

IDENTIFYING RESEARCH NEEDS FOR ASSESSING SAFE USE OF HIGH INTAKES OF FOLIC ACID

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INTRODUCTION

The National Toxicology Program ([NTP](#)) 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 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 acid¹, screening of the literature was undertaken to identify the potential adverse health effects for which further research might be warranted. 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.

The scope of the literature review document and workshop agenda will be finalized based on comments received through a Request for Information. Future updates on this project, including draft protocols for conducting the full literature review, will be posted online (<http://ntp.niehs.nih.gov/go/38144>). Individuals interested in receiving updates on this project are encouraged to register to the NTP Listserv (<http://ntp.niehs.nih.gov/go/getnews>).

BACKGROUND

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

¹ Over 29,000 references identified in Pubmed search using the terms “folic acid” or “folate” in September 2012

intake levels (ULs)²— 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.

OBJECTIVES

Identify research needs and develop a research agenda for evaluating the safe use of high intakes of folic acid. This effort will be informed by a state of the science literature review and facilitated by a workshop of qualified experts. The outcome of the workshop will be disseminated in a publicly available workshop report.

To achieve these objectives, the workshop will:

- Identify research needs and gaps based on a review of the current science.
- Evaluate the strengths and weaknesses of the available science for addressing these needs and gaps.
- Propose research approaches for addressing the needs and gaps.

METHODS

Criteria for Identifying Relevant Studies

The PICO criteria³ (P_opulation, I_ntervention or exposure, Control or comparator and O_utcomes of interest) will be used to design the review process. These criteria are broad by design, as the primary objective of the screening effort is to identify areas of greatest need for research as well as model systems that could be used to address these research needs. See [Appendix 1: Literature Search](#)

² Institute of Medicine (U.S.). Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Panel on Folate Other B Vitamins and Choline, and Subcommittee on Upper Reference Levels of Nutrients, Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. 1998, Washington, D.C.: National Academy Press. xxii, 564: available at <http://fnic.nal.usda.gov/dietary-guidance/dri-reports/thiamin-riboflavin-niacin-vitamin-b6-folate-vitamin-b12-pantothenic#overlay-context=dietary-guidance/dri-reports/research-synthesis-workshop-summary> .

³ The Cochrane Collaboration: Asking an Answerable Question (http://ph.cochrane.org/sites/ph.cochrane.org/files/uploads/Unit_Five.pdf)

Method for the search strategy and **Appendix 2: Criteria for Initial Screening of Studies** for additional details on screening of the search results.

Population:

Humans, experimental animals, and *in vitro* model systems exposed to folate or folic acid are considered relevant.

Studies are excluded if subjects had comorbidities likely to contribute to a folate deficiency, including impaired renal function, alcoholism, or gastrointestinal disorders impairing folate absorption such as celiac's disease.

Intervention or Exposure:

Exposure to folate, folic acid, folacin, folinic acid, tetrahydrofolate, methyltetrahydrofolate, and 5-methylfolate are considered relevant. Exposure to total folate is included because many studies report intakes in this unit rather than folic acid alone. Additionally, baseline folate status is likely to affect response to supplemental or fortified sources of folic acid. Although folic acid is currently the primary form of added folate, other forms may have been evaluated and may gain use in the future.

Data on folate intakes will be captured as reported because there is no standard reporting format for folate and folic acid intakes. After the data collection stage, if sufficient information in individual studies is available, intakes will be converted to a common unit of measurement to facilitate comparisons among studies. To compare results across studies in which a common intake unit is not available or can not be estimated, stratified analyses based on intake measurement units will also be done.

Studies are excluded that focus on evaluating the effect of folic acid supplementation after an intervention such as surgery or medication. This includes exclusion of studies of chemotherapeutic agents where the focus is on the impact of folic acid on treatment efficacy, and there is a known interaction between folic acid and some chemotherapeutics.

Although the workshop is focused on high intakes of folic acid, there are no *a priori* exclusions in the initial screening process based on a dose level of folic acid or a specific blood folate concentration, because these determinations cannot be made consistently without evaluating the full article text. Studies considered for full data extraction will be selected by focusing on exposure to folic acid above 400µg per day (or total folate above 600 µg/d)⁴ or circulating folate concentrations above 10 nmol/L (4ng/mL) for serum or 340 nmol/L (151ng/mL) for red blood cell (RBC)⁵, when specified. These cut-offs are based on cut-offs for assessing folate status as identified by authoritative bodies. That is, the Institute of Medicine's highest recommended intake is for women of childbearing age: "400 µg of folic acid daily from fortified foods, supplements, or both in addition to consuming food folate from a varied

⁴ The Institute of Medicine defined the unit of measurement for folate as dietary folate equivalents (DFEs). However, many studies do not report intakes as DFEs. Information on the proportion of total intake from naturally occurring folate sources vs. from synthetic forms of folate is necessary to convert reported intakes into DFE units.

