Columbia University Superfund Research Program: "Health Effects and Geochemistry of Arsenic and Manganese

PI: Joseph Graziano, PhD

Annual Progress Report, 12/15/11

Research Highlight #1: Arsenic Exposure, Arsenic Methylation Capacity, and Risk of Cardiovascular Disease in Bangladesh

PI: Habibul Ahsan

Epidemiologic studies have documented associations between arsenic exposure from drinking water and an elevated risk of cardiovascular disease (CVD) (1, 2). However, the individual susceptibility to CVD due to variability in arsenic methylation capacity has not been well established. The primary metabolic pathway of inorganic arsenic (InAs) in humans involves one-carbon methylation. Once ingested, InAs is methylated to monomethylarsonic acid (MMA^{+5}) which, after reduction to MMA^{+3}, can undergo a second methylation to dimethylarsinic acid (DMA). The relative distribution of urinary arsenic metabolites varies from person to person and has been interpreted to reflect arsenic methylation capacity (3, 4). A series of epidemiologic studies have reported associations between suboptimal methylation capacity, indicated as a high proportion of urinary MMA, and risks of skin lesions, skin cancer, urothelial carcinoma, bladder cancer, and lung cancer in arsenic-exposed populations (5, 6). However, research on the potential effect of arsenic methylation capacity on CVD risk is limited. As part of project 2, we conducted a prospective case-cohort study nested in the original cohort of the Health Effects of Arsenic Longitudinal Study (HEALS) (7) in Araihazar, Bangladesh, to assess the association between arsenic methylation capacity and the subsequent risk of diseases of the circulatory system. We also assessed the joint effect of urinary MMA% with cigarette smoking and well water arsenic levels. A total of 369 incident fatal and non-fatal cases of diseases of the circulatory system, including 211 cases of heart disease and 148 cases of stroke, respectively, were identified from 11,746 participants who have been exposed to arsenic from drinking water ranging from 0.1 µg/L to 864 µg/L (mean 99 µg /L) at baseline. A subcohort of 1,109 subjects randomly selected from the 11,224 participants with available baseline data on water and urinary arsenic exposure was selected as the control group. The percentage of InAs, MMA, and DMA (InAs%, MMA% and DMA%) in total urinary arsenic at baseline was calculated after subtracting AsB and AsC (i.e., nontoxic arsenic species from dietary sources) from the total.

Participants with higher levels of urinary MMA% had a significant increased risk of diseases of the circulatory system, particularly heart disease. The HRs for overall diseases of circulatory system in increasing MMA% tertiles were 1.00 (reference), 1.23 (95% CI, 0.87-1.77), and 1.38 (95% CI, 0.98-1.93), adjusting for potential confounders including sex, age, body mass index, and smoking status. The HRs for heart disease in increasing MMA% tertiles were 1.00 (reference), 1.62 (95% CI, 1.05-2.50), and 1.53 (95% CI, 1.00-2.34). Participants with a secondary methylation index (SMI), i.e., the ratio of DMA to MMA, of ≥ 7.2 had a statistically significant 38% (HR = 0.62; 95% CI, 0.41-0.93) and 42% (HR = 0.58; 95% CI, 0.36-0.93) reduction in risk of diseases of the circulatory system and heart disease, respectively, compared with those who had a SMI of ≤ 4.8. There was no association between MMA% or SMI and stroke risk. In addition, the joint effect of a higher level of MMA% and ever-smoking was greater (HR = 3.35; 95% CI, 1.84-6.12) than the effect of ever-smoking alone (HR = 2.34; 95% CI, 1.23-4.47) or higher MMA% alone (HR = 1.16; 95% CI, 0.70-1.94).

To the best of our knowledge, the present study is the first large prospective study to investigate associations between arsenic methylation capacity and the risk of diseases of the circulatory system in a population exposed to arsenic from drinking water. Similar to the literature on arsenic methylation capacity and cancer risk, our findings suggest that individuals with suboptimal or incomplete arsenic methylation capacity, as indicated by a relatively higher MMA% in urine, are more susceptible to the effects of arsenic exposure on

cardiovascular disease. Our data also support that cigarette smoking is an important factor that influences the health effects of arsenic exposure and arsenic methylation capacity. These findings, which are being submitted for publication, have major research and policy implications.

References:

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Research Highlight #2: Glutathione, arsenic methylation and global DNA methylation in Bangladesh
PI: Mary Gamble

Over 70 million people in Bangladesh are chronically exposed to inorganic arsenic (InAs) in drinking water (1). Exposure to arsenic is associated with increased risk for cancers of the skin, lung, bladder, liver, and kidney (2), as well as negative effects on the circulatory (3), nervous (4), and respiratory systems (5). In the liver, InAs undergoes a series of methylation reactions that produce monomethyl (MMA) and dimethyl (DMA) arsenical species (6). Since these methylated forms have shorter circulating half-lives than InAs, arsenic methylation has generally been considered to be a detoxification pathway. Reduced methylation capacity (as indicated by an increased percentage of MMA and decreased percentage of DMA in urine) is associated with increased risks of skin and bladder cancer (reviewed in (7)). A reduction in global DNA methylation has also been shown to be associated with increased odds of developing arsenic-induced skin lesions (8). Thus, understanding the modifiable factors that influence methylation capacity may help us to develop inventions to reduce arsenic toxicity.

The folate-dependent *one-carbon metabolic pathway* regulates the methylation of DNA and arsenic by providing methyl groups from s-adenosylmethionine, or SAM (6). A related pathway, known as the *transsulfuration pathway*, is important for the production of glutathione (GSH), the body's primary antioxidant (9). The concentrations of GSH and its oxidized form, GSSG, are the primary determinants of the redox environment within the cell: a more oxidized redox environment (lower GSH and higher GSSG) is associated with increased oxidative stress (10). The regulation of one-carbon metabolism and the transsulfuration pathway are highly inter-related: under conditions of oxidative stress, homocysteine is directed away from the production of SAM and toward the generation of GSH (11). Additionally, arsenic methyltransferase (AS3MT) and DNA methyltransferases—the enzymes responsible for transferring methyl groups to arsenic and DNA, respectively—have both been identified as containing potentially redox-sensitive cysteine residues in their active sites (12). As such, we wished to test the hypothesis that redox status influences the methylation of As and DNA.

We conducted a cross-sectional study of 375 participants in Bangladesh in which we assessed the associations of redox status (blood GSH and GSSG) with global DNA methylation and arsenic metabolites (InAs, MMA, and DMA) in urine. We also examined modification of these associations by folate nutritional status. We found that in folate-deficient participants, those in the highest quintile of blood GSSG had a 4.7% higher urinary inorganic As (uInAs), 3.0% higher MMA, and 7.7% lower DMA, as compared to the lowest quintile (p_{trend}=0.03, 0.02, and 0.0007, respectively). Those in the highest quintile of blood GSSG also had 11.2% lower global DNA methylation levels compared to the lowest quintile (p_{trend}=0.0061). No significant associations were observed in the folate-sufficient group.

We conclude that a more oxidized intracellular redox environment, as indicated by increased blood GSSG, is associated with decreased As and DNA methylation, but only in folate deficient participants. Alterations of redox status may prove to be a modifiable mechanism through which environmental exposures influence methylation capacity: antioxidant and/or folate supplementation may increase arsenic and DNA methylation capacity in populations under chronic oxidative stress. Further research should directly examine effects of manipulating redox status on As and DNA methyltransferase activities and further elucidate the protective influences of folate against redox-associated reductions in methylation.

