NTP
National Toxicology Program

Clearing New Ground with New Tools: Identifying Research Needs for Assessing Safe Use of High Intakes of Folic Acid

Abee L. Boyles, PhD
Office of Health Assessment and Translation
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
June 16, 2015

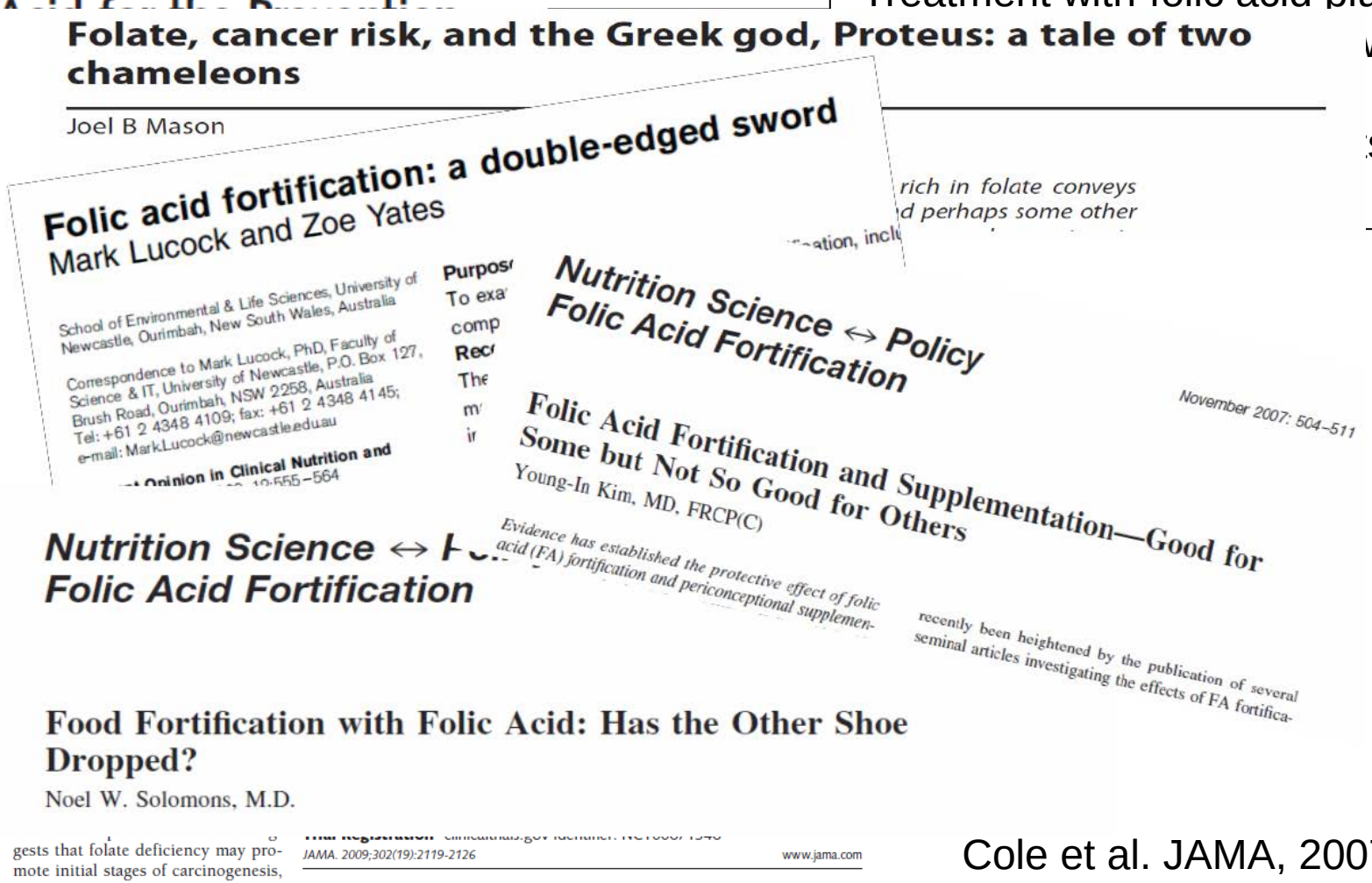
Outline

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

- Scientific Problem and Challenges
- Examining the Evidence
  - Identifying and Summarizing Studies
  - Expert Panel Recommendations
- Value of the Project

