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

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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

[Diagram of US Department of Health and Human Services (DHHS) with branches to NIH, CDC, FDA, NIEHS, NIOSH, NCTR]
Concerns for Safe Use of Folic Acid
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

![Literature Search Results by Year](image)

- 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
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
## 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.
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 $B_{12}$

**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 $B_{12}$
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
Scientific Material for Expert Panel

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

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
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Questions?