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Project 1: ***Genotoxic and Cell Signaling Pathways of Arsenic in Mammalian Cells***
PI: Tom Hei, PhD

1) The overall goals of this project remain unchanged.

2) During the current funding period, we examined the pro-apoptotic function of sodium arsenite in melanoma cells with or without concurrent treatment with statins, a class of cholesterol-lowering drugs. Treatment of melanoma cells by sodium arsenite or statins (simvastatin and lovastatin) dramatically enhanced the induction of heme oxygenase-1 (HO-1) and a down-regulation of cyclooxygenase-2 (COX-2) protein levels. Furthermore, treatment of melanoma cells with sodium arsenite or statins with an additional inhibitor of HO-1 expression resulted in a synergism in apoptosis induction. In contrast, monotreatment required high doses of statins (20–40 μM) for effective induction of apoptosis. As an alternative approach, pretreatment of melanoma cells with statin at decreased doses (5–20 μM) dramatically enhanced TRAIL-induced apoptosis, due to suppression of the NF-κB and STAT3-transcriptional targets. Combined treatment with sodium arsenite and TRAIL or simvastatin and TRAIL efficiently induced apoptotic commitment in human neuroblastoma cells as well. In summary, our findings on enhancing effects of combined treatment of cancer cells using sodium arsenite and statin provide the rationale for further preclinical evaluation.

To provide mechanistic insights on the neurotoxic effects of arsenic observed in Project 3, we continued our studies in determining if arsenic treatment of rat neuron-like PC12 cells would result in programmed death/apoptosis under defined culture conditions. In the last funding period, we observed arsenite-induced apoptosis in both cancer (melanoma) cells and neuron-like PC12 cells 48 h after treatment with 2-4 μM arsenite. Both melanoma cells and PC12 cells were characterized by surface expression of neuron growth factor-receptor (NGF-R). In the current year, we further confirmed that NGF (ligand) added to the cell media could suppress arsenite-induced apoptosis only in neuron-like PC12 cells via induction of the PI3K-AKT pathway, but not in arsenate-sensitive melanoma cells. This differential response to a combination of arsenite and NGF will allow the protection of neurons from cytotoxic effects of arsenite, which has been used as a therapeutic regimen in cancer therapy.

Publications:

Ivanov, V., Partridge, M.A., Huang, S.X., and **Hei, T.K**. Suppression of the proinflammatory response of metastatic melanoma cells increases TRAIL induced apoptosis. ***J. Cell Biochem***. 112(2):463-75, 2011. PMID: 21268068. doi: 10.1002/jcb.22934.

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Huang, S.X., Jaurand, M. C., Kamp, D. W., Whysner, J., and **Hei, T.K**. Role of mutagenicity in asbestos fiber induced carcinogenicity and other diseases. ***J. Toxicol. Environ. Hlth. B Crit Rev*** 2011;14:179-245. PMCID: PMC3118525

Ivanov,V., and **Hei, T.K**. Regulation of apoptosis in human melanoma and neuroblastoma cells by statins, sodium arsenite and TRAIL: a role of combined treatment versus monotherpy. ***Apoptosis****:* 16:1268-1284, 2011. PMID: 21910007 PMCID: in process.

Project 2: ***A Cohort Study of Health Effects of Arsenic Exposure in Bangladesh***
PI: Habibul Ahsan

This prospective cohort study recruited 11,746 men and women in Araihazar, Bangladesh, during 2000-2002 to investigate the health effects of arsenic exposure, with an initial focus on skin lesions and skin cancers. Between 2006 and 2008, the cohort was expanded to 20,033 individuals. Expansion participants were enrolled into the cohort through in-person interviews and had blood and urine samples collected in the same manner as the original cohort. The design of this multidisciplinary project and cohort description was published (Ahsan et al., 2005). We have numerous publications utilizing the baseline cross-sectional data on arsenic exposure and adverse health effects, including prevalent skin lesion cases, as well as longitudinal analyses of mortality, incident skin lesions, diabetes, and respiratory disease with the prospective data.

In-person interviews and clinical examinations of the cohort participants are conducted every 2 years. The ten-year follow-up visit of the original cohort and 4-year follow-up visit of the expansion cohort is underway using the same study instrument. To date, we have completed laboratory measurement of urinary total arsenic concentration in all baseline, two-year follow-up, 4-year follow-up, and 6-year follow-up samples from the original HEALS cohort and all baseline and two-year follow-up samples of the expansion cohort.

Utilizing the data collected from the first three follow-up visits (2-, 4-, and 6-year visits) of the original cohort, our prospective analyses based on individual-level data clearly suggest *increased mortality in relation to increases in arsenic exposure* based on water and urinary arsenic. These findings were recently published (Argos et al. Lancet 2010). We also published a manuscript in which we observed an increased risk of cardiovascular disease mortality in relation to increases in arsenic exposure (Chen et al. BMJ 2011). Additionally, we utilized the prospective data through 6-years of follow-up to assess skin lesion incidence and observed a clear dose-dependent association between arsenic exposure and skin lesion risk, even at low exposure levels (water arsenic concentration <100 µg/L) (Argos et al. AJE 2011). More recently, we have published two publications reporting modification of the association between arsenic exposure and incident skin lesion status by dietary patterns (Pierce et al. AJE 2011) and by smoking status in men (Melkonian et al. AJE 2011).

The objectives of our current analyses and follow-up interviews are to specifically examine the aims stated in the renewal of this project and have not been modified since the last progress report. Several other manuscripts are being drafted for publication reporting results of our prospective cohort analyses of modification of the effects of arsenic on disease-specific mortality and other health outcomes.

In addition to the above-mentioned components, resources from this prospective cohort study have also yielded many other ancillary studies and publications including 6 additional R01 grants from NIH to investigate the genetic and nutritional aspects as well as chemoprevention of arsenic-related health effects.

Student Involvment:

Pre-doctoral:

Stephanie Melkonian, MS, is working under supervision of Dr. Ahsan and has been conducting analyses of associations of arsenic exposure and its interaction with smoking, nutrients, and other lifestyle factors in relation to risk of skin lesions in the HEALS cohort. Her first paper on smoking and occupational factors has been published in American Journal of Epidemiology. A second paper on nutrient-skin lesions association is being prepared for publication. She has also worked on a methodological study evaluating the validity of arsenic exposure assessment in HEALS and its implications on the risk estimates on health outcomes. This work has led to a manuscript that is being submitted for publication.

Lital Yinon, MS, is working with Drs. Yu Chen and Ahsan conducting analyses to evaluate association of blood pressure and blood pressure variation with total/cardiovascular diseases mortality in the HEALS. She is also developing ideas to assess changes in urinary arsenic overall time and its relationship with health effects for her dissertation project.

Post-doctoral:

Gene Pesola, MD, has been evaluating relationship between arsenic exposure and dyspnea in HEALS cohort. This work has led to a publication in European Journal of Respiratory Diseases. In addition, he has also been evaluating relationship between dyspnea and proteinuria and mortality in HEALS cohort as part of his PhD dissertation under supervision of Dr. Ahsan.

Fen Wu, PhD, has been working with Drs. Chen and Ahsan. She has analysed effects of arsenic exposure on EKG abnormality, intima media thickness, peripheral vascular disease, and serum markers for cardiovascular disease. She also conducted analyses to evaluate association between urinary arsenic metabolites and cardiovascular disease.