⁵ Based on WHO definition of folate deficiency (de Benoist et al. 2008 Food and Nutrition Bulletin 29 (2): S238-S244), this level is slightly more conservative than the standards used in clinical practice (305nmol/L for RBC).

diet”.⁶ The WHO defined folate deficiency as below 10 nmol/L (4ng/mL) for serum or 340 nmol/L (151ng/mL) for RBC based on elevations in total plasma homocysteine in the US National Health and Nutrition Examination Survey III (1988-1994) (de Benoist et al. 2008 Food and Nutrition Bulletin 29 (2): S238-S244). These levels will be used as a practical cut-offs for the evaluation of safety of folic acid as they are recent guidelines for assessing folate status. By including studies in the science review that are at or above recommended intakes or clinical indicators of adequate status, information on the availability of evidence defining safe ranges of intake as well as intakes associated with potential adverse effects can be identified.

Control or Comparator:

No *a priori* restrictions are made on the type of control or comparator groups considered or to specific study designs. If the same amount of folic acid was given to all participants in a randomized controlled trial (both treated and placebo groups), it is not included

Outcomes of Interest:

Studies that focused on evaluating the association between folic acid or folate and a health outcome relevant to human health were considered relevant in the initial screening stage with the following exceptions:

- Kidney disease which is associated with folate deficiency from increased requirements
- Gastrointestinal disorders leading to deficiency from impaired folate absorption
- Homocysteine blood concentration without an additional health effect
- Infectious disease studies conducted in areas with endemic infectious diseases where folate deficiency is more of a concern. While it is acknowledged that treatment of folate deficiency with folic acid may increase susceptibility to infectious diseases in these environments, these health effects are not a high priority for evaluating folic acid safety in the United States. Studies that focus on management of infectious disease rather than a concern that folic acid may increase the risk of contracting an infectious disease are also excluded.

Search Methods for Identification of Studies

The initial literature search was performed in November of 2011 and was not limited by language or publication date. As noted above, the literature search was designed to exclude studies of cotreatment with folic acid and chemotherapeutic agents. For the purposes of refining the scope of the workshop the PubMed literature was screened back to 1992, well before the last review of folic acid by the Institute of Medicine. However, the literature on health outcomes that will be discussed at the workshop will include studies published prior to the 1992 and studies identified in Embase, Web of

⁶ Institute of Medicine (U.S.). Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Panel on Folate Other B Vitamins and Choline, and Subcommittee on Upper Reference Levels of Nutrients, Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. 1998, Washington, D.C.: National Academy Press. xxii, 564: available at <http://fnic.nal.usda.gov/dietary-guidance/dri-reports/thiamin-riboflavin-niacin-vitamin-b6-folate-vitamin-b12-pantothenic#overlay-context=dietary-guidance/dri-reports/research-synthesis-workshop-summary>. The 600 µg/day dose of total folate is the sum of the pre-fortification intakes of dietary folate for women of child-bearing age and the 400 µg/day folic acid to meet the additional needs relative to risk of NTDs. Median intakes for women of child-bearing age from the CSFII were approximately 200 µg/day (pg 474, IOM report).

Science, and Scopus. The search will be updated and additional references screened and data extracted prior to the workshop.

The details of the electronic database searches are presented in [Appendix 1: Literature Search Method](#). The PubMed search includes both MeSH and text words. The Web of Science and Scopus searches use keywords only. Embase uses the controlled vocabulary Emtree.

Additional sources of published data are included as identified by NTP staff, reference lists of review articles, and subject matter experts.

Grey literature, including meeting abstracts and unpublished data from personal author communication are considered to supplement a peer-reviewed publication, but a study that is entirely unpublished or otherwise not peer-reviewed is not considered.

Data Collection

Selection of Studies

First, two reviewers independently screen titles and abstracts for relevance. [Appendix 2: Criteria for Initial Screening of Studies](#) details the screening approach used. Those studies considered relevant or uncertain in the title/abstract screen move forward. Studies that do not fulfill the criteria are excluded and their bibliographic details listed with the reason for exclusion. Next, the full text of references deemed relevant or uncertain in the title/abstract screen are reassessed by two independent reviewers with the same inclusion/exclusion criteria as in the title/abstract screen. Any discrepancies are resolved by consensus of the two reviewers and a complete record of the conflicts is maintained.

