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USPSTF Coordinator
c/o USPSTF
540 Gaither Road
Rockville, MD 20850

Re: Opportunity for Comment - U.S. Preventive Services Task Force Draft Research Plan on Folic Acid Supplementation for the Prevention of Neural Tube Defects

The Council for Responsible Nutrition (CRN) appreciates the opportunity to comment on the U.S. Preventive Services Task Force (USPSTF) Draft Research Plan on Folic Acid Supplementation for the Prevention of Neural Tube Defects. CRN, based in Washington, D.C., is the leading trade association representing dietary supplement manufacturers and ingredient suppliers. CRN's member companies manufacture popular national brands as well as the store brands marketed by major supermarkets, drug store and discount chains. They include some of the largest and most well-known ingredient suppliers, product manufacturers and marketers, direct sellers and specialty retailers of dietary supplements and dietary ingredients as well as specialty products sold by healthcare professionals.

CRN has organized its comments according to the questions posed by the USPSTF in the USPSTF Public Comment Form.

Do you have any comments about the analytical framework?

The proposed analytical framework (as well as all other aspects of the draft research plan) is focused on folic acid supplementation. The USPSTF should be aware that both folic acid and synthetic folates are currently used in foods and dietary supplement products. Synthetic folates include (6S)-5-methyltetrahydrofolic acid, calcium salt and (6S)-5-methyltetrahydrofolic acid,

glucosamine salt. CRN recommends that the USPSTF consider addressing research conducted on synthetic folates in the research plan.

Do you have any comments about Key Question 1?

CRN has no comments for this section.

Do you have any comments about Key Question 2?

CRN has concerns about Key Question 2a, which is, "What are the harms associated with folic acid supplementation to the mother, fetus, neonate, or child?" The phrasing of the question as currently written assumes that there are harms associated with folic acid supplementation to the population groups specified; however, harms in these population groups have not been established. CRN recommends that the question be re-worded as follows: "Are there harms associated with folic acid supplementation specific to the mother, fetus, neonate, or child?"

Key Question 2b, "Do the harms of folic acid supplementation vary by dose, timing, and duration of therapy?" should be consistent with Key Question 2a and specify population groups that will be addressed, namely mothers, fetuses, neonates, or children. CRN recommends the following wording: "Do any harms of folic acid supplementation to the mother, fetus, neonate, or child vary by dose, timing, and duration of therapy?"

Do you have any comments about the contextual questions?

CRN has no comments for this section.

Do you have any comments about the research approach?

CRN has concerns regarding the inclusion and exclusion criteria for studied populations. While Key Question 2 is specific to potential harms to the mother, fetus, neonate, or child, there are no exclusions listed for assessing harm, and in fact, all populations exposed to long-term folic acid supplementation are included. Conversely, for Key Questions 1a, 1b, and 1c, the proposed research approach specifically excludes prepubertal girls, men, and women without the potential for childbearing (e.g., postmenopausal, genetic uterine or ovarian abnormalities). As currently written, the research plan indicates that the USPSTF intends to identify benefit in a select population but generalize harm from data on all populations with long-term use of folic

acid. The analyses of benefit and harm should be consistent with respect to the populations assessed. Men or women without the potential for childbearing may respond differently to long-term folic acid supplementation than women of childbearing age. Therefore, any harms that may be identified in men or women without the potential for childbearing may not apply to the mother, fetus, neonate, or child. CRN recommends that the same inclusion and exclusion criteria specified for Key Questions 1a, 1b, and 1c be applied to Key Questions 2a and 2b.

If the USPSTF intends to assess the potential harms of long-term folic acid supplementation in populations other than women of childbearing age, CRN suggests that additional Key Questions are added:

Key Question 2c: Are there harms associated with long-term folic acid supplementation in populations other that women of childbearing age?

Key Question 2d: Do any harms of long-term folic acid supplementation in other populations vary by dose, timing, and duration of therapy?

The inclusion criteria for proposed Key Questions 2c and 2d would allow for studies in men and postmenopausal women.

If USPSTF adds Key Questions 2c and 2d, the analytic framework should be amended accordingly.

Respectfully Submitted,

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