispanic Caucuses to leverage support and engagement from congressional members, especially in Hispanic communities impacted by NTD disparities. The longstanding history of working with, and on behalf of, the Hispanic community and its existing relationship with corporate partners by some members of the Working Group, such as UnidosUS, also helped leverage engagement among food manufacturers/retailers, and buy-in from the Hispanic community. Regular communication by conference call and email, and timely contributions to the draft petition allowed the group to keep the process moving to its conclusion. When skill gaps were identified, members of the Working Group reached out to other individuals and organizations with expertise in those areas for assistance. In

this way, the Working Group was able to respond to FDA's requests and ensure that it was current on the latest research.

Critical next steps include continuing to ensure that CMF with folic acid is available in local and regional markets that serve the Hispanic communities that consume these products, that there is awareness about the availability of these products, and that labeling and packaging reflects the new folic acid content. Further, partners are exploring the possibility of including CMF containing folic acid in additional CMF-based retail products. Finally, CDC plans to continue to monitor NTD prevalence through population-based surveillance, as well as to utilize NHANES data to monitor changes in usual intake of folic acid and blood folate concentrations among the U.S. population and selected subgroups, such as Hispanic women, to evaluate the impact of adding folic acid to CMF. This will help to ensure that the ultimate goal of reducing the prevalence of NTD-affected pregnancies is achieved.

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