Concerns for Safe Use of Folic Acid

"Treatment with folic acid plus
with
and
s with



Folic
of Co
A Ranc

Bernard F. Co
John A. Baron
Robert S. San
Robert W. Hai
Dennis J. Ahn
Robert S. Bres
Gail McKeown
Robert W. Sur
Richard I. Rot
Carol A. Burk
Dale C. Snove
Timothy R. Cl
John I. Allen,
Douglas J. Rol
Gerald J. Beck
John H. Bond
Tim Byers, MI
Jack S. Mande
Leila A. Mott,
Loretta H. Pe
Elizabeth L. B
Judy R. Rees,
Norman Marc
Fred Saibil, M
Per Magne Ue
E. Robert Cre
for the Polyp

Folate, cancer risk, and the Greek god, Proteus: a tale of two chameleons

Joel B Mason

rich in folate conveys
d perhaps some other

ation, incl

Folic acid fortification: a double-edged sword

Mark Lucock and Zoe Yates

School of Environmental & Life Sciences, University of Newcastle, Ourimbah, New South Wales, Australia

Correspondence to Mark Lucock, PhD, Faculty of Science & IT, University of Newcastle, P.O. Box 127, Brush Road, Ourimbah, NSW 2258, Australia
Tel: +61 2 4348 4109; fax: +61 2 4348 4145;
e-mail: MarkLucock@newcastle.edu.au

Purpos
To exa
comp
Rec
The
m
ir

Opinion in Clinical Nutrition and

Nutrition Science ↔ Policy
Folic Acid Fortification

November 2007: 504–511

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

Young-In Kim, MD, FRCP(C)

Evidence has established the protective effect of folic acid (FA) fortification and periconceptional supplemen-

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

Nutrition Science ↔ F
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

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

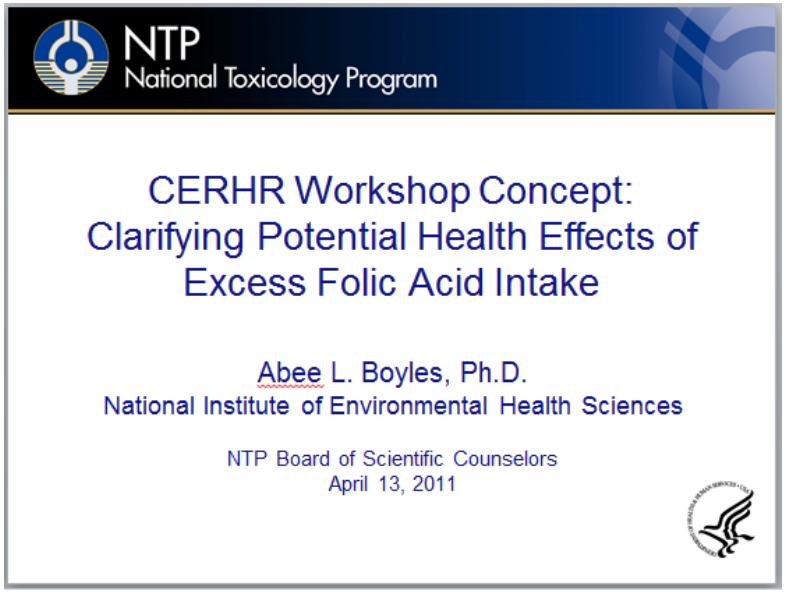
Original Workshop Concept

Goals

1. Clarify the state of the human literature for evaluating potential effects of folic acid intake above the Recommended Dietary Allowance (RDA)

2. Examine the support or sufficiency of the animal and *in vitro* literature for evaluating effects applicable to humans

3. Identify data gaps for future research to inform conclusions about potential human health effects



2011-2015 Changes

2011

- Center for the Evaluation of Risks to Human Reproduction (CERHR)
- Narrative reviews
- Reproductive focus

2015

- Office of Health Assessment and Translation (OHAT)
- Systematic review methodology
- Wider range of outcomes

