

# Identifying Research Needs for Assessing Safe Use of High Intakes of Folic Acid

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Office of Health Assessment and Translation  
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## What is the US National Toxicology Program (NTP)?

- **Interagency program**

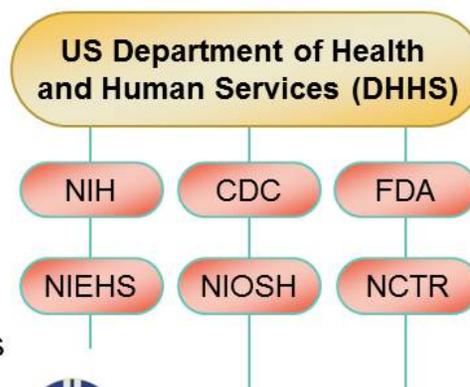
- Established in 1978
- Headquartered at NIEHS

- **Testing activities**

- Thousands of agents evaluated in comprehensive toxicology studies
- Including testing of dietary supplements

- **Analysis activities**

- Report on Carcinogens
- NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
- Office of Health Assessment & Translation



National Toxicology Program  
U.S. Department of Health and Human Services

<http://ntp.niehs.nih.gov>



# Concerns for Safe Use of Folic Acid

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- Norman Maro
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## Folate, cancer risk, and the Greek god, Proteus: a tale of two chameleons

Joel B Mason

## Folic acid fortification: a double-edged sword

Mark Lucock and Zoe Yates

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 Opinion in Clinical Nutrition and Metabolism 2007; 12: 495-504

## Nutrition Science ↔ Policy Folic Acid Fortification

## Folic Acid Fortification and Supplementation—Good for Some but Not So Good for Others

Young-In Kim, MD, FRCPC

## Nutrition Science ↔ Policy Folic Acid Fortification

## Food Fortification with Folic Acid: Has the Other Shoe Dropped?

Noel W. Solomons, M.D.

gests that folate deficiency may promote initial stages of carcinogenesis,

JAMA. 2009;302(19):2119-2126

www.jama.com

“Treatment with folic acid plus

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rich in folate conveys  
d perhaps some other

November 2007: 504-511

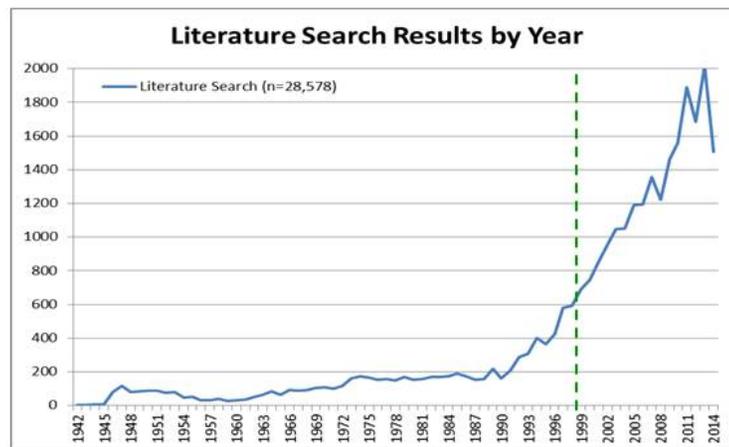
recently been heightened by the publication of several seminal articles investigating the effects of FA fortifica-

Cole et al. JAMA, 2007  
Ebbing et al. JAMA, 2009



## Project Development

- NTP initiated a project to evaluate potential health impacts of high intake of folic acid
- Partnered with Office of Dietary Supplements
- Initiated broad search to capture all relevant literature



- Over 70% of studies published after 1998 IOM report setting the RDA and UL for folic acid.



## Public and Stakeholder Input

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- Review process
  - Internal NTP review
  - NTP Points of Contact
  - NTP Board of Scientific Counselors
- Request for Information for the public to respond to
  - Literature review approach
  - Decisions based on preliminary results
  - Nominate experts
- Public Website: <http://ntp.niehs.nih.gov/go/38144>



## Assembling the Literature

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1. **Literature Screen:** searching for and selecting relevant studies following PICO/PECO\* criteria as in a systematic review
2. **Detailed Tagging of Human Studies:** collecting additional information on exposure(s) and outcome(s) to identify high priority topics
3. **Outcome Prioritization:** identifying high priority health effect categories for consideration by the expert panel
4. **Data Extraction:** summarizing information from the selected human studies into a web-based resource and created study summaries

