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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Literature Review Approach "Identifying Research Needs for Assessing Safe Use of High Intakes of Folic Acid"; Request for Information and Comments

SUMMARY: The National Toxicology Program (NTP) at the National Institute of Environmental Health Sciences (NIEHS) in conjunction with the NIH Office of Dietary Supplements (ODS) is planning a workshop to identify research needs based on consideration of the state of the science related to the safe use of high intakes of folic acid. The NTP and the ODS invite comments on an approach document, "Identifying Research Needs for Assessing Safe Use of High Intakes of Folic Acid," for review of the pertinent literature. The document is available on the NTP Folic Acid Request for Information (RFI) website (http://ntp.niehs.nih.gov/go/38143). Information gathered through this request will be used in prioritizing topics for the state of the science workshop.

DATES: The deadline for receipt of information and comments is May 28, 2013.

ADDRESSES: Comments should be submitted at http://ntp.niehs.nih.gov/go/38143.

FOR FURTHER INFORMATION CONTACT: Abee L. Boyles, Ph.D., Health Scientist, Office of Health Assessment and Translation, Division of the NTP, NIEHS, PO Box 12233, MD: K2-04, Research Triangle Park, NC 27709; telephone: (919) 541-7886; fax: (301) 480-3230; email: abee.boyles@nih.gov. Courier address: NIEHS, Room 2158, 530 Davis Drive, Morrisville, NC 27560 or Regan Bailey, Ph.D., R.D., Nutritional Epidemiologist, ODS, NIH, 6100 Executive Blvd., Room 3B01, Bethesda, MD 20892-7517; telephone: (301) 496-0187; fax: (301) 480-1845; email: regan.bailey@nih.gov.

SUPPLEMENTARY INFORMATION:

Background: The NTP in conjunction with the NIH ODS is planning a workshop to identify research needs based on consideration of the state of the science related to the safe use of high intakes of folic acid. The benefit of supplemental folic acid for pregnant women to prevent neural tube defects in their children is well established; at the same time, there is interest in understanding potential adverse health impacts from high intakes of folic acid. This project aims to identify research needs and inform the development of a research agenda for evaluating the safe use of high intakes of folic acid.

Due to the vastness of the research on folate and folic acid, screening of the literature was undertaken to identify the potential adverse health effects for which further research might be warranted. An approach document, "Identifying Research Needs for Assessing Safe Use of High Intakes of Folic Acid," is available on the RFI website (http://ntp.niehs.nih.gov/go/38143) and should be referenced in responding to the RFI.

This document (1) outlines the approach used to screen the literature, (2) describes the results of the screening effort, and (3) proposes a list of health outcomes for discussion at the workshop. As background for the workshop, a literature review document on these health outcomes will be prepared using systematic review methodology.

Humans require folate, a water-soluble B-complex vitamin, for the synthesis of nucleic acids and to provide methyl groups for biochemical reactions within cells. These functions are needed for everyday growth and cell division, including during critical periods of rapid growth and cell division such as embryonic development. Thus, folate is necessary for all individuals, but is especially important for women who may become pregnant. Evaluating the potential for adverse health effects associated with high folic acid intakes has been challenging because of the lack of systematic studies and other sources of evidence on this topic. In 1998, the Food and Nutrition Board of the Institute of Medicine set Dietary Reference Intakes that included the Recommended Dietary Allowances (RDAs) and tolerable upper intake levels (ULs) — the highest level of daily intake likely to pose no risk of adverse health effects to almost all of the population — for folic acid and other B vitamins. The folic acid UL (1000μg) was established with the paucity of data available to the committee at the time; i.e., limited but suggestive evidence that excessive folate intake may precipitate or exacerbate neuropathy in vitamin B12-deficient individuals. Since this 1998 publication that set the UL for folic acid, many publications have reported on health effects over a range of folic acid intakes. Some studies have raised concerns that high intake of folic acid may be associated with potential adverse health effects.

Folate is present in the diet through its natural occurrence in food, as a food

additive, and as an ingredient in dietary supplements. Naturally occurring folate is unlikely to be associated with potential adverse effects because it has lower bioavailability than folic acid and its consumption is also limited by the bulk and caloric content of foods. Therefore, the primary substance of interest for considering the safety of high intake is folic acid, the form of folate commonly added to foods and dietary supplements.

Information gathered through this RFI will be used in prioritizing topics for the state of the science workshop. The date and location of the workshop have not yet been determined, but when set, will be announced in the Federal Register, the NIH Guide, and on the OHAT project website (http://ntp.niehs.nih.gov/go/38144). The overarching goals of this workshop are to identify research needs and inform the development of a research agenda for evaluating the safe use of high intakes of folic acid. The workshop will bring together experts from multiple disciplines including, but not limited to, epidemiology, nutrition, medicine, and toxicology.

Request for Comments: The NTP and the ODS invite comments on an approach document, "Identifying Research Needs for Assessing Safe Use of High Intakes of Folic Acid," for review of the pertinent literature, which is available at http://ntp.niehs.nih.gov/go/38143. They also request information on issues related to evaluating potential adverse health effects of high intake of folic acid. The RFI website contains specific questions for the following topics:

- Health effects of most concern for high folate intake
- Assessments of folic acid intake and folate levels that are relevant and validated for high exposure

- Critical co-factors for the evaluation of potential health impacts of folic acid
- Experts in the field who should be considered for inclusion in the workshop

Responses are invited from all interested parties, such as the nutrition research community, health professionals, educators, policy makers, industry, and the public. Responses to this RFI are voluntary. The comments collected will be analyzed and considered in planning and development of future initiatives. We do not intend to publish a summary of responses received or any other information provided, except very broad characterizations, such as the number of responses received. Despite this, proprietary, classified, or confidential information should not be included in your response. This RFI is for planning purposes only and is not a solicitation for applications or an obligation on the part of the U.S. Government to provide support for any ideas identified in response to it. Please note that the U.S. Government will not pay for the preparation of any comment submitted or for its use of that comment.

Background Information on NTP and ODS: The NTP is an interagency program, established in 1978 (43 FR 53060) and headquartered at the NIEHS, whose mission is to evaluate agents of public health concern by developing and applying tools of modern toxicology and molecular biology. The NTP carries out literature analysis activities in the Office of Health Assessment and Translation and the Office of the Reports on Carcinogens within the Division of the NTP. The NTP also designs and conducts laboratory studies and testing programs and analyzes its findings to assess potential hazards to human health from exposure to environmental substances, including dietary supplements (see http://ntp.niehs.nih.gov/).

The mission of the ODS is to strengthen knowledge and understanding of dietary

supplements by evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public to foster an enhanced quality of life and health for the U.S. population. The purpose and responsibilities of the ODS are to explore more fully the potential role of dietary supplements as a significant part of the efforts of the United States to improve health care; to promote scientific study of the benefits of dietary supplements in maintaining health and preventing chronic disease and other health-related conditions; to conduct and coordinate scientific research within NIH relating to dietary supplements; to collect and compile the results of scientific research relating to dietary supplements, including scientific data from foreign sources; and to serve as the principal advisor to the Secretary of the Department of Health and Human Services and the Assistant Secretary for Health and to provide advice on issues relating to dietary supplements to the Director of NIH, the Director of the Centers for Disease Control and Prevention, and the Commissioner of the Food and Drug Administration (see http://ods.od.nih.gov/). The Dietary Supplement Health and Education Act of 1994 (Public Law 103-417, DSHEA), authorized the establishment of the ODS at the NIH in 1995.

Dated: April 1, 2013

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