Folic Acid Contributed Significantly to OHAT Methods

- First OHAT Project using:
  - Comprehensive literature search
  - Systematic screening approach
  - Database data extraction and display
  - Online resource for experts and the public

- NTP Monograph represents only a portion of the knowledge gained from this project.
- Other OHAT projects build on the lessons learned

Folic Acid Project Challenges

- Food fortification is contentious despite evidence that folic acid fortification is most effective birth defects prevention method.
- Countries considering fortification must balance potential adverse effects with the proven efficacy.
- We developed an agreed framework with federal partners to address these sensitivities.
  - Substance of concern for high intake is folic acid, the form of folate added to foods and dietary supplements (not natural food folate)
  - Objectives focus on evaluating the science for safety, not policy

Public and Stakeholder Input

- Public Website: http://ntp.niehs.nih.gov/go/38144
- 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
- Steering Committee was formed to help prioritize topics and select experts.

Steering Committee

- 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

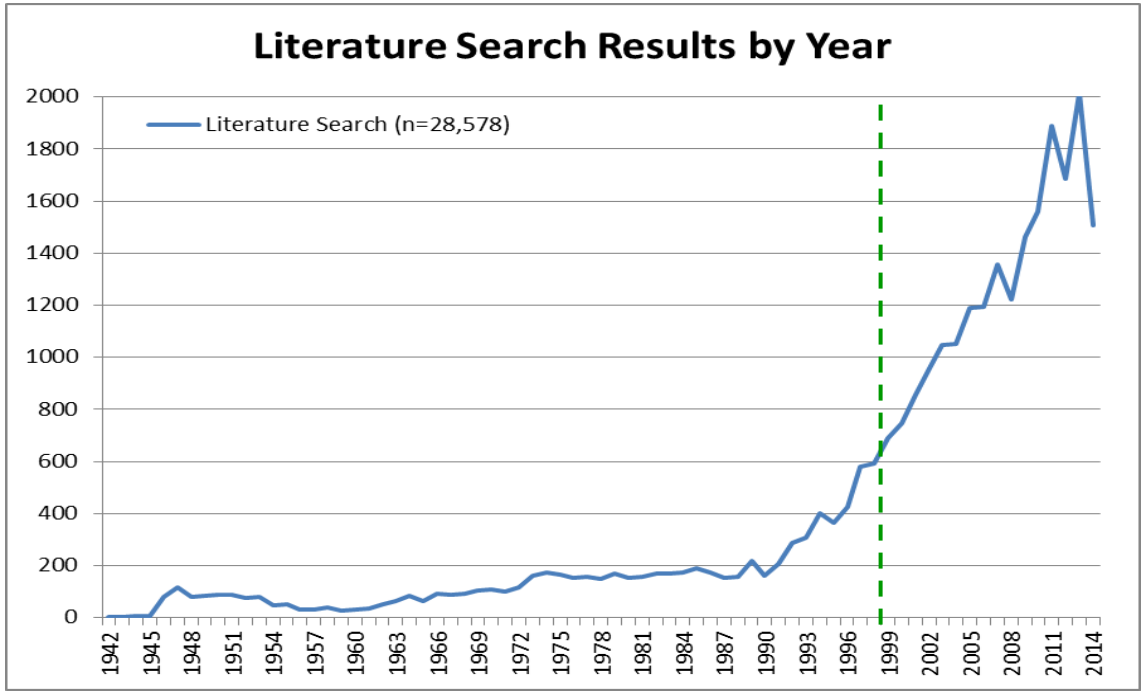
Outline

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

- Scientific Problem and Challenges
- **Examining the Evidence**
  - **Identifying and Summarizing Studies**
  - **Expert Panel Recommendations**
- Value of the Project

Project Development

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



- Over 70% of studies published after 1998 report setting the RDA and tolerable upper intake level (UL) for folic acid.

Assembling the Literature

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**

Contributors

NTP/NIEHS

- Stephanie D. Holmgren
- Denise Lasko
- Anna Lee Mosley
- Andrew A. Rooney
- Andy Shapiro
- Kristina A. Thayer
- Vickie R. Walker
- Mary Wolfe
- Yun Xie

ODS, NIH/OD

- Paul M. Coates
- Elizabeth A. Yetley

Integrated Laboratory Systems, Inc.