\* Population, Intervention or Exposure, Control or comparator, and Outcomes of interest



## Broad Literature Screen

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### ***Population:***

- Humans, experimental animals, and *in vitro* model systems

### ***Intervention or Exposure:***

- Exposure to folate, folic acid, folacin, folinic acid, tetrahydrofolate, methyltetrahydrofolate, and 5-methylfolate

### ***Control or Comparator:***

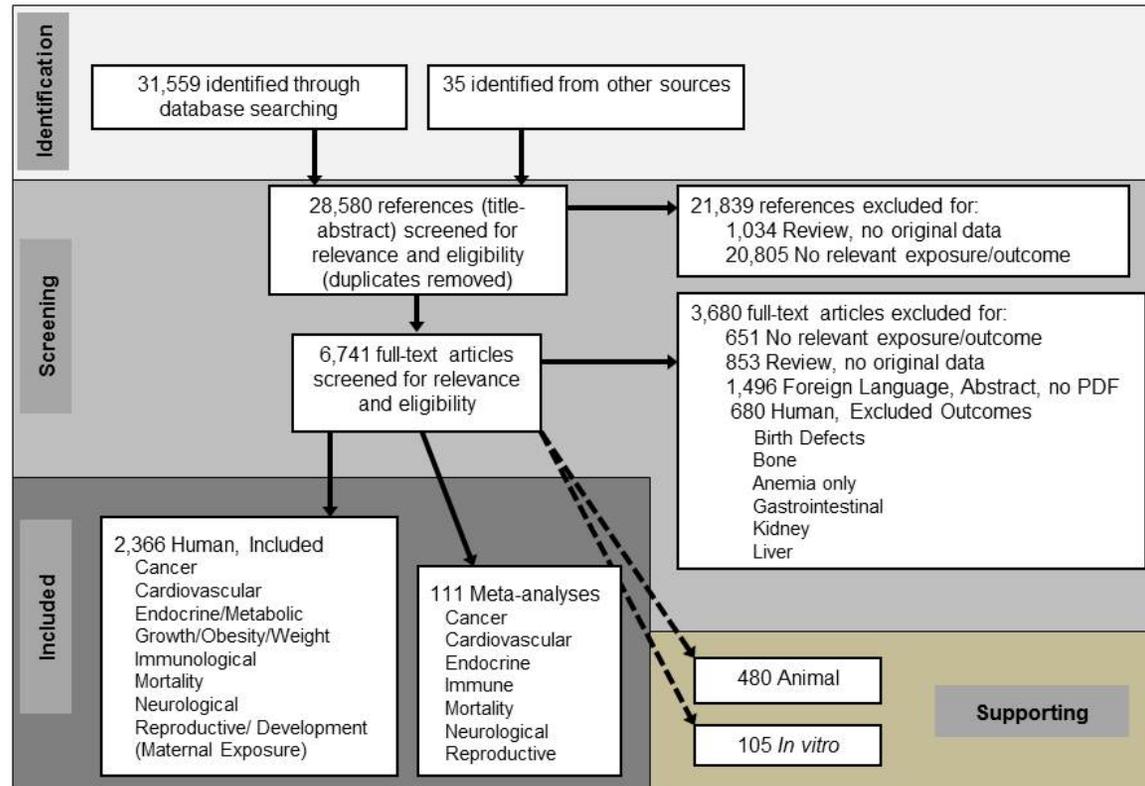
- All study designs included, without restrictions on control

### ***Outcomes of Interest:***

- All health outcomes were captured in the search, but some excluded in the screening process



## Literature Screen: December 2014





## Size of Health Effect Categories

Health Effect Category	Human – Primary (n=2,363)	Human – Meta-analyses (n=111)	Animal (n=480)	<i>In Vitro</i> (n=105)
Cancer	604	50	95	62
Neurological	540	14	78	20
Cardiovascular	486	39	79	15
Reproductive/Developmental	290	12	99	16
Immunological	149	1	29	12
Endocrine/Metabolic	207	1	76	4
Growth/Obesity/Weight	132	7	64	3
Mortality	104	16	9	2
Maternal Exposure*	255	12	127	

\*Maternal folate exposure includes outcomes in offspring across multiple categories, and this tabulation does not include studies of birth defects or other excluded outcomes.



