Research Brief 152: Folic Acid Supplementation Lowers Blood Arsenic by Increasing Arsenic Methylation

http://www.niehs.nih.gov/sbrp/

Background:

Methylation (the addition of methyl groups) of ingested inorganic arsenic to methylarsonic (MMA) and dimethylarsinic acids (DMA) occurs by enzymatic reactions that transfer the methyl group from S-adenosyl-methionine (SAM) to arsenic. Methylation of arsenic facilitates its urinary elimination and is considered a detoxification process. Because folate compounds play an important role in regulation of SAM levels, folate may also influence arsenic methylation and toxicity.

Chronic arsenic exposure currently affects more than 100 million people worldwide.

The Columbia University SBRP is a collaboration of highly interactive research projects focused on improving our understanding of health effects, geochemistry, hydrology and remediation of arsenic in groundwater. image of people pumping water from a hand pumped wellTheir aim is to lower the health risks associated with exposure to arsenic in groundwater, by guiding the focus of interventions in high-risk areas. The Columbia SBRP has established the Health Effects of Arsenic Longitudinal Study, a cohort study with a population of nearly 12,000 individuals exposed to a wide range of inorganic arsenic (InAs) from drinking water in Araihazar, Bangladesh. The Columbia group has also made methodological advances increasing our capabilities to measure total arsenic and arsenic metabolites in blood, where concentrations are an order of magnitude lower than those in urine. They found that blood arsenic is a biomarker of arsenic exposure and is directly associated with the risk for arsenic-induced skin lesions.

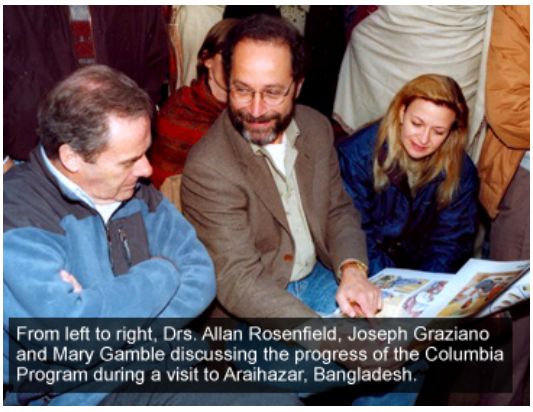
Dr. Mary Gamble is building upon this work to investigate nutritional influences on arsenic metabolism and toxicity. Her research team documented a high prevalence of hyperhomocysteinemia (abnormally high levels of homocysteine in the blood; caused by deficiencies in folic acid, B6 or B12) and folate deficiency among Bangladeshi adults; these conditions were both associated a reduced capacity to methylate arsenic.

Advances:

In a recent, randomized, double-blind, placebo controlled trial of folic acid supplementation, Dr. Gamble and colleagues analyzed total arsenic and arsenic metabolites in urine and showed that folic acid supplementation resulted in an increase in the proportion of total urinary arsenic excreted as DMA and a reduction in MMA and InAs in urine. Because DMA has a shorter circulating half-life than other arsenic metabolites, Dr. Gamble hypothesized that facilitation of arsenic methylation via folic acid supplementation might lower total blood arsenic concentrations.

Her team tested this hypothesis by measuring total arsenic and arsenic metabolites in blood of 130 participants with low plasma folate before and after 12 weeks of supplementation with folic acid (400 µg/day, equivalent to the US Recommended Daily Allowance) or placebo. Folic acid supplementation lowered total blood arsenic concentrations by increasing the methylation of InAs and MMA to DMA, which is rapidly excreted in urine. This was evidenced by reductions in the concentrations of InAs and MMA in blood and a rapid increase in the concentration of DMA in urine. Specifically:

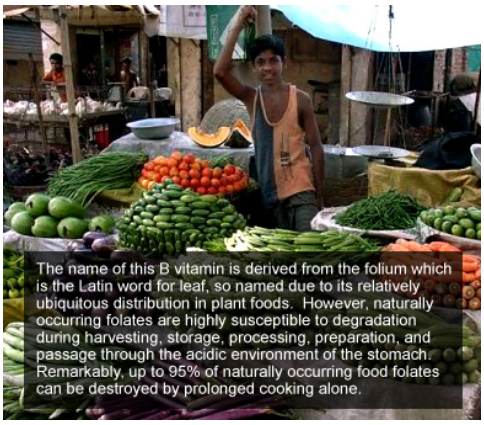
- 85% of all participants in the folic acid group experienced a decline in levels of MMA in blood (bMMA).
- Average bMMA reduction in the folic acid group was 22%, with greater declines observed for individuals who had higher bMMA at the beginning of the trial.
- There was no change in DMA in blood in the folic acid group after the 12 week intervention, because once DMA is formed, it is rapidly excreted in urine.
- Inorganic arsenic in blood decreased by nearly 19% for the folic acid group.
- Folic acid supplementation reduced total blood arsenic by 14%.



From left to right, Drs. Allan Rosenfield, Joseph Graziano and Mary Gamble discussing the progress of the Columbia Program during a visit to Araihazar, Bangladesh.

Significance:

This study indicates that folic acid supplementation lowers total blood arsenic primarily by lowering concentrations of MMA in blood. These findings imply that folic acid supplementation may reduce body stores of arsenic. Dr. Gamble concludes that therapeutic strategies to facilitate arsenic methylation, particularly in populations with a high prevalence of folate deficiency and/or hyperhomocysteinemia such as Bangladesh, may lower blood arsenic concentrations, and thereby contribute to the prevention of arsenic-induced illnesses. This research, which provides information critical to the identification of potential targeted interventions for preventing arsenic toxicity, could have significant impacts on public health and policy.



For More Information Contact:

Mary V. Gamble
Environmental Health Sciences
Mailman School of Public Health
New York, NY 10032
Tel: 212-305-7949
Email: mvg7@columbia.edu

To learn more about this research, please refer to:

Gamble, Mary V., X. Liu, Vesna Slavkovich, J. Richard Pilsner, Vesna Ilievski, Pam Factor-Litvak, Diane Levy, S. Alam, Mohammad N. Islam, Faruque Parvez, Habibul Ahsan, and Joseph H. Graziano. 2007. Folic acid supplementation lowers blood arsenic. American Journal of Clinical Nutrition (http://www.ajcn.org/) Exit NIEHS Website. (in press)

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