NTP
National Toxicology Program

Questions to Subpanels for Addressing the Charge

Subpanel: Diabetes and Thyroid Disorders

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.

- Majority Opinion:
  - Diabetes: Not consistent evidence for an affect for folates (includes folic acid supplementation, folate intake, and blood measures of folate status) in adults for Type I, Type II, and measures of impaired glucose or insulin homeostasis or metabolism – there is limited reporting on Type I
  - Prenatal exposures: Inconsistent results between the trial and observational studies, but increasing fat mass and insulin resistance in the observational study should be further investigated
  - Thyroid: Available evidence does not address the effect of folic acid on thyroid disease
- Minority Opinion(s):

Areas of Consistency

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

- Majority Opinion:
  - Research with existing cohorts/databases
  - Research with new studies
- Minority Opinion(s):

Areas of Consistency

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

- Majority Opinion:
  - Low Hanging Fruit:
    - Use existing GWAS studies with candidate gene approach to examine folate metabolism pathway genes and Type II diabetes risk
    - Consider examining other prospective studies with relative outcome and exposure measurements (e.g., nurses' health study or women's health initiative)
    - Consider using data from randomized trials with child follow-up
  - Future Studies:
    - Need to distinguish between supplementation, fortification/enrichment, and food folate
    - Measurement of folate needs to be prospective and should consider UMFAs and total folate
    - Need to consider baseline intake and deficiency prevalence
    - Examine subgroup susceptibility according to genetic polymorphisms, environmental exposures (e.g., environmental diabetogens) and other modifiers (e.g., medications and vitamin B_{12})
    - Consider different periods of vulnerability
      - Pre-conception and prenatal

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.

- Majority Opinion:
  - Diabetes:
    - Human studies do not provide additional rational for animal studies that would look at folic acid alone as a risk factor for diabetes
    - However, animal studies that look at modifying factors (e.g., diabetogenic chemicals) may provide additional insight into susceptible subgroups in humans
    - Animal studies could include consideration of different stages of vulnerability
- Minority Opinion(s):

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.

- Majority Opinion:
  - Diabetes: No, given the design of most studies and the lack of prospective studies or trials
- Minority Opinion(s):

Areas of Uncertainty

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

- Majority Opinion:
  - Thyroid: Available evidence does not address the effect of folic acid on thyroid disease
- Minority Opinion(s):

Areas of Uncertainty

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

- Majority Opinion:
  - Thyroid: No compelling reason to study this particular endpoint over others
- Minority Opinion(s):

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.

- Majority Opinion:
- Minority Opinion(s):

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.

- Majority Opinion:
- Minority Opinion(s):

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.

- Majority Opinion:
  - Thyroid: No, not at this time.
- Minority Opinion(s):

Summary and Recommendations for Research

- Summary of available research
  - Diabetes: Based on limited data, there is not consistent evidence for an effect of high folic acid intakes or high folate status on diabetes risk or glucose/insulin metabolism
  - Prenatal exposures: Inconsistent results between the trial and observational studies, but increasing fat mass and insulin resistance in the observational study should be further investigated
  - Thyroid: Available evidence does not address the effect of folic acid on thyroid disease

Summary and Recommendations for Research

- Recommendations (diabetes)
  - Studies that could be done now
    - Use existing prospective cohorts with valid and reliable measurements of exposure and outcome
    - Use existing GWAS studies to do Mendelian randomization studies with candidate genes
    - Follow-up with adults and children in folic acid supplementation trials
  - Future studies
    - Use valid and reliable prospective measurements of folic acid intake or folate status
    - Need to consider baseline intake and deficiency prevalence
    - Consider the impact confounders that affect folate metabolism and diabetes risk (e.g., medications)
    - Examine subgroup susceptibility according to genetic polymorphisms, environmental exposures (e.g., environmental diabetogens), and nutritional factors
    - Consider different periods of vulnerability, especially preconception and prenatal
    - Look at folic acid as well as total folate in assessing risk of toxicities