Project 2 - Supported 2010-2011 Publications:

Argos M, Kalra T, Rathouz PJ, Chen Y, Pierce B, Islam T, Ahmed A, Hassan R, Parvez F, Graziano J, Ahsan H. A Prospective Study of Arsenic Exposure from Drinking Water and Incidence of Skin Lesions in Bangladesh. *Amer J Epidemiol* 2011;174(2):185-94. PMCID: PMC3167679

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Melkonian S, Argos M, Pierce BL, Chen Y, Islam T, Ahmed A, Syed EH, Parvez F, Graziano J, Rathouz PJ, Ahsan H. A Prospective Study of the Synergistic Effects of Arsenic Exposure and Smoking, Sun Exposure, Fertilizer Use, and Pesticide Use on Risk of Premalignant Skin Lesions in Bangladeshi Men. *Amer J Epidemiol* 2011;173(2):183-91 PMCID: PMC3011951

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Wu Fen, Jasmine F, Kibriya MG, Liu M, Wóojcik O, Parvez F, Roy S, Rahaman R, Segers S, Slavkovich V, Islam T, Levy D, van Geen A, Graziano J, Ahsan H, and Chen Y. Association between arsenic exposure from drinking water and serum levels of cardiovascular markers. *Amer J Epidemiol*. In press, 2011.

Project 3: *Consequences of Arsenic and Manganese Exposure on Childhood Intelligence*
PI: Joseph Graziano

This project builds upon our discovery that exposure to arsenic (As) and manganese (Mn) in drinking water has adverse effects on intelligence in children. Two studies, in Bangladesh and New England, are in progress. Several years ago we launched a study of elementary school children in New Hampshire (NH) to determine whether exposure to As impairs intellectual functioning in a U.S. population. Because recruitment in NH was not proceeding at a sufficient rate, we expanded our study into Maine (ME) where recruitment is excellent and As exposure is more prevalent. To date, 413 children have been recruited and completed the protocol and results will soon follow.

The second portion of this project takes place in Bangladesh, where our research seeks to determine whether exposure to As and Mn has an adverse effect on motor function and on intelligence. This study involves a 2 x 2 design, i.e., high/low (<10 ppb) drinking water As and high/low (< 400 ppb) water Mn, with 75 children in each cell. Thus, half of the children in the study are drinking water with As and Mn levels below the WHO guideline. We completed the recruitment of all 300 children, 7-9 years of age. Our first publication (Wasserman et al, 2011) relates to child intelligence: When adjusted only for each other, both As and Mn in blood (BAs; BMn) were significantly negatively related to most WISC-IV subscale scores. With further adjustment for socio-demographic features and ferritin, BMn remained significantly associated with reduced Perceptual Reasoning and Working Memory scores; associations for BAs, and for other subscales, were expectably negative, but largely non-significant. Urinary As (per gram creatinine) was significantly negatively associated with Verbal Comprehension scores, even with adjustment for BMn and other covariates. Mn by As interactions were not significant in adjusted or unadjusted models.

A second publication (Khan et al, 2011a) describes a novel finding, i.e., that BMn (but not BAs) is adversely associated with child behavior. Using the Child Behavior Checklist, Teacher's Report Form (TRF), we observed that water manganese (WMn) was positively and significantly associated with TRF internalizing, externalizing and total TRF scores in models adjusted for WAs and sociodemographic covariates. We also observed a dose-response relationship between WMn and TRF externalizing and TRF total scores among the participants of the study. We did not find any associations between WAs and various scales of TRF scores. We have also discovered that Mn exposure is associated with reduced math scores in school (Khan et al, 2011b).

An additional manuscript (Parvez et al, 2010) describes another novel finding, i.e., that As exposure is associated with deficits in motor function in 7-9 year old children. The next phase of the Bangladesh work involved remediation of the ongoing As and Mn exposures via the installation of deep tube wells (low in As and Mn) in each child's village, coupled with arsenic-related education. We have just completed a re-evaluation of intelligence and motor function in these 300 children, nearly two years after the provision of safe water.

Student Involvement: Three doctoral students will have defended their dissertations from this project.

Christine George, Dr. Graziano's PhD student, spent one year in Bangladesh with support of a Fulbright scholarship. She will defend her PhD dissertation on February 8th, 2012. She has been accepted for a two-year position in the post-doctoral program of the Earth Institute at Columbia University where she will investigate heavy metal exposure due to mining activities in Zambia.

Khalid Khan, who completed his DrPH degree in EHS in 2010 and spent several months with us as a post-doctoral fellow before accepting a post-doctoral position in Oregon Health and Science University where he is working on pesticide exposure and child development. He had been responsible for the assessment of child behavior, and the development of a classroom based arsenic education program.

Faruque Parvez, who conducted the studies of motor function, successfully defended his DrPH degree in October, 2011. He is staying in the EHS department a project director for two of the ongoing Bangladesh studies (Projects 2 and 3), with the title of Associate Research Scientist.

Publications:

George, CM, van Geen, A, Slavkovich, V, Singha, A, Levy, D, Islam, T, Ahmed, KM, Moon-Howard, J, Tarozzi, A, Liu, X, Factor-Litvak, P, Graziano, J: A cluster-based randomized controlled trial promoting community participation in arsenic mitigation efforts in Singair, Bangladesh. Submitted.

Khan, K, Factor-Litvak, P, Wasserman, GA, Liu, X, Ahmed, E, Parvez, F, Slavkovich, V, Levy, D, Mey, J, van Geen, A, Graziano, JG: Manganese exposure from drinking water and children's classroom behavior in Bangladesh. *Environ Health Perspect* 2011;119:1501-6. PMID: 21493178. PMCID: in process.

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Parvez, F, Wasserman, GA, Factor-Litvak, P, Liu, X, Ahsan, H, Slavkovich, V, Sultana, Re, Sultana, Ru, Levy, D, Kline, J, Siddique, A, Islam, T, Graziano, JH: Arsenic exposure and motor function among children in Bangladesh. *Environ Health Perspect*, 2011;119(11):1665-70. PMID: 21742576 PMCID: in process.

Wasserman, GA, Liu, X, Parvez, F, Factor-Litvak, P, Ahsan, H, Levy, D, Kline, J, van Geen, A, Mey, J, Slavkovich, V, Siddique, A, Islam, T, Graziano, JH: Arsenic and manganese exposure and children's intellectual function. *Neurotoxicology* 2011;32:450-7. PMID: 21453714. PMCID: in process.

Project 4: *One-Carbon Metabolism, Oxidative Stress and Arsenic Toxicity in Bangladesh*
PI: Mary V. Gamble

Nutritional status may account for some of the considerable variability in progression from arsenic (As) exposure to manifestations of disease. Methylation of ingested inorganic As (InAs) to methylarsonic- (MMA) and dimethylarsinic acids (DMA) relies on folate-dependent one carbon metabolism and facilitates urinary As elimination. Our SRP project builds upon our Nutritional Influences on As Toxicity (NIAT) studies which demonstrated that folic acid supplementation increases As methylation and lowers blood As and blood MMA concentrations.

In the first aim, we tested the hypothesis that at the time of enrollment, participants who subsequently developed As-induced skin lesions (SLs) had lower folate and/or higher homocysteine as compared to non-skin lesion controls. The results of this study were positive and have been published. We also tested the hypothesis that markers of oxidative stress would be associated with risk for SLs. Analyses of all 3 of our biomarkers of oxidative stress, which included urinary 8-oxo-2'-deoxyguanosine, plasma malondialdehyde and protein carbonyls, revealed that none were positively associated with with risk for SLs. A manuscript describing these null findings is in preparation.