## Detailed Tagging of Human Studies

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### GOAL: Inform Outcome Prioritization

- Detailed outcome (“preterm birth” vs. “reproductive”)
- Exposure (treatment, intake, blood level)
- Level of exposure (deficiency – high)
- Life stage of exposure and outcome
  
- **Was any adverse effect reported?**



## Steering Committee

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- Nicole F. Dowling - National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention
- Amanda MacFarlane - Nutrition Research Division, Health Canada
- Edward McCabe - March of Dimes Foundation
- Linda D. Meyers - American Society of Nutrition
- Robert M. Russell - Tufts University, retired
- Yu (Janet) Zang - Center for Food Safety and Applied Nutrition, U. S. Food and Drug Administration



## Outcome Prioritization

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- Prioritized outcomes considering:
  - Reports of adverse effects in studies of intake over 400ug/day or blood levels above the deficient range
  - Size and design of studies reporting adverse effects
- High Priority Health Effect Categories
  - Cancer Pooled and Meta-analyses
  - Cognition and Vitamin B<sub>12</sub>
  - Hypersensitivity-related Outcomes
  - Thyroid and Diabetes-related Disorders



## Cancer Pooled and Meta-analyses

### **History:**

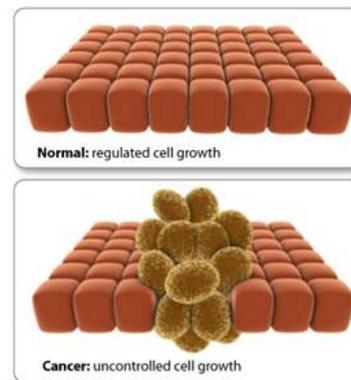
- Early chemotherapeutic agents were anti-folates

### **Studies for data extraction:**

- Focus on existing pooled and meta-analyses (n=43)

### **Expert Panel might consider:**

- Length of follow-up
- Methods, including study quality assessment
- Supplementary information from non-human studies





## Cognition and Vitamin B<sub>12</sub>

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### ***History:***

- Basis for the tolerable upper intake level (UL) of 1mg

### ***Studies for data extraction:***

- Primary human studies (n=28)
- Meta-analyses (n=2)

### ***Expert Panel might consider:***

- Cognitive assessment method
- Statistical analysis of folate and vitamin B<sub>12</sub>





## Hypersensitivity-related Outcomes

### ***History:***

- Most studies published in the last 10 years

### ***Studies for data extraction:***

- Primary human studies (n=43), includes:
  - respiratory infection (n=16), asthma (n=15),  
allergy and atopic disease (n=14), wheeze (n=9),  
hypersensitivity test (n=6), eczema (n=5), food allergy (n=2)
- Meta-analysis asthma and wheeze (n=1)

### ***Expert Panel might consider:***

- Developmental windows of susceptibility
- Biological mechanisms considering supplementary information





## Thyroid and Diabetes-related Disorders

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### ***History:***

- Metabolism may be “preprogramed” by nutrition

### ***Studies for data extraction:***

- Thyroid (n=10)
- Diabetes (n=38), meta-analysis (n=1)
- Insulin resistance (HOMA, n=21)
- Metabolic syndrome (n=12)

### ***Expert Panel might consider:***

- Potential for reverse causation
- Biological plausibility of associations





## Scientific Material for Expert Panel

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### Monograph

- Foundation for panel discussions
- Description of methods for collection of health effects data
  - Does not review exposure data or provide detailed synthesis
- Details for high priority health effect categories
  - Explanation of why each is a high priority
  - Brief summary of data extraction available in each category's Health Assessment Workspace Collaborative (HAWC)
- Other health outcomes
  - Explanation of why they are **not** a focus
  - References listed in Supplementary Material



## Scientific Material for Expert Panel

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### Other Background Materials

- Supplementary Material
  - Reference Lists: identified studies by health effect areas
    - Animal and in vitro studies related to high priority areas
    - Human studies on other (non-priority) health effects
  - Study Summaries (text-based output from HAWC)
- Web-based format: HAWC, [hawcproject.org](http://hawcproject.org)
  - Graphical display of health effects data
  - Displays individual study data and cross-study data-pivots
  - Interactive

**HAWC Demo Today:** Dr. Andrew Rooney, OHAT



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- Anna Ciesielski Jones
- Grace Megumi Sotherden
- Fikri Yucel



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**Questions?**