- Neepa Y. Choski
- Claudine A. Gregorio

MDB, Inc.

- Lesley Skalla

Social & Scientific Systems

- Anna Ciesielski Jones
- Grace Megumi Sotherden
- Fikri Yucel

1. Broad Literature Screen

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

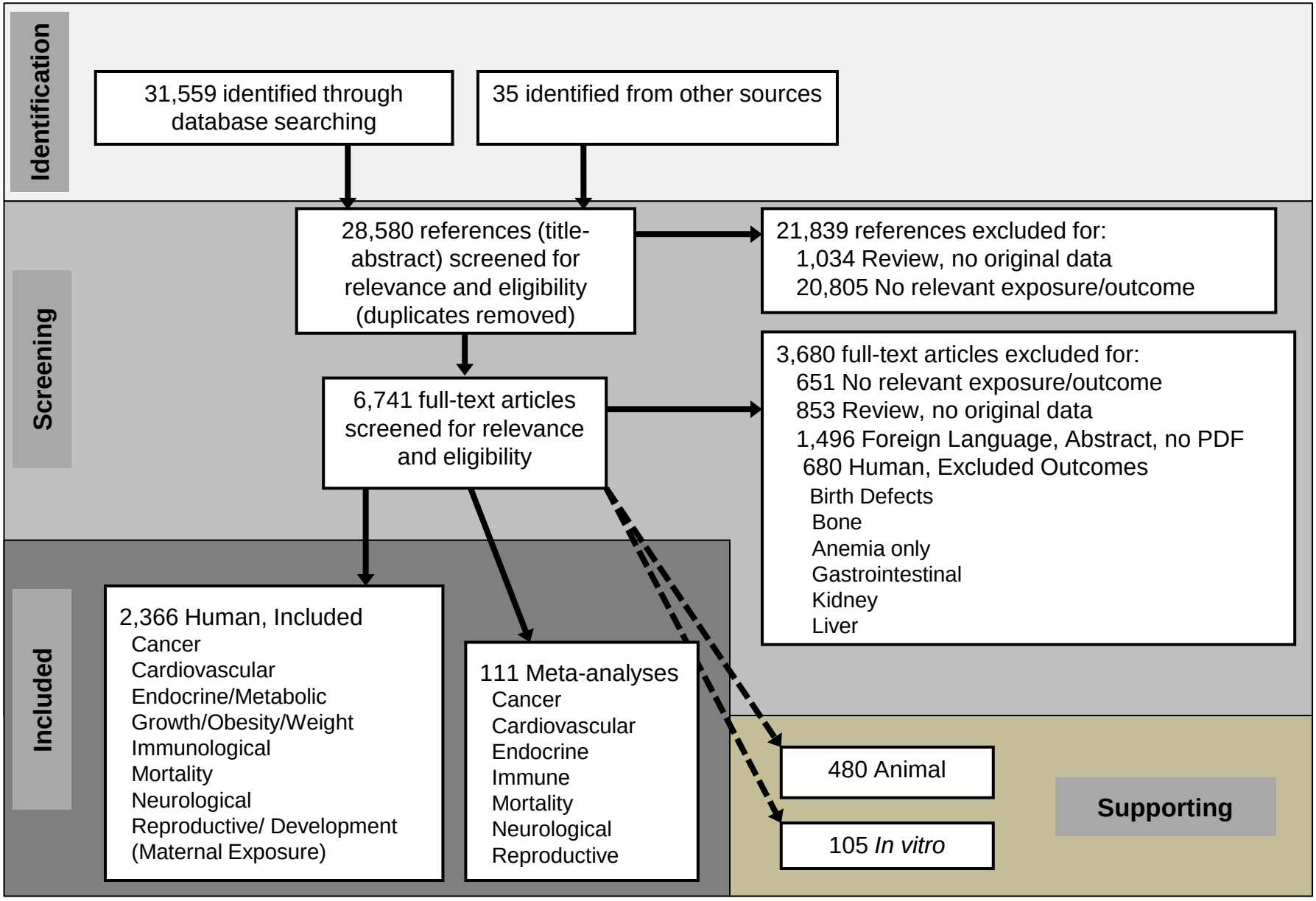
Control or Comparator:

- 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



2. Detailed Tagging of Human Studies

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?**

3. Outcome Prioritization

- 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_{12}
  - Hypersensitivity-related Outcomes
  - Thyroid and Diabetes-related Disorders

Health Assessment Workspace Collaborative (HAWC)

- Developed by Andy Shapiro, POB (hawcproject.org)
  - Study Summaries: populations, exposures, outcomes, and results
  - Visualizations: comparable results across multiple studies

- Publically Available Assessments (https://hawcproject.org/assessment/public/)
  - Cancer: 43 pooled and meta-analyses
  - Cognition and Vitamin B_{12}: 28 human studies, 2 meta-analyses
  - Hypersensitivity-related Outcomes: 42 human studies, 1 meta-analysis
  - Thyroid and Diabetes-related Disorders: 72 human studies, 1 meta-analysis

Scientific Material for Expert Panel

Monograph

- 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 HAWC
- Other health outcomes
  - Explanation of why they are **not** a focus
  - References listed in Supplementary Material
- Foundation for expert panel discussions

Expert Panel Meeting

- May 11-12, 2015 at NIH in Bethesda, MD
- Opening Talks
  - Role of Folic Acid in Birth Defects Prevention – Epidemiologic Perspectives, **Dr. Gary Shaw**, Stanford University
  - Sources of Folic Acid and Supplement Use – **Dr. Regan Bailey**, ODS
  - Blood Levels of Folate Over Time, Current U.S. Levels, and Differences Between Assessment Methods – **Dr. Christine Pfeiffer**, Centers for Disease Control and Prevention
- Public Comments – written and oral
- 30 registered attendees
- 45 registered webcast viewers

Expert Panel Members and Rapporteurs

- **Chair**
  - Cutberto Garza, MD PhD – Boston College
- **Cancer**
  (Rapporteur: Katherine E. Pelch, PhD – OHAT)
  - Tim Byers, MD – Univ. Colorado **Subpanel Chair**
  - Todd M. Gibson, PhD – St. Jude's Children's Hospital
  - Jesse F. Gregory, III, PhD – Univ. Florida
  - Young-In Kim, MD – Univ. Toronto
  - Joel B. Mason, MD – Tufts Univ.
- **Cognition and B_{12}**
  (Rapporteur: Paul R. Thomas, EdD, RDN – ODS)
  - Robert Clarke, MD – Univ. Oxford, UK
  - Paul F. Jacques – DSc, Tufts Univ.
  - Joshua W. Miller, PhD – Rutgers Univ.
  - Martha C. Morris, ScD – Rush Univ. **Subpanel Chair**
  - Jeanne I. Rader, PhD – retired from CFSAN, FDA
- **Hypersensitivity-related**
  (Rapporteur: Adam J. Kuszak, PhD – ODS)
  - Elizabeth Matsui, MD – Johns Hopkins Univ.
  - James L. Mills, MD, MS – NICHD, NIH
  - Anne M. Molloy, PhD – Trinity College, Dublin
  - Patrick J. Stover, PhD – Cornell Univ. **Subpanel Chair**
  - Henk van Loveren, PhD – Maastricht U., Netherlands
- **Thyroid and Diabetes-related**
  (Rapporteur: Kara Koehrn, MEM – US EPA)
  - Joseph M. Braun, PhD – Brown Univ. **Subpanel Chair**
  - Barry Shane, PhD – Univ. California, Berkley
  - Miroslav Stýblo, PhD – Univ. NC, Chapel Hill

Charge to the Panel

- The expert panel was charged to carry out a state-of-science evaluation for four general health effect categories to identify areas for further research. To address this charge, the expert panel was asked to:
  - Identify the areas of consistency and areas of uncertainty in the available science
  - Identify research needs based on review of the available science
  - Propose research approaches for addressing the research needs and gaps in the available science
- Each subpanel evaluated the literature assembled for its health effect category and presented their summaries and conclusions on the 2nd day
  (All presentations available: http://ntp.niehs.nih.gov/go/751400)