For the second aim, we proposed to examine the extent to which urinary As metabolites reflect As metabolites in blood in Bangladeshi adults. This work is completed and has been published.
For the dose-response study of aim three, 375 participants were enrolled, and biological samples were analyzed for reduced and oxidized glutathione, reduced and oxidized cysteine, malonyldialdehyde and protein carbonyls. Our analyses suggest that As exposure is associated with decreased concentrations of reduced glutathione (GSH) in whole blood and reduced concentrations of both reduced and oxidized cysteine in plasma, consistent with the hypothesis that As exposure is associated with depletion of glutathione (see Highlight #2). Since GSH is the body's primary antioxidant, this would be expected to be associated with increased oxidative stress. However, arsenic exposure was not significantly associated with the other markers of oxidative stress.

Having completed our stated aims for this non-continuing project, we also generated some exciting preliminary data for the new Project 3. An emerging body of evidence suggests that As exposure leads to epigenetic dysregulation. We have previously demonstrated that chronic As exposure is associated with increased global DNA methylation. We hypothesize that the mechanism underlying this relates to As-induced alterations in histone modifications. This work involves a cross-disciplinary collaboration with Max Costa at NYU that will take advantage of samples collected from our folate trial to carry out a set of aims related to nutrition/environment/epigenetic interactions. We will characterize the influence of As exposure on histone modifications, relate changes in histone modifications to changes in DNA methylation, and characterize the impact of FA supplementation on these marks. Finally, using the Infinium Human Methylation450 array, we will identify a set of genes that are differentially methylated by As exposure and determine gene-specific histone modifications at these loci. Collectively, these aims will begin to elucidate the molecular events that underlie the effects of As and folate on DNA methylation.

Student Involvement in Project 4 (Gamble, PI)

J. Richard Pilsner, a former PhD student who graduated in 2007, helped to train Bangladeshi laboratory technicians to run analyses of glutathione concentrations in Aim 3 of Project 4.

Khalid Khan, a former DrPH student who graduated in 2010, worked on analyses of urinary 8oxo-deoxyguanosine for Aim 1 of Project 4.

Faruque Parvez, who defended his DrPH thesis in October 2011, was instrumental in over-seeing field staff for Aim 3 of Project 4.

Megan Niedzwiecki, Dr. Gamble's PhD student worked on laboratory and data analyses for the folate and oxidative stress (FOX) study from Aim 3 of Project 4. She studied the effects of redox status on methylation of arsenic and DNA (see Highlight) which will be a focus of her thesis. Her work was selected for oral presentation at the 2011 SRP Meeting in Kentucky.

Megan Hall, Dr. Gamble's former post-doctoral research fellow (currently an Associate Research Scientist) worked on statistical analyses for the FOX study. She focused on the effects of arsenic exposure on glutathione concentrations. Her work was also selected for oral presentation at the 2011 SRP Meeting in

Kentucky. Dr. Hall now has a K99/R00 award from NIEHS to study nutritional influences, particularly of choline and betaine, on arsenic methylation.

Kristin Harper, Dr. Gamble's post-doctoral research fellow, worked on Aims 1 and 3 of Project 4. She is analyzing the associations between arsenic exposure and biomarkers of oxidative stress (manuscript in preparation). She is also working on analyses of differentially methylated CpGs by arsenic exposure using Illumina's new 450K array and was instrumental in generating preliminary data for our new SRP Project 3 (Gamble PI).

Brandilyn Peters, Dr. Gamble's PhD student is also working on analyses of differentially methylated CpGs by arsenic exposure and was, along with Kristin (above), instrumental in generating preliminary data for our new SRP Project 3.

Caitlin Howe is a PhD student currently rotating in Dr. Gamble's laboratory. She has been working on analyses related to aim 2 of Project 4 in which we are analyzing associations between s-adenosylhomocysteine and s-adenosylmethionine and arsenic methylation.

Publications during the recent funding period:

Pilsner JR, Hall MN, Liu X, Ahsan H, Ilievski V, Slavkovich V, Levy D, Factor-Litvak P, Graziano JH, Gamble MV. Associations of Plasma Selenium with Arsenic and Genomic Methylation of Leukocyte DNA in Bangladesh. *Environ Health Perspect* 2011;119(1):113-8. PMCID: PMC3018489

Lawley SD, Cinderella M, Hall MN, Gamble MV, Nijhout HF, and Reed MC. Mathematical model insights into arsenic detoxification. *Theor Biol Med Model*. 2011;8:31. PMCID: PMC3224592

Chen Y, Parvez F, Liu M, Pesola GR, Gamble MV, Slavkovich V, Islam T, Ahmed A, Hasan R, Graziano JH, and Ahsan H. (2011). Association between arsenic exposure from drinking water and proteinuria: results from the Health Effects of Arsenic Longitudinal Study. *Int J Epidemiol* 2011;40:828-35. PMCID: PMC3147073.

Gonda TA, Takaishi S, Salas MC, Kim Y, Gamble MV, Shibata W, Muthupalani S, Abrams J, Fox JG, Wang TC, Tycko B. Folic acid increases global DNA methylation and reduces inflammation to prevent Helicobacter associated gastric cancer in mice. *Gastroenterology*, 2011; in press.

Project 5: *Mobilization of Natural Arsenic in Groundwater*
PI: Benjamin C. Bostick
Co-Investigators: Yan Zheng, Martin Stute, Brian J. Mailloux

In 2011 we focused on: (1) Radiocarbon analysis of Microbial DNA and Phospholipid fatty acids, (2) Microfocused X-ray Techniques on flow through columns, and (3) magnetite formation and arsenic immobilization.

Radiocarbon analysis of Microbial DNA and Phospholipid fatty acids

The determination of the source of organic carbon for microbial respiration in both pristine and contaminated aquifer systems has proven to be extremely difficult. To overcome these difficulties we have been developing methods to determine the ^{14}C and ^{13}C signature of DNA and Phospholipid fatty acids (PLFAs) collected from groundwater wells. Isotopic analyses of PLFAs are traditionally only performed on sediment samples since most filters are not compatible with the organic solvents used during extractions. To overcome

this limitation we have developed and field-tested an organic carbon free filter that can be baked at 450°C for 24 hours to remove all contaminants. This filter has now been successfully used in the field to collect samples. This filter will greatly expand the locations where PLFA analyses can be performed.

We have recently implemented a method to analyze the radiocarbon signature (age) of microbial DNA extracted from large (10,000 L) groundwater filtrate samples. Samples have been collected from three sites and the complete analysis has been performed on one site. The data clearly shows that young carbon from anthropogenic waste is not the main driver of arsenic release. The results do indicate that slow recharge over 100's to 1000's of years is supplying carbon to the aquifer and driving microbial respiration and subsequent arsenic release. Metagenomic analysis of the same samples indicates that the microbial population is optimized to utilize the recalcitrant carbon sources and reduce Fe(III). This method can be utilized to greatly improve our understanding of carbon utilization in both pristine and contaminated aquifers.

Spectroscopic analysis of dynamic flow through columns

We have developed a method in which column transport experiments are conducted within a microfocused X-ray beam to simultaneously monitor grain-scale solid phase reactions and column scale transport to better understand the relationship between mineral dissolution, adsorption-desorption, and contaminant fate and transport groundwater. This method provides a valuable tool to directly observe the solid phase at the grain scale, and link solid phase transformations to solute retention and transport. The method has been applied to better understand arsenic mobilization by oxalic acid at the Vineland Superfund site. The method has also been applied on Bangladesh sediments to understand the sustainability of the deep, Pleistocene, low arsenic aquifers.

