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NTP Board of Scientific Counselors Meeting
June 16, 2015
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
Further research is needed to investigate the possibility that folic acid supplementation might increase the risk of colorectal neoplasia.

Concerns for Safe Use of Folic Acid

“Treatment with folic acid plus vitamin B12 was associated with increased cancer outcomes and all-cause mortality in patients with ischemic heart disease…”

- Cole et al. JAMA, 2007
- Ebbing et al. JAMA, 2009
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
<table>
<thead>
<tr>
<th>2011</th>
<th>2015</th>
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<tbody>
<tr>
<td>• Center for the Evaluation of Risks to Human Reproduction (CERHR)</td>
<td>• Office of Health Assessment and Translation (OHAT)</td>
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<tr>
<td>• Narrative reviews</td>
<td>• Systematic review methodology</td>
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<td>• Reproductive focus</td>
<td>• Wider range of outcomes</td>
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A Vanguard Project

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

- Scientific Problem and Challenges
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- Value of the Project
• 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

![Literature Search Results by Year](chart.png)

• 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
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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, methytetrahydrofolate, 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

Identification

- 31,559 identified through database searching
- 35 identified from other sources

Screening

- 28,580 references (title-abstract) screened for relevance and eligibility (duplicates removed)
- 21,839 references excluded for:
  - 1,034 Review, no original data
  - 20,805 No relevant exposure/outcome

- 6,741 full-text articles screened for relevance and eligibility

- 3,680 full-text articles excluded for:
  - 651 No relevant exposure/outcome
  - 853 Review, no original data
  - 1,496 Foreign Language, Abstract, no PDF
  - 680 Human, Excluded Outcomes

Included

- 2,366 Human, Included
  - Cancer
  - Cardiovascular
  - Endocrine/Metabolic
  - Growth/Obesity/Weight
  - Immunological
  - Mortality
  - Neurological
  - Reproductive/Development (Maternal Exposure)

- 111 Meta-analyses
  - Cancer
  - Cardiovascular
  - Endocrine
  - Immune
  - Mortality
  - Neurological
  - Reproductive

Supporting

- 480 Animal
- 105 In vitro
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
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 B₁₂**
(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
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
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 B₁₂ 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.
History:

• Metabolism may be “preprogrammed” 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.
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- Value of the Project
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?