Data Extraction and Evaluation of Risk of Bias

Once the scope of the workshop has been finalized, relevant studies will undergo data extraction and evaluation for internal validity (“risk of bias”⁷) in a standardized manner by one reviewer and independently checked for accuracy by a second reviewer. Determination of what would constitute a high or low risk of bias is critical to evaluating confidence in study results, particularly when assessing the appropriateness of exposure and outcome assessments. Specific details of the data extraction and approach to assess risk of bias will be disseminated in future versions of this approach.

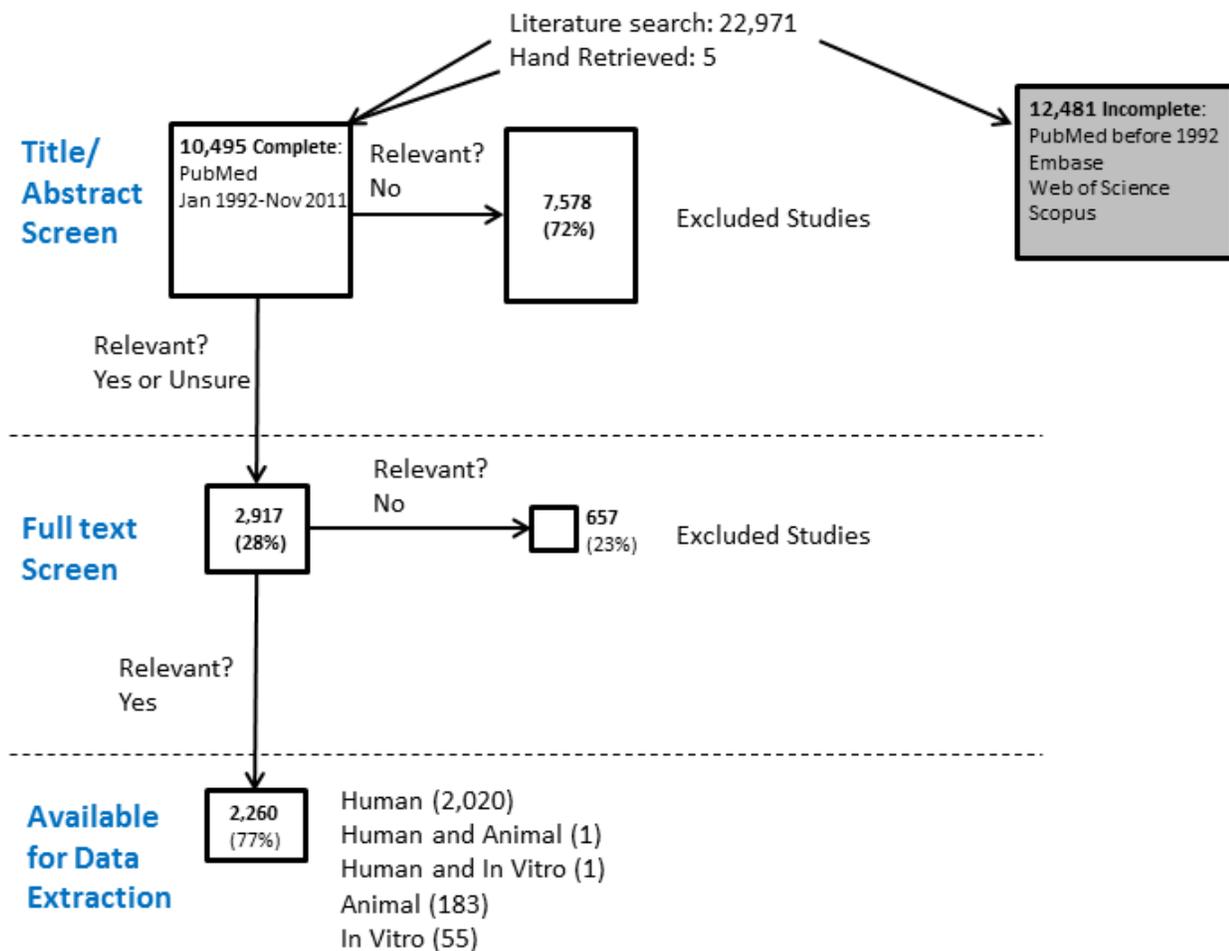
⁷Risk of bias - “a systematic error or deviation from the truth, in results or inferences.” It is interchangeable with internal validity, which is defined as “the extent to which the results of a study are correct for the circumstances being studied.” Evaluating the risk of bias of a study refers to assessing the extent to which “the study results reflect bias in study design or execution in addition to the true effect of the intervention or exposure under study.” (AHRQ Methods Guide: <http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=998#4932>)

PRELIMINARY RESULTS

Screening Progress

Articles from the literature search were not screened randomly. Articles retrieved from PubMed were screened first beginning with the most recent publications. This allowed OHAT staff to focus the initial screening efforts on the most recent articles likely to pertain directly to emerging issues on the topic. Title and abstract screening and full article screening were completed for studies published through 1992, well before the 1998 Institute of Medicine’s Dietary Reference Intakes evaluation where the UL of 1000µg folic acid was set.

Literature Screening Progress: Studies screened for relevance to the question "Does this article pertain to health effects of high intake of folic acid in humans or animals?"



Health Effects Areas: Number of human and non-human animal studies identified by major area of health effect.

Health Effect Category	Human Studies	Non-Human Animal Studies
Cardiovascular	470	39
Cancer	416	33
Neurological/Sensory	371	28
Reproductive	234	25
Neural Tube Defects	190	12
Other Birth Defects (non-NTD)	139	12
Anemia/Hematological	104	4
Endocrine/Metabolic	96	30
Immune	88	4
Growth	76	25
Mortality	73	3
Bone	51	3
Development	23	17
Respiratory	16	1
Liver	10	15
Digestive (with other categories)	10	2
Kidney (non-dialysis)	4	6
Other	78	11

PROPOSED HEALTH OUTCOMES FOR CONSIDERATION AT THE WORKSHOP

Health effects areas were considered for data extraction based on the extent of the body of literature and if there were any author reported associations of folic acid or folate with adverse health effects in these areas. All studies of those health effects that meet the inclusion criteria will be data extracted (including those that show beneficial, adverse, or no effect).

Based on these criteria, data extraction will proceed for the following outcomes:

- Cancer, all types
- Cardiovascular disease and related health outcomes
- Diabetes, insulin resistance and metabolic syndrome
- Immune function changes and respiratory effects
- Mortality, any cause
- Outcomes in children from exposure during pregnancy, excluding birth defects
- Vitamin B12 deficiency including neuropathies, hematological indices, and MMA level as a subclinical health outcome
- Neurological outcomes related to cognition and cognitive decline, but unrelated to vitamin B12 deficiency

Data will not be extracted for the following health outcomes:

- Birth defects: the benefit of folic acid in preventing NTDs and other birth defects is established; there are many studies showing benefit and very few studies that show adverse effects
- Bone: no studies of adverse effects were identified
- Other neurological conditions not related to cognition (such as depression, schizophrenia, or sensory perception): no studies of adverse effects were identified
- Other endocrine and metabolic effects: few studies of adverse effects in outcomes not related to diabetes or metabolic syndrome, e.g., thyroid
- Kidney: mostly folate deficiency from increased requirements, no studies of adverse effects in subjects without kidney disease
- Gastrointestinal: most disorders lead to deficiency from impaired absorption
- Homocysteine concentration alone: there are a large number of metabolic studies evaluating the inverse relationship between folate and homocysteine concentrations
- Anemia unrelated to vitamin B12 deficiency: the majority of studies of anemia were conducted in areas that typically have poor diets where deficiency, including iron and folate deficiencies, is the greater concern
- Infectious disease: studies conducted in areas with endemic infectious diseases are typically concerned with addressing deficiency. While it is acknowledged that treatment of folate deficiency with folic acid may increase susceptibility to infectious diseases in these environments, these health effects are not a high priority for evaluating folic acid safety in the United States. Many of these studies also focus primarily on management of the disease.
- Liver: no studies of adverse effects identified
- Growth: no studies of adverse effects identified
- Development: no studies of adverse effects identified

Input will be invited on the proposed health outcomes for consideration at the workshop through the Request for Information published in the NIH Guide and the Federal Register. Updated versions of this approach and additional opportunities for input will be communicated via the project website (<http://ntp.niehs.nih.gov/go/38144>).

APPENDIX 1: LITERATURE SEARCH METHOD

The strategy for this search is broad and comprehensive in order to ensure inclusion of relevant papers. After removing duplicate articles in EndNote and Distiller SR, there are 22,971 references in the library. Consideration of dose is not included in the search strategy.