Magnetite formation and arsenic immobilization

Magnetite strongly adsorbs As(III) and As(V), and can incorporate As(V) into its structure. Accordingly, magnetite is a potentially attractive mineral phase in which to immobilize As in the solid phase in many contaminated environments as the magnetite would be stable across redox zones. We have performed laboratory microcosm experiments, and initial results indicate this could be a promising remedial method in environments where As is commonly released into groundwater.

Students and Post-docs whose research is supported completely or in part by Project 5:

Kathleen A Radloff, Ph.D. 2010, Earth and Environmental Engineering, Columbia, then post-doc at LDEO
Ivan Mihajlov, 3rd yr PhD student, Earth and Environmental Sciences, Columbia University
Radost K. Stanimirova-Undergraduate, Environmental Science, Barnard College
Rachel F. Silvern-Undergraduate, Environmental Science, Barnard College
Sarah M. Lyon-Undergraduate, Environmental Science, Barnard College
Aleq Abdullah-Undergraduate, Environmental Science, Barnard College
Stephen Barten, Undergraduate, Environmental Science, Columbia College
Yousef Aly, High School, Oceanside High School

Project 5-Supported 2010 Publications:

Radloff KA, Y Zheng, HA Michael, M Stute, B Bostick, I Mihajlov, M Bounds, MR Huq, I Choudhury, MW Rahman, P Schlosser, KM Ahmed, A van Geen. Arsenic adsorption protects deep groundwater from widespread contamination in Bangladesh. *Nature Geoscience* 2011;4:793-8.

Dhar RK, Y Zheng, CW Saltikov, KA Radloff, B Mailloux, KM Ahmed, A van Geen, Microbes enhance mobility of arsenic in Pleistocene aquifer sand from Bangladesh, *Environ Sci Technol*, 2011;45(7):2648-54. PMID: 21405115. dx.doi.org/10.1021/es1022015.

Bostick BC, Radloff KA, Harvey CF, Stahl M, Oates P, Lan VM, Mai NN, Trang PTK, Viet PH, Berg M, Stengel, C, and van Geen, A. 2011. Arsenic Mineralogy and Phase Partitioning Across a Sharp Gradient in Arsenic

Concentrations in Van Phuc, Vietnam *Conference on Arsenic in Groundwater in Southern Asia*, Hanoi Vietnam.

Wovkulich K, Mailloux BJ, Dong BCBH, Bishop ME, and Chillrud SN. Submitted. Use of Microfocused X-ray Techniques to Investigate the Mobilization of As by Oxalic Acid. *Geochimica et Cosmochimica Acta* (in revision).

Project 6: *Mobilization of anthropogenic arsenic in groundwater*
PIs: Steven Chillrud, Martin Stute, Brian Mailloux,

Project 6 investigates the geochemistry and remediation of As associated with the Vineland Superfund site in southern New Jersey. Due to decades of improper chemical storage and disposal by Vineland Chemical, the site was extensively contaminated with As. Despite a decade of extensive remediation including a large pump-and-treat system, groundwater As concentrations can still be several hundred µg/L. Our past work, including laboratory experiments and a small *in situ* pilot study, suggests that introduction of oxalic acid in the subsurface shows promise for dramatically lowering the As remediation time-scale.

Our activities over the last year have focused on additional laboratory experiments on samples from the Vineland Site, data analyses and manuscript preparations, and a series of meetings with the Vineland Site Managers (EPA Region 2 and USACE) to plan future activities. These meetings resulted in two activities- first was to plan a large collaborative geoprobe survey to better understand the site hydrology and geochemistry in order to be able to identify portions of the site that may be amenable to different remediation strategies such as the *in situ* injection of oxalic acid. This survey has been postponed by EPA due to flood damage related to Hurricane Irene among other issues. A second result is that we were asked to investigate additional alternative strategies to pump-and-treat since it was suggested that not any one treatment scenario would necessarily work for the entire site. Particularly, we were asked to explore *in situ* immobilization approaches. Consequently, we have been investigating the concept of *in situ* amendment injections to promote the production of magnetite as a long-term As sink. Magnetite has the distinct advantage of being stable under a wide range of redox conditions, including Fe-reducing conditions where As is typically mobilized and bioavailable. Furthermore, magnetite can not only sorb As but incorporate into its structure As(V), the predominant form of solid-bound As in Vineland aquifer measured to date. However, it is quite difficult to synthesize magnetite under reductive conditions under neutral or mildly acidic conditions common at most sites, including Vineland. Together, we have been conducting a series of laboratory microcosms using Vineland aquifer sediments and groundwater amended with various combinations of nitrate, sulfate, Fe(II) (as ferrous sulfate) and lactate, to promote formation of different Fe (hydr)oxides and sulfides and study how they affect As, and to test the hypothesis that combinations of nitrate plus Fe(II) can facilitate magnetite formation at circum-neutral pH. Synchrotron-based XAS analyses confirm that magnetite (> 500 mg magnetite/kg solids) was produced together with ferrihydrite at pH ~6 in microcosms having Fe(II) and nitrate. These NO_3-Fe(II) microcosms also kept dissolved As concentrations low (< 36 µg/L) over the investigated period (> 5 weeks), while other microcosms were ineffective or enhanced As release. Additional Fe(II) and nitrate microcosms are underway to further improve magnetite yields and As retention . Finally, we collected aquifer sediments from the Dover Municipal Landfill Site for evaluation of alternative remediation strategies.

Students and Postdocs involved in studies in 2011:
Jing Sun, Ph.D. student, Earth and Environmental Sciences, Columbia University
Karen Wovkulich, Ph.D. awarded Oct 2011, Earth and Environmental Sciences, Columbia University
Hannah Perls, undergraduate, Earth and Environmental Sciences, Columbia University

Governmental agency staff we interact with on Vineland Superfund Site:
Ron Naman, John Frisko and Nica Klaber from EPA Region 2; Steve Creighton and Laura Bittner from USACE-Philadelphia; Craig Wallace and Chad Vansciver from NJDEP

Publications:

Wovkulich, K., Stute, M., Protus, T. J., Mailloux, B. J. and Chillrud, S. N. (2011), Injection System for Multiwell Injection Using a Single Pump. Ground Water Monitoring & Remediation, 31: 79–85. doi: 10.1111/j.1745-6592.2011.01325.x

Wovkulich, K. B.J. Mailloux, B.C. Bostick, H. Dong, M.E. Bishop, S.N. Chillrud. Use of microfocused x-ray techniques to investigate mobilization of Arsenic by Oxalic Acid. Geochim. Cosmo. Acta, submitted 2011.

Project 7: *Mitigation of Arsenic Mobilization in Groundwater*
PI: Alexander van Geen
Co-Investigators: Benjamin Bostick, Brian Mailloux, Martin Stute

Research carried out under this project in 2011 has focused on 3 themes: (1) deep aquifers of Bangladesh as sources of low-As drinking water, (2) implications of microbial contamination of shallow and deep low-As wells in Bangladesh, (3) training and education at the village and school level in Bangladesh to reduce As exposure. These activities have resulted in 12 publications and 10 manuscripts under review.

We have shown through a combination of field experiments and basin-scale modeling that adsorption of As onto aquifer sands provides considerable, though still finite, protection of deep aquifers against intrusion of low-As groundwater from shallower depths. We continue to monitor the As content of groundwater pumped from 100 community wells supplying thousands of residents of the HEALS (Project #2) study area with low-As drinking water. Using hydrogeological and geochemical techniques, we have attributed a handful of deep well failures documented in the HEALS study area over the past decade to (a) cracked or disconnected PVC pipe used in well construction or (b) drawdown at the local scale of high-As groundwater that is not separate from the filter depth by an impermeable clay layer. Drawdown of the deeper aquifer by massive groundwater pumping for the municipal water supply of Dhaka likely was a contributing factor. Such findings have direct implications for the 100,000 deep wells installed throughout the country over the past decade that have been tested only once upon installation, if at all.

