

Questions to Subpanels for Addressing the Charge

Subpanel: Hypersensitivity

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

May 11-12, 2015



Major Challenges Faced by the Sub-Group

1. Observational studies
2. Confounding factors
3. Mixed results from animal studies
4. Lack of high folic acid exposure
5. Folic acid vs. folate quantified
6. Methods to quantify folate
7. Small effect sizes
8. Multiple comparison corrections lacking
9. Endpoints as secondary outcomes
10. Some studies dealt with deficiency, not excess folic acid



Summary of Outcomes

- Sensitization / Atopy / Allergy
 - Total IgE
 - Specific IgE
 - Food allergy
- Asthma
 - Wheeze
- Eczema / Atopic dermatitis
- Respiratory Infection



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

Sensitization Consensus Opinion:

- There is mixed evidence for a relationship between folic acid or folate status and total and specific IgEs.
- This is an important public health issue to resolve because atopic diseases are the most common chronic childhood diseases (i.e., asthma, allergic rhinitis, eczema, food allergy). Therefore more research is recommended.

Asthma / Wheezing Consensus Opinion:

- Folic acid and high folate status have not been shown to induce asthma.
- Wheezing itself is not a singular biological condition.
- The literature does not support a relationship between folic acid exposure and wheezing at the studied doses.



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

Eczema / Atopic Dermatitis

- Eczema is a general condition; atopic dermatitis.
- All studies (including pre- and post-natal exposure), except a multivitamin study, showed no association between eczema / atopic dermatitis and folic acid or folate status.
- Pathway and mechanistic insights are lacking.
- This is a low priority research area.

Respiratory Infection

- Preponderance of evidence does not suggest a relationship between folic acid intake and respiratory infection susceptibility.



Should a systematic review be considered for any of the areas? If so, which ones? Pre/post natal asthma outcome

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

- For all outcomes, no new systematic reviews are warranted, due to a paucity of data and heterogeneity of the current literature.



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

Sensitization and Asthma:

- Address limited health effects data on “high” folic acid exposure levels for both prenatal and postnatal time periods.
- Need to better understand how folic acid/folate functions in biological pathways in sensitization and asthma.
 - Well-designed human maternal and cord blood, human cell culture, mast cell and basophil responses and animal studies (RCT, prospective or observational) to identify pathways and biomarkers.
 - Complementary animal and human cell culture studies.
- More well-controlled human studies, especially in pregnant women and in children, to elucidate the effect of folic acid exposure on sensitization and asthma.
 - Better assessment of confounders (diet, other nutrients, environmental exposures)
 - Better assessment of effect modifiers (age, dose, genetics, nutrients, disease)



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

Eczema / Atopic dermatitis

Respiratory Infection

- Unless new data emerges, these are not priority areas for future research.