NTP
National Toxicology Program

Questions to Subpanels for Addressing the Charge

Subpanel: Cognition in Conjunction with Vitamin B12 Deficiency

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

May 11-12, 2015

Areas of Consistency

Identify the health outcomes and describe the areas of consistency in the research.

- Biochemical: B12 status (Hcy, MMA)
- Neurological: Cognitive function, cognitive change
- Consistency of research: Findings of deleterious associations between high folic acid/low B12 with biochemical outcomes (Hcy, MMA) and neurological outcomes (cognition) are confined to the observational studies, but this is based on limited number of studies, different cognitive outcomes and different vitamin status cutoffs.
- RCT evidence finds that cognitively intact individuals have no evidence of cognitive risk with high folic acid supplementation. However, RCTs were not designed to answer the question as to whether high folic acid in the presence of low B12 is beneficial or deleterious to neurological outcomes.

Areas of Consistency

Are there areas of consistency where additional research would clarify the findings?

- Meta-analyses of observational study data to investigate interactions between low B12 and high folic acid using biochemical and dietary intake data and vitamin status levels
- Mendelian randomization based on markers of B12 and folate status with cognitive outcomes
- Minority opinion: Conduct randomized trials of folic acid lowering on the response to B12 supplementation (e.g., effects on neurological outcomes) in populations with low B12 status, recognizing potential ethical issues associated with interventions in individuals with low B12.

Areas of Consistency

If further research is needed, identify key issues and propose approaches to address the needs.

- For human studies, specify key aspects of design and critical confounding factors to address in the study design or analysis.

- Explore effect modifications in the interaction of low B12-high folic acid, including: hematological measures, race/ethnicity, alcohol, aspirin, smoking, n-3 fatty acids, genotypes, mood/depression, age, antacids, folic acid fortification/enrichment/supplement use.

Areas of Consistency

If further research is needed, identify key issues and propose approaches to address the needs.

- For animal or in vitro studies, propose how areas of uncertain biological plausibility in the human literature might be addressed

Examine the effects of folic acid supplementation in the presence of B12 deficiency using appropriate animal models:

- Examine various doses, forms, and timing (in utero, weaned, older) of folate exposure in B12 deficiency.
- Outcomes: Behavior (learning and memory), biochemical modifications (e.g., gene expression, DNA methylation).

Areas of Consistency

Should a systematic review be considered for any of the areas? If so, which ones?

For any proposed systematic review* of specific outcomes, specify the PICO/PECO criteria and critical aspects of study quality assessment that should be incorporated.

- Meta-analyses of observational study data to investigate interactions between low B12 and high folic acid using biochemical and dietary intake data, and vitamin status levels.
- Population: Older adults
- Exposure: Low B12-high folate status
- Comparison: Normal B12 and non-high folate
- Outcome: Cognitive function or decline

Areas of Uncertainty

Identify the health outcomes and describe the areas of uncertainty in the research.

- Cognitive function, cognitive change, dementia types
- Hematological (anemia), MCV, RDW (red cell distribution width)
- Mood/depression
- Peripheral neuropathy, evoked potential
- Cognitive development in children

Areas of Uncertainty

Are there areas of uncertainty where additional research would clarify the findings?

- Effects of different cut points for high folate in the presence of B12 deficiency
- Definitions of B12 deficiency/insufficiency
- Effect size estimates of cognitive impairments by low B12-high folic acid
- Effects of different folate forms (folic acid vs. reduced folates)
- Deleterious effects by duration of folic acid exposure
- Importance of concomitant hematologic problems
- Effect modification by severity and/or stage of B12 deficiency or other potential effect modifiers mentioned previously

Areas of Uncertainty

If further research is needed, identify key issues and propose approaches to address the needs.

- For human studies, specify key aspects of design and critical confounding factors to address in the study design or analysis.

- Observational studies on high folic acid-low B12 on unstudied outcomes to design RCTs
- Prospective studies of changes in identified outcomes; i.e., assessed at multiple time-points
- Include consideration of previously described factors as confounders/effect modifiers
- Additional randomized trials with design as previously described on new outcomes

Areas of Uncertainty

If further research is needed, identify key issues and propose approaches to address the needs.

- For animal or in vitro studies, propose how areas of uncertain biological plausibility in the human literature might be addressed.

- See as above. Animal studies on additional health outcomes that are uncertain

Areas of Uncertainty

Should a systematic review be considered for any of the areas to address uncertainty? If so, which ones?

For any proposed systematic review of specific outcomes, specify the PICO/PECO criteria and critical aspects of study quality assessment that should be incorporated – particularly to address study design issues that may contribute to uncertainty in this area.

- The data do not exist for the specified areas of uncertainty.

Summary and Recommendations for Research

Summary

- The hypothesis that high folic acid/folate in the presence of low B12 exacerbates neurological problems based on early case reports has some supportive evidence from observational studies, but the data are limited.
- The data from epidemiological studies are difficult to interpret because of heterogeneity in vitamin status cut points and in the cognitive outcomes and the omission of other neurological outcomes.
- Existing intervention studies were not designed to address this question.
- The mechanisms by which folic acid may exacerbate B12 deficiency are unclear.

Recommendations

- Meta-analysis of the existing larger observational studies to quantify effect sizes in various groups.
- Mendelian randomization studies can help inform causal relevance of these associations.
- Pending results of meta-analyses and Mendelian randomization studies, conduct animal and in vitro studies using appropriate models to identify potential biological mechanisms, as well as further human investigations including studies that examine the timing of exposure (e.g., in utero, weaning, older).