We have shown that groundwater in Bangladesh is not as free of microbial pathogens as widely believed. Our concern that shallow low-As wells are particularly likely to be contaminated by shallow sources such as latrines and ponds receiving latrine effluents has been borne out by two independent observations: (a) monthly monitoring of both high- and low-As shallow wells using the fecal indicator *E. coli* (Colilert) and (b) analysis of a unique data set of diarrheal disease data collected from tens of thousands of households over a period of 7 years. The underlying mechanism likely involves modulation of the rate of local recharge by the presence (high-As in shallow wells) or absence (low-As) of a protective clay layer that provides some protection against aquifer contamination. One surprising observation resulting from this work is that particularly high rates of childhood diarrhea appear to be associated with intermediate-depth wells (140-300 ft). Although further study is needed, drinking groundwater drawn from deep community wells thankfully appears to be less likely to cause childhood diarrhea than any other sources of low-As groundwater.

Project 7 continues to be involved in the field research of one graduate student (Christine George) and one post-doctoral student (Khalid Khan) at the Mailman School of Public Health. This work has shown that village health-workers trained in the use of field-kit for As can induce villagers to seek neighboring low-As wells if their own household turns is elevated in As. Data collection has been completed to determine through a

randomized controlled trial whether school-level education amplifies the reduced exposure of children anticipated from the installation of deep community wells in Araihazar.

Students supported at least in part under Project 7 in 2011
Kathleen A Radloff, Ph.D. 2010, Earth and Environmental Engineering, Post-doc at Lamont in 2011.
Ivan Mihajlov, Earth & Environmental Sciences, Columbia, PhD candidate.
Christine George, Mailman School of Public Health, Columbia, PhD candidate.
Pamela Mishkin, senior at Horace Mann High School

Publications in 2011:

Khan, K, Factor-Litvak, P, Wasserman, GA, Liu, X, Ahmed, E, Parvez, F, Slavkovich, V, Levy, D, Mey, J, van Geen, A, Graziano, JG: Manganese exposure from drinking water and children's classroom behavior in Bangladesh. *Environ Health Perspect* 2011;119:1501-6. PMID: 21493178. PMCID: in process.

Khan, K, GA Wasserman, X Liu, E Ahmed, F Parvez, V Slavkovich, D Levy, J Mey, A van Geen, JH Graziano, P Factor-Litvak, Manganese exposure from drinking water and children's academic achievement, revision submitted to *Neurotoxicology*, 2011; in press.

Wu J, A van Geen, KM Ahmed,Y Akita, MJ Alam, PJ Culligan, V Escamilla, J Feighery, AS Ferguson, P Knappett, BJ Mailloux, LD McKay, ML Serre, PK Streatfield, M Yunus, M Emch, Increase in diarrheal disease associated with arsenic mitigation in Bangladesh, *PLoS ONE*, 2011; in press.

Wu, F, F Jasmine, MG Kibriya, M Liu, O Wojcik, F Parvez, S Roy, R Rahaman, S Segers, V Slavkovich, T Islam, D Levy, A van Geen, J Graziano, H Ahsan, Y Chen, Association between arsenic exposure from drinking water and plasma levels of cardiovascular markers, *Amer J Epidemiol*, in press, 2011.

Radloff KA, Y Zheng, HA Michael, M Stute, B Bostick, I Mihajlov, M Bounds, MR Huq, I Choudhury, MW Rahman, P Schlosser, KM Ahmed, A van Geen. Arsenic adsorption protects deep groundwater from widespread contamination in Bangladesh. *Nature Geoscience* 2011;4:793-8.

Wasserman, GA, X Liu, F Parvez, P Factor-Litvak, H Ahsan, D Levy, J Kline, A van Geen, J Mey, V Slavkovich, AB Siddique, T Islam, JH Graziano, Arsenic and manganese exposure and children's intellectual function, *Neurotoxicology* 2011;32:450-7.

Parvez F, GA Wasserman, P Factor-Litvak, X Liu, V Slavkovich, AB Siddique, Rebeka Sultana, Ruksana Sultana, T Islam, D Levy, JL Mey, A van Geen, KM Khan, J Kline, H Ahsan, JH Graziano, Arsenic exposure and motor function among children in Bangladesh, *Environ Health Perspect* 2011;119:1665-70.

Ferguson AS, BJ Mailloux, KM Ahmed, A van Geen, LD McKay, and PJ Culligan, Hand-pumps as reservoirs for microbial contamination of well water, *J Water Health* 2011;9(4):708-17.

Chen Y, JH Graziano, F Parvez, M Liu, V Slavkovich, T Kalra, M Argos, T Islam, A Ahmed, M Rakibuz-Zaman, R Hasan, D Levy, A van Geen, and H Ahsan, Arsenic exposure from drinking water and cardiovascular disease mortality: A prospective cohort study in Bangladesh, *British Med J* 2011;342:d2431.

Knappett, PSK, V Escamilla, A Layton, LD McKay, M Emch, DE Williams, MR Huq, MJ Alam, L Farhana, BJ Mailloux, A Ferguson, GS Sayler, KM Ahmed, A van Geen. Impact of population and latrines on fecal contamination of ponds in rural Bangladesh. *Sci Tot Environ*, 2011; 409(17):3174-82. PMCID: PMC3150537.

Escamilla, V., B. Wagner, M. Yunus, P.K. Streatfield, A. van Geen, M. Emch, Effect of deep tube well use on childhood diarrhoea in Bangladesh, *Bull World Health Organ* 2011;89:521-7. PMCID:PMC3127267.

Dhar, RK, Y Zheng, CW Saltikov, KA Radloff, B Mailloux, KM Ahmed, A van Geen, Microbes enhance mobility of arsenic in Pleistocene aquifer sand from Bangladesh, *Environ Science Technol*, 2011;45(7):2648-54. dx.doi.org/10.1021/es1022015.

van Geen A, KM Ahmed, Y Akita, MJ Alam, PJ Culligan, J Feighery, A Ferguson, M Emch, V Escamilla, P Knappett, AC Layton, BJ Mailloux, LD McKay, JL Mey, ML Serre, PK Streatfield, J Wu, M Yunus, Fecal contamination of shallow tubewells in Bangladesh inversely related to arsenic, *Environ Sci Technol*, DOI: 10.1021/es103192b, 2011; in press. PMCID: PMC3037737

George CM, D Levy, T Islam, KM Ahmed, J Moon-Howard, A Tarozzi, X Liu, P Factor-Litvak, A van Geen, JH Graziano, A cluster-based randomized controlled trial promoting community participation in arsenic mitigation efforts in Singair, Bangladesh, submitted.

Ferguson AS, AC Layton, BJ Mailloux, PJ Culligan, DE Williams, AE Smartt, J Feighery, L McKay, P Knappett, E Alexandrova, T Arbit, M Emch, V Escamilla, KM Ahmed, MJ Alam, PK Streatfield, M Yunus, A van Geen, Comparison of fecal indicators with pathogenic bacteria and rotavirus in groundwater, submitted to *Environ Sci Technol*, submitted.

George CM, JH Graziano, Y Zheng, JL Mey, A van Geen, Evaluation of the effectiveness of building local capacity to conduct arsenic testing services in Bangladesh, *Environmental Health*, in revision.