Medline (PubMed): 23 Nov 2011

Concept	Search Set	Search Terms	Number of Results
Folic Acid	#1	Folic acid[mh] OR "Folic acid"[tiab] OR "Pteroylglutamic Acid"[tiab] OR "pteroylmonoglutamic acid" [tiab] OR tetrahydrofolate*[tiab] OR "5-Methyltetrahydrofolic acid"[tiab] OR "5-methyltetrahydrofolate"[tiab] OR leucovorin[tiab] OR "folinic acid"[tiab] OR folate*[tiab]	40220
Dietary Supplement	#2	Dietary supplements[mh] OR "food, fortified"[mh] OR vitamins[mh] OR Supplement*[tiab] OR fortif*[tiab] OR diet[tiab] OR dietary[tiab] OR food[tiab] OR feed*[tiab] OR fed[tiab] OR enrich*[tiab] OR intake[tiab] OR ingest*[tiab] OR vitamin*[tiab] OR consum*[tiab]	1221041
Folic Acid AND Dietary Supplement	#3	#1 AND #2	15771
Chemotherapy	#4	Antineoplastic Combined Chemotherapy Protocols[mh] OR carboplatin[mh] OR methotrexate[mh] OR fluorouracil[mh] OR oxaliplatin[Supplementary Concept] OR irinotecan[Supplementary Concept] OR chemotherapy[mh] OR radiation[mh] OR "antineoplastic agents"[mh] OR camptothecin[mh] OR Chemotherapy[tiab] OR monotherapy[tiab] OR carboplatin[tiab] OR fluorouracil[tiab] OR oxaliplatin[tiab] OR irinotecan[tiab] OR radiation[tiab] OR antineoplas*[tiab] OR camptothecin[tiab] OR methotrexate[tiab] OR "drug target"[tiab] OR "drug targets"[tiab] OR drug delivery systems[mh] OR "drug delivery"[tiab]	1679456
Remove chemotherapy-related results.	#5	# 3 NOT #4	13873

Leucovorin is the active metabolite of folic acid.

EMBASE: 25 Nov 2011

Concept	Search Set	Search Terms	Number of Results
Emtree terms	#1	'folic acid'/exp AND ('diet supplementation'/exp OR 'vitamin'/exp)	33,133
Text terms	#2	((("Folic acid" OR "Pteroylglutamic Acid" OR "pteroylmonoglutamic acid" OR tetrahydrofolate* OR "5-Methyltetrahydrofolic acid" OR "5-methyltetrahydrofolate" OR leucovorin OR "folinic acid" OR folate*) NEAR/6 (Supplement* OR fortif* OR diet* OR food OR feed* OR fed OR enrich* OR intake OR ingest* OR vitamin* OR consum* OR administrat* OR administer*)):ti,ab	13,251
	#3	#1 AND #2	10,759
Chemotherapy/tumor/cancer	#4	'antineoplastic agent'/exp OR 'carboplatin'/exp OR 'methotrexate'/exp OR 'fluorouracil'/exp OR 'oxaliplatin'/exp OR 'irinotecan'/exp OR 'chemotherapy'/exp OR 'radiation'/exp OR 'camptothecin'/exp OR 'drug delivery system'/exp OR 'nanomaterial'/exp OR ((chemotherapy OR Monotherapy OR carboplatin OR fluorouracil OR oxaliplatin OR doxorubicin OR irinotecan OR radiation OR antineoplas* OR camptothecin OR methotrexate OR "drug target" OR "drug targets" OR "drug delivery" OR nano*):ti,ab)	1,770,072
Remove Chemotherapy related results	#5	#3 NOT #4	9,521

Web of Science: 25 Nov 2011

Concept	Search Set	Search Terms	Number of Results
Folic Acid	#1	("Folic acid" OR "Pteroylglutamic Acid" OR "pteroylmonoglutamic acid" OR tetrahydrofolate* OR "5-Methyltetrahydrofolic acid" OR "5-methyltetrahydrofolate" OR leucovorin OR "folinic acid" OR folate*)	39,934
Dietary Supplement	#2	(Supplement* OR fortif* OR diet* OR food OR feed* OR fed OR enrich* OR intake OR ingest* OR vitamin* OR consum* OR administrat* OR administer*)	2,594,240
Folic Acid and Dietary Supplement	#3	#1 AND #2	18,026
Chemotherapy related	#4	(chemotherapy OR Monotherapy OR carboplatin OR fluorouracil OR oxaliplatin OR doxorubicin OR irinotecan OR radiation OR antineoplas* OR camptothecin OR methotrexate OR "drug target" OR "drug targets" OR "drug delivery" OR nano*)	1,377,565
Remove Chemotherapy related results	#5	#3 NOT #4	14,785

