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

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May 11, 2015
**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

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[US Department of Health and Human Services (DHHS)]

- NIH
- CDC
- FDA
- NIEHS
- NIOSH
- NCTR

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National Toxicology Program
U.S. Department of Health and Human Services
http://ntp.niehs.nih.gov
Concerns for Safe Use of Folic Acid

"Treatment with folic acid plus vitamin B12 and folate, and perhaps some other, is the key to health and wellness."

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

- 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](http://ntp.niehs.nih.gov/go/38144)
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


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**

**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
      - 1,406 Foreign Language, Abstract, no PDF
      - 880 Human, Excluded Outcomes
      - Birth Defects
      - Bone
      - Anemia only
      - Gastrointestinal
      - Kidney
      - Liver

**Included**
- 2,368 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
## Size of Health Effect Categories

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

*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

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

- 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

• 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
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>

**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

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
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
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
  – Graphical display of health effects data
  – Displays individual study data and cross-study data-pivots
  – Interactive

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

**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
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Questions?