Knappett PSK, LD McKay, A Layton, DE Williams, MJ Alam, MR Huq, J Mey, JE Feighery, PJ Culligan, BJ Mailloux, J Zhuang, V Escamilla, M Emch, E Perfect, GS Sayler, KM Ahmed, A van Geen, Fecal contamination of shallow groundwater modulated by the geological setting of ponds, *Environ Sci Technol*, in revision.

Aziz, Z, M. Stute, R. Versteeg, P. Schlosser, MR Huq, KM Ahmed, A van Geen, Distribution of As in shallow Bangladesh aquifers of Bangladesh controlled by desorption and flushing: An evaluation at the village-scale using a 3-D groundwater flow model, *Water Resources Res*, in revision.

Soumya HB, A Pfaff, L Bennear, A Tarozzi, KM Ahmed, A Schoenfeld, A van Geen, Rising gains over time from the provision of health-risk information: evidence from the groundwater arsenic crisis in Bangladesh, submitted to *Bulletin of the World Health Organization*, August 2011.

Bennear L, A Tarozzi, A Pfaff, HB Soumya, KM Ahmed, A van Geen, Bright lines, risk beliefs, and risk avoidance: Evidence from a randomized intervention in Bangladesh, revision submitted to *J Enviro Econom Manage*, October 2011.

Wu, J, M Yunus, PK Streatfield, A van Geen, V Escamilla, Y Akita, M Serre, M Emch, Impact of tubewell access and depth on childhood diarrhea in Matlab, Bangladesh, 2nd revision submitted to *J Environ Health*, December 2011.

Administrative Core.
Director: Joseph Graziano
Deputy Director: Alexander van Geen

General Activities: The Administrative Core continues to function smoothly. Dr. Graziano, the Program Director, and Dr. van Geen, the Associate Director, have been working together with SRP investigators to submit a competitive renewal application in April, 2011, an application that has apparently been successful. The Director and Deputy Director lead a weekly series of meetings among biomedical and non-biomedical scientists, respectively, to develop sets of research aims that would be most appropriate for support by the SRP Program. We communicate continuously with regard to the integration of our biomedical and non-biomedical research programs, and hold joint monthly meetings of all participating faculty to maximize the interactions across biomedical and non-biomedical projects. This communication is evidenced by the number of truly multi-disciplinary publications that have come from our program, involving close collaboration between biomedical, earth, and social scientists.

Last fall we held the annual meeting of our External Advisory Committee, a day and a half event held offsite. During that time each project PI presented preliminary specific aims of their proposed project for our competitive renewal application. The meeting was extraordinarily helpful and resulted in the deletion of one proposed project. Our External Advisory Committee continues to provide valuable input to our program. The composition of the committee includes: a) Chien-Jen Chen, Committee Chair, and Chairman of the Graduate Institute of Taiwan; b) Andrew Gelman, Professor of Statistics at Columbia University; c) Zoltan Szabo, Research Hydrologist, USGS; d) Margaret Karagas, Chair, Section of Biostatistics and Epidemiology, Dartmouth University; e) Allan Smith, Professor of Epidemiology, University of California, Berkeley; f) X. Chris Le, Professor of Public Health Sciences, University of Alberta; g) Peggy O'Day, Associate Professor of Natural Sciences, University of California, Merced; and Robert Wright, Associate Professor of Environmental Health Sciences and Pediatrics at Harvard.

All of our scientific team has assembled monthly for a joint two hour meeting which rotates between the Health Sciences Campus and the Lamont-Doherty Earth Observatory Campus; the two campuses are separated by a 20 minute University bus ride. In the past year, many of these sessions have been devoted to discussions and planning for our competitive renewal application. Others have been devoted to two hours of seminars, typically one hour for biomedical and one for non-biomedical presentations. In the past year our seminar series was suspended for several months during the preparation of our competitive renewal application. Rather, those hours were used to bring our group together to discuss the logistics and science of the application. During the past year we have begun to offer our seminars as a webinar, one that is now attended by many outsiders from government and academia.

Seminars that have occurred in the past year include:

December 6th , 2010
"Immunotoxic effects of developmental arsenic exposure," presented by Courtney Kozul-Horvath, Dept. of Immunology, Dartmouth Medical School

January 24th, 2011
"Microbe-arsenic interactions in Asian and European aquifers: from mobilization to bioremediation," presented by Jonathan Lloyd, Director of Research, School of Earth, Atmospheric and Environmental Sciences, The University of Manchester.

"Effect of arsenic on histone tail modifications," presented by Max Costa, Professor and Chairman, Dept. of Environmental Medicine, NYU School of Medicine.

February 28th, 2011
"A framework to study gene-environment interactions in children," presented by Robert Wright, Dept. of Environmental Health, Harvard School of Public Health.

"Impact of fecal contamination of shallow low-arsenic wells in Bangladesh on diarrheal disease," presented by Alexander van Geen, Lamont-Doherty Earth Observatory, Columbia University.

March 21st, 2011

"Laboratory and field studies directed to accelerating arsenic remediation at a major US Superfund site in New Jersey," presented by Karen Wovkulich, PhD student, Lamont-Doherty Earth Observatory, Columbia University.

September 19, 2011

"Arsenic and respiratory disease," presented by Matthew Perzanowski, Dept. of Environmental Health Sciences, Mailman School of Public Health, Columbia University.

"Direct evidence of contamination of a Pleistocene aquifer by incursion of high-arsenic groundwater in the Red River delta, Vietnam, presented by Alexander van Geen, Lamont-Doherty Earth Observatory, Columbia University.

October 17th, 2011

"Who should make decisions about providing drinking water? An experiment with allocation of decision-making authority in rural Bangladesh," presented by Malgosia Madajewicz, International Research Institute for Climate & Society, Columbia University

"Glutathione and arsenic methylation in Bangladesh," presented by Megan Niedzwiecki, PhD student, Dept. Environmental Health Sciences, Mailman School of Public Health, Columbia University.

December 2nd, 2011

"Arsenic in Illinois glacial aquifers: Geochemistry and removal at water treatment plants," presented by Thomas Holm, Illinois State Water Survey, Prairie Research Institute, University of Illinois at Urbana-Champaign

"Update on the Bangladesh vitamin E and selenium trial (BEST)," presented by Habibul Ahsan, Dept. of Health Studies, University of Chicago.

December 19th, 2011

"Throwing the baby out with the drinking water: Unintended consequences of arsenic mitigation efforts in Bangladesh," presented by Erica Field, Dept. Economics, Duke University

"Arsenic and Cataracts," presented by Norman Kleiman, Dept. of Environmental Health Sciences, Mailman School of Public Health, Columbia University.