Scopus: 25 Nov 2011

Concept	Search Set	Search Terms	Number of Results
Folic Acid	#1	("Folic acid" OR "Pteroylglutamic Acid" OR "pteroylmonoglutamic acid" OR tetrahydrofolate* OR "5-Methyltetrahydrofolic acid" OR "5-methyltetrahydrofolate" OR leucovorin OR "folinic acid" OR folate*)	38,386
Dietary Supplement	#2	(Supplement* OR fortif* OR diet* OR food OR feed* OR fed OR enrich* OR intake OR ingest* OR vitamin* OR consum* OR administrat* OR administer*)	3,754,513
Folic Acid and Dietary Supplement	#3	#1 AND #2	19,892
Chemotherapy related	#4	(chemotherapy OR Monotherapy OR carboplatin OR fluorouracil OR oxaliplatin OR doxorubicin OR irinotecan OR radiation OR antineoplas* OR camptothecin OR methotrexate OR "drug target" OR "drug targets" OR "drug delivery" OR nano*)	68164 (ti,ab,kw)
Remove Chemotherapy related results	#5	#3 AND NOT #4	19,522

APPENDIX 2: CRITERIA FOR INITIAL SCREENING OF STUDIES

Does this article pertain to health effects of folic acid above reference values for assessing the adequacy of folate status or adequate folate intakes in animal model studies?

Studies Included:

- Human studies that assess health effects of folic acid (including folate, folacin, or folinic acid) above 400µg per day or above 10 nmol/L (4ng/mL) for serum or 340 nmol/L (151ng/mL) for red blood cell (RBC) concentrations⁸, when intake is not specified, including mixtures containing folate. If a study only reports intakes as total folate, then intakes above 600 µg/day will be considered relevant.
- Animal studies that include adverse effects, tolerability, safety or mechanisms of action of folic acid (including folate, folacin, or folinic acid) above the standard dose (not of deficiency)⁹, including studies of mixtures containing folic acid
- In vitro studies that include a higher than standard dose of folic acid (possibly in mixtures)
- Methylation/Epigenetic studies if they pertain to a health effect of folic acid

Exposures Excluded:

- Studies of methotrexate (or other chemotherapeutics).
- Studies focused on folic acid's role in the efficacy of clinical interventions including surgery, dialysis, or medication. This would include studies of the effect of folic acid after heart transplant or studies of valproic acid in conjunction with folic acid in birth defects.
- Studies (including case reports) where folic acid is part of the therapeutic treatment giving equal amounts to all participants.
- Alcohol and tobacco smoke exposure are linked to folate deficiency, so studies of co-exposure of folic acid and alcohol are not relevant to the topic of higher daily intakes of folic acid. Studies of co-exposure with alcohol and tobacco smoke will only be included if an independent folic acid effect is examined as well.
- If plasma or serum folate is only considered as an adjustment factor for another exposure-outcome analysis, the study is not relevant to the question.
- Studies of dietary patterns, such as vegetarian or Western diet, where folate is measured but not directly analyzed for association with a health effect.

Outcomes Excluded:

- Homocysteine concentration alone will not be considered as an independent health outcome, but it will be considered in the context of disease.
- Gastrointestinal outcomes where impaired folate absorption is the primary concern in gastrointestinal disorders, and they are unlikely to be examined for risk from higher daily intakes of folic acid.

⁸ Based on WHO definition of folate deficiency (de Benoist et al. 2008 Food and Nutrition Bulletin 29 (2): S238-S244)}, this level is slightly more conservative than the standards used in clinical practice (305nmol/L for RBC).

⁹ Standard dose is considered the control diet amount

- Renal/Kidney where impaired kidney function (particularly end stage disease) contributes to folate deficiency and there are many studies of greater supplement use in these populations that do not pertain to primary health effects of higher daily intakes of folic acid.
- Infectious diseases where folate has been examined in association with malaria or other infectious diseases more common in populations where folate deficiency is the primary concern. *Helicobacter pylori* and Human papillomavirus will be considered in the context of cancer promotion.
- Any condition present at birth (Down's, cystic fibrosis, etc.) will only be considered if maternal folate intake or exposure is assessed, as management of these conditions with folic acid is not related to the primary question.