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VIA ELECTRONIC SUBMISSION:
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Dr. Yun Xie
NTP Designated Official
Office of Liaison, Policy and Review
DNTP, NIEHS
P.O. Box 12233, MD K2-03
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Re: Expert Panel Meeting on Identifying Research Needs for Assessing Safe Use of High Intakes of Folic Acid

Dear Dr. Xie:

The Alliance for Natural Health USA ("ANH-USA"), a non-profit organization, submits this comment in response to the "Expert Panel Meeting on Identifying Research Needs for Assessing Safe Use of High Intakes of Folic Acid" published in the Federal Register of December 8, 2014 (79 Fed. Reg. 72692) by the National Toxicology Program ("NTP").

Commenter Background

As background, Robert Verkerk, Ph.D., the Scientific Director of ANH-USA, is an internationally acclaimed scientist with over 25 years of experience in the field of agriculture and healthcare sustainability. ANH-USA is a membership-based organization consisting of 424,000 consumers, food and dietary supplement companies, and healthcare practitioner members, with 1.2 million people a year relying on ANH-USA for information about the politics of natural health. ANH-USA works to promote and protect citizen access to information in the market concerning the actual and potential benefits of healthy food and dietary supplements as well as access to these healthy products that consumers need to maintain optimal health. Through public education, ANH-USA arms consumers with the tools they need to make informed, individualized decisions and to take personal

responsibility for their health. Our ultimate goal is to promote disease prevention, reduce medical intervention, and reduce the cost of healthcare in the United States. Among ANH-USA's members are practitioners, medical doctors, scientists, business entities, and patients who manufacture, sell, distribute, recommend and/or use dietary supplements.

ANH-USA's Comments

Research needs are limited to folic acid (pterylmonoglutamic acid) and should not, at least in the context of investigating the potential risk of high dosages, include reduced forms of folate such as folinic acid, stabilised 5'-methyltetrahydrofolate or food forms folates. These reduced forms have never been associated with any adverse events at high dosages, as recognized in the NTP's draft monograph.[1] Additionally, the investigation of the causes and effects of high blood levels of folic acid (monoglutamic form) linked to high intakes of this form and resultant high levels of unmetabolized folic acid (UMFA) in serum appears to have been omitted in the NTP draft monograph.[2]

Given the rapid emergence of high-throughput human gene sequencing and bioinformatics science, it is concerning that there are, as yet, no suggestions in the NTP document to investigate the role of multiple polymorphisms on folic (and homocysteine) metabolism.[3] Especially relevant are polymorphisms in reduced folate carrier 1 (RFC1) gene (A80G), methylenetetrahydrofolate reductase (MTHFR) (C677T, A1298C), methionine

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[1] Bailey RL, Mills JL, Yetley EA, Gahche JJ, Pfeiffer CM, Dwyer JT, Dodd KW, Sempos CT, Betz JM, Picciano MF. Unmetabolized serum folic acid and its relation to folic acid intake from diet and supplements in a nationally representative sample of adults aged > or =60 y in the United States. *Am J Clin Nutr*. 2010; 92(2): 383-9.

[2] It is particularly surprising that research of the UMFA issue has not been included given Dr. Yetley's co-authorship both of the draft monograph and the following study.

[3] Liang S, Zhou Y, Wang H, Qian Y, Ma D, Tian W, Persaud-Sharma V, Yu C, Ren Y, Zhou S, Li X. The effect of multiple single nucleotide polymorphisms in the folic acid pathway genes on homocysteine metabolism. *Biomed Res Int*. 2014; 2014:560183. doi: 10.1155/2014/560183.

Barnabé A, Aléssio AC, Bittar LF, de Moraes Mazetto B, Bicudo AM, de Paula EV, Höehr NF, Annichino-Bizzacchi JM. Folate, Vitamin B12 and Homocysteine status in the post-folic acid fortification era in different subgroups of the Brazilian population attended to at a public health care center. *Nutr J.* 2015; 14(1): 19.

Dulucq S, St-Onge G, Gagné V, Ansari M, Sinnett D, Labuda D, Moghrabi A, Krajinovic M. DNA variants in the dihydrofolate reductase gene and outcome in childhood ALL. *Blood.* 2008; 111(7): 3692-700.

Askari BS, Krajinovic M. Dihydrofolate reductase gene variations in susceptibility to disease and treatment outcomes. *Curr Genomics.* 2010; 11(8): 578-83.

synthase reductase (MTRR) (A66G) and dihydrofolate reductase (DHFR) (C-1610G/T, C-680A, and A-317G).[4]

To investigate the paradoxical role of folic acid in cancer promotion and protection, it is necessary to investigate the effect of folic acid supplementation on subjects in whom it has been confirmed there is an absence of premalignant lesions prior to initiation of folic acid supplementation.[5] It would not be deemed ethical, given the current state of the science, to carry out intervention studies using folic acid on subjects with existing lesions or malignancies (although this does not apply to intervention studies with forms of reduced forms of folate). In addition to folic acid and folate, blood levels should be measured throughout such studies as well as monitoring dietary intake of food folates and any supplemental intake of 5MTHF. Long-term follow-up is required, and full account should be taken of confounding factors such as smoking or disturbances in folate metabolism via SNPs.

In relation to research effects on the possible role of high dose folic acid supplementation on cognitive decline, it is essential to investigate the interaction with B12 intake as well as B6 intake. This is because of recent and emerging evidence that concomitant high intakes of B12 and B6 will negate any adverse effects and in fact may reduce cognitive decline and associated brain shrinkage as compared with non-supplementing population groups.[6]

Additionally, there is a need for further studies to investigate the relative contribution of folic acid from fortified foods and dietary supplements among different population groups, including pre-conceptual and pregnant women, the elderly, those with specific polymorphisms affecting folic acid metabolism and grain-free populations.[7] Such

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[4] *Id*.

[5] Mason JB, Dickstein A, Jacques PF, et al. A temporal association between folic acid fortification and an increase in colorectal cancer rates may be illuminating important biological principles: a hypothesis. *Cancer Epidemiol Biomarkers Prev.* 2007; 16: 1325–9.

Cole BF, Baron JA, Sandler RS, et al. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. *JAMA* 2007; 297: 2351–9.

[6] Morris MC, Evans DA, Bienias JL, et al. Dietary folate and vitamin B12 intake and cognitive decline among community-dwelling older persons. *Arch Neurol* 2005; 62: 641–5.

Douaud G, Refsum H, de Jager CA, Jacoby R, Nichols TE, Smith SM, Smith AD. Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment. *Proc Natl Acad Sci U S A.* 2013; 110(23): 9523-8.

[7] Dwyer JT, Wiemer KL, Dary O, Keen CL, King JC, Miller KB, Philbert MA, Tarasuk V, Taylor CL, Gaine PC, Jarvis AB, Bailey RL. Fortification and health: challenges and opportunities. Adv Nutr. 2015; 6(1): 124-31.

research would be invaluable in a review of the U.S. folic acid food fortification program. It is the view of ANH-USA that use of dietary supplements provides a much more flexible and appropriate approach that takes into account the needs of different population groups and individuals than food fortification.

Sincerely,

ALLIANCE FOR NATURAL HEALTH USA
[Signature Redacted]

Gretchen DuBeau, Esq.
Executive and Legal Director

[Signature Redacted]

Robert Verkerk, BSc MSc DIC Ph.D. FACN
Scientific Director

Datta M, Vitolins MZ. Food Fortification and Supplement Use - Are There Health Implications? *Crit Rev Food Sci Nutr.* 2014 Jul 18:0. [Epub ahead of print].