Core A: *Data Management Core*
PI: Diane Levy

1. Project 2:
    a. The customized (recently modified) data entry system in Bangladesh is currently being utilized to enter follow up data for HEALS:
        i. Follow up 4 for 11,746 original participants
        ii. Follow up 2 for 8,267 new participants (ACE)

    All data are periodically automatically transferred to Columbia University SQL database located in NY.
2. Project 3:
    a. New Hampshire/Maine
        i. Data for 382 children have been entered. Data entry includes a demographic/well questionnaire, WISC and WASI tests, and a home assessment questionnaire
        ii. Data sets were assembled for interim analysis
    b. Bangladesh
        i. Phase I datasets were updated and distributed for analysis.
        ii. Phase II data are currently being entered in the database. As of now 110 test results have been entered and manual scoring for fine motor tasks for those children has been completed.
3. Project 4:
    a. Periodic uploads of laboratory data to Microsoft SQL server database. The following data have been added: plasma folate, B12, homocysteine, cysteine, Cystatin C; leukocyte DNA methylation; urinary 8-OHdG (8-hydroxydeoxyguanosine); serum retinol and carotenoids (including leutein/zeaxanthin (one variable); beta-cryptoxanthin, lycopene, alpha-carotene, and beta-carotene) serum tocopherol, arsenic (total and metabolites for both blood and urine), glutathione, glutathione disulfide, cysteine, cystine, global DNA methylation by [3H]-methyl incorporation assay, global DNA methylation by pyrosequencing (LUMA, Line-1, and Alu), plasma malondialdehyde. Protein carbonyl, s-adehosylmethionine (SAM) and s-adenosylhomocysteine (SAH) data will be added very soon.
    b. Data sets have been distributed to PI and biostatistician for analyses
    c. Collectively, data from Project 4 and ancillary studies have resulted in 23 publications (19 published/in review and 4 in preparation.)
4. Additional efforts:
    a. Health Education of School Children in Bangladesh: (Khan, PI)
        i. Database was programmed to collect follow up questionnaire data.
        ii. Data entry was completed for the project.
        iii. Datasets for analysis will be created before the end of 2011.
    b. Young Adult Manganese Study: (Graziano, PI)
        i. Created web based data entry environment for test results using the existing Bangladesh children's study as the template for the database
        ii. Programmed database and data entry screens to accept questionnaire data
        iii. Supervised data entry staff
        iv. Created data sets for analysis
    c. Created/taught data management workshop for NIEHS and Superfund investigators, staff and students.
    d. Continued support for undergraduate and graduate students working with PIs on Arsenic related projects.
    e. Continued maintenance of secure database and web servers. Projects detailed above are direct beneficiaries of these services.

f. Management of data flow continues using the Issue Tracking System and the Query Tracking Systems.
g. Attending weekly project team meetings to provide data management consultation as projects move forward.

Core B: *Trace Metals Core Laboratory*
PI: Joseph Graziano
Laboratory Director: Vesna Slavkovich

The primary purpose of the Trace Metals Core Laboratory, which is jointly funded by SRP and our P30 Center, is to provide Center investigators with the capability to obtain analyses of biological samples for a broad array of metals. In addition, the facility provides method development for these analyses, standardization, and quality control. The Trace Metals Core provides analytical support to projects #2, #3 and #4.

Collectively, during the past five years, the lab has performed more than 110,000 measurements of metals in urine, blood, nail and other tissue samples, using either atomic absorption spectrophotometry or inductively coupled plasma mass spectrophotometry (ICP-MS), as needed. During the past year, this Core Lab conducted more than 20,000 "routine" analyses of biological samples from projects 2, 3 and 4. A main focus of the Core's activities has been analytical support for As and creatinine measurements for the HEALS Cohort Study (Project #2), which has now completed its fourth biannual follow-up visit. Roughly one half of the laboratories analyses have gone to support Dr. Mary Gamble's studies of folate and creatine supplementation in the FACT Study (Folate and Creatine Trial; N = 800), as well as Dr. Ahsan's BEST study (Bangladesh Vitamin E and Selenium Trial; N = 8000). In addition, in support of Dr. Gamble's FOX study (Project #3: Folate, Arsenic and Oxidate Stress), urinary, and blood measurements were conducted, including measurements of arsenic metabolites by HPLC-ICP-MS-DRC technology.

This laboratory is jointly funded by our NIEHS P30 Center, which supports roughly one-third of the laboratories total budget. Support for the FACT and BEST studies, both R01 grants, is derived in part from the P30 Center's support of the lab.

One issue that will need to be addressed in the coming year is the need to replace our 10 year-old ICP-MS. The cost of a new instrument is approximately $200,000. Dr. Graziano plans to write a "shared instrumentation" grant to NIH in March, 2012, to address this need.

Students involved with this work:

Christine George, Dr. Graziano's minority Ph.D. student, who has a degree in Environmental Engineering from Stanford University.

Seyed Zonoor, an undergraduate from UCSF, also worked in the lab during the summer of 2010 and subsequently became a full-time employee of the lab; he is now attending medical school at The NY State University at Stony Brook.

Tiffany Sanchez, a minority Columbia undergraduate, followed a similar path. She worked in the lab during the summer of 2010, became a full-time employee of the lab, and is now a student in our PhD program in EHS.

Several undergraduate students were employed or volunteered as lab personnel for the summer of 2011. These include Nina Balac and Yukari Sumizu, Columbia College students; Acile Hammoud, a junior at the American University in Lebanon; and Kristijan Ilievski, a New York City high school student.

Trace Metals Core-Supported Publications:

Every publication listed for Projects 2, 3 and 4 has relied on the Trace Metal Core.

Core C: *Biogeochemistry Core*
PIs: Alexander van Geen and Steven Chillrud
Co-investigators: Brian Mailloux and Benjamin Bostick, also Jacob Mey and James Ross.

The Biogeochemical analytical core laboratory is housed at Lamont-Doherty Earth Observatory (LDEO). It provides sample preparation and analyses to six projects of the Columbia Superfund program. Analyses have been carried out by high-resolution inductively coupled plasma mass spectrometry for up to 33 elements for water, soil, sediment, leachate, and plant material (HR ICP-MS). Two new HR ICP-MS instruments (Element2) were recently delivered to replace our aging Axiom. We have purchased a hand-held InnovX X-ray fluorescence analyzer and a hand-held Minolta spectral reflectance spectrophotometer for analyzing fresh drill cuttings in the field are calibrating these instruments against conventional methods. We have also purchased a Shimadzu Organic Carbon Analyzer to enhance our ability to identify the electron donors that drive Asian and US aquifers towards reduction and, therefore, the release of As to groundwater.

On behalf of the projects working in Bangladesh (projects 2, 3, 4, 5, 7) 3258 samples and solutions were analyzed by HR-ICP-MS. In support of project 5 work in New Hampshire and Maine, 637 analyses by HR-ICP-MS were made. For Project 6, another 611 samples and solutions were analyzed by HR-ICP-MS related to the work at the Vineland Superfund Site, and 22 hand held XRF measurements were made on sediment samples in support of the new work at the Municipal Landfill Superfund Site in Dover NH. For the Research Translation Core, 191 hand held XRF analyses were made in support of the government partnership with NJGS on Newark Basin Rock Core.

Manuscripts involving collaborators supported by Core C:

George CM, JH Graziano, Y Zheng, JL Mey, A van Geen, Evaluation of the effectiveness of building local capacity to conduct arsenic testing services in Bangladesh, *Environ Health*, in revision.

Knappett PSK, LD McKay, A Layton, DE Williams, MJ Alam, MR Huq, J Mey, JE Feighery, PJ Culligan, BJ Mailloux, J Zhuang, V Escamilla, M Emch, E Perfect, GS Sayler, KM Ahmed, A van Geen, Fecal contamination of shallow groundwater modulated by the geological setting of ponds, *Environ Sci Technol*, revision requested November 2011.

Aziz, Z, M. Stute, R. Versteeg, P. Schlosser, MR Huq, KM Ahmed, A van Geen, Distribution of As in shallow Bangladesh aquifers of Bangladesh controlled by desorption and flushing: An evaluation at the village-scale using a 3-D groundwater flow model, *Water Resources Research*, under revision February 2011.

Wu, F, F Jasmine, MG Kibriya, M Liu, O Wojcik, F Parvez, