NTP
National Toxicology Program

Questions to Subpanels for Addressing the Charge

Subpanel: Cancer

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

May 11-12, 2015

Pre-Clinical Areas of Consistency

- Inadequate dietary folic acid intake increases colon cancer risk in rodent model systems.

- There is consistency in showing an acceleration of colon cancer development in the few studies that have tested the effects of folic acid intake above basal requirements in rodent model systems.

Pre-Clinical Research Needs

- Study effects of folic acid above basal requirements on the growth of cancers other than the colon, especially those where there is a suggestion of a clinical effect in humans (e.g., prostate, mammary).
- Compare effects of folic acid to those of reduced folates.
- Better define the dose-response relationship for each outcome.
- Identify and employ those animal models that are most relevant to human folate metabolism and carcinogenic processes.
- Better define critical life stages and other timing effects of exposure.
- Better study possible interplay between folic acid and other 1-carbon nutrients.
- Better study effect modification by other covariates (e.g., alcohol, age, genetics, sex).
- Explore maternal and paternal effects of folates and folic acid on offspring cancer risk.

Clinical Areas of Consistency

- Inadequate dietary folate intake increases colorectal cancer risk in humans.
- There is no benefit for cancer reduction from supplements among people whose baseline folate status is adequate.
- There is a consistent enough suggestion in human studies of an adverse effect on cancer growth from supplemental folic acid to justify further research.

Clinical Research Needs

- Clarify whether the existing suggestive evidence from clinical trials for increased risk is driven by effects in specific subgroups.
  - e.g.: by age, pre-existing neoplasia, genetics, other factors
- Utilize new observational studies to identify subgroups that are at risk of tumor acceleration.
- Determine if other 1-carbon nutrients are modifiers of the potential adverse folic acid effects.
- Define whether the form of ingested folate impacts on risk.
- Determine effects of withdrawal from folic acid supplementation on polyp growth.
- Define the above issues in other implicated cancer sites in addition to colorectal cancer (e.g., prostate).

Pre-Clinical Summary/Research Recommendations

- Although inadequate dietary folic acid intake increases colon cancer risk in rodent model systems, there is consistency in showing an acceleration of colon cancer development in the few studies that have tested the effects of folic acid intake above basal requirements in these systems.
- Study effects of folic acid above basal requirements on the growth of cancers other than the colon, especially those where there is a suggestion of a clinical effect in humans (e.g., prostate).
- Compare the effects of folic acid to those of reduced folates and overall folate status on cancer growth, define the dose response of each, evaluate the interplay of other 1-carbon nutrients, study mechanisms of effects, and evaluate the modification by other covariates (e.g., alcohol, age, genetics, sex).
- Identify and employ those animal models that are most relevant to human folate metabolism and carcinogenic processes.
- Better define critical life stages and other timing effects of exposure.
- Explore maternal and paternal effects of folates and folic acid on offspring cancer risk.

Clinical Summary/Research Recommendations

- Although inadequate dietary folate intake increases colorectal cancer risk in humans, there is no benefit for cancer reduction from supplements among people whose baseline folate status is adequate.
- There is a consistent enough suggestion in human studies of an adverse effect on cancer growth from supplemental folic acid to justify further research.
- There is a need to clarify whether the existing suggestive evidence from clinical trials for increased risk is driven by effects in specific subgroups (e.g.: by age, pre-existing neoplasia, genetics, other factors), and assess long-term outcomes among subjects from prior folic acid trials.
- New studies are needed to identify subgroups that are at risk of tumor acceleration.
- Define whether the form of ingested folate impacts on risk and whether other 1-carbon nutrients are modifiers of the potential pro-tumorigenic effects of excess folic acid.
- Define the above issues in other implicated cancer sites in addition to colorectal cancer (e.g., prostate).