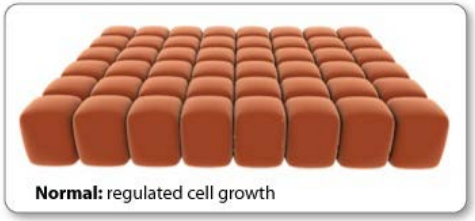
Cancer

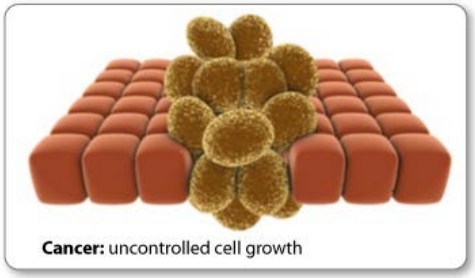
History:

- Early chemotherapeutic agents were anti-folates

Highlights of Expert Panel Recommendations:

- Consistency “showing an acceleration of colon cancer development in the few studies that have tested the effects of folic acid intake above basal requirements” in rodent model systems
- A “consistent enough suggestion in human studies of an adverse effect on cancer growth from supplemental folic acid” justifies further research.
- Pre-clinical research needed to clarify mechanisms.
- Timing of exposure (life stage, parental effects)
- Consideration of other 1-carbon nutrients
- Identification of susceptible subgroups





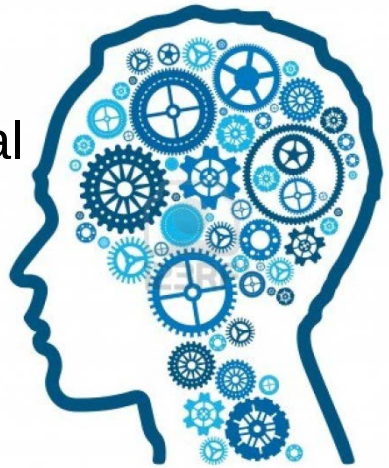
Cognition and Vitamin B_{12}

History:

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

Highlights of Expert Panel Recommendations:

- Some evidence from observational studies supports “the hypothesis that high folic acid/folate in the presence of low B_{12} exacerbates neurological problems” but the data are limited and mechanisms are unclear.
- Meta-analysis to quantify effect sizes
- Mendelian randomization studies to inform causal relevance of these associations
- Animal and in vitro studies to identify potential biological mechanisms
- Human studies considering the timing of exposure (e.g. in utero, weaning, older)



Hypersensitivity-related Outcomes

History:

- Most studies published in the last 10 years

Highlights of Expert Panel Recommendations:

- For sensitization and asthma, there was “limited health effects data on high folic acid exposure levels.”
- Need studies to identify biological pathways and biomarkers for sensitization and asthma
- Particularly in pregnant women and children, need to better assessment of confounders and effect modifiers of sensitization and asthma.
- Related outcomes (eczema, respiratory infection) are not priority areas unless new data emerges.

Thyroid and Diabetes-related Disorders

History:

- Metabolism may be “preprogramed” by nutrition

Highlights of Expert Panel Recommendations:

- For prenatal exposures there were “inconsistent results between the trial and observational studies, but increasing fat mass and insulin resistance in the observational study should be further investigated.”
  - Follow-up of existing cohorts and trials
  - Mendelian randomization in existing GWAS studies
- For thyroid disease, the available evidence did not directly address the effect of high intake of folic acid on thyroid disease.
- Future studies of diabetes should consider timing, confounders, and susceptible subgroups.

Expert Panel Conclusions

- Recommendations of each subpanel were discussed by the full panel
- Attendees made public comments
- Panel voted unanimously to accept the recommendations.
- Also voted to recommend better methods for estimating exposure/intake (total folate and specific forms)
- NTP Monograph including the Expert Panel Report will be published this summer.

Outline

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

- Scientific Problem and Challenges
- Examining the Evidence
  - Identifying and Summarizing Studies
  - Expert Panel Recommendations
- **Value of the Project**

Clearing New Ground With New Tools

Folic Acid Research Community

- Recommendations support new research efforts.
- If the RDA and UL are re-evaluated, the NTP Monograph provides a comprehensive literature review.
- Method and study summaries are publically available for research.

Benefits to OHAT

- Systematic review methods successfully implemented.
- Stakeholders engaged in a transparent process.
- Identified areas where we need new approaches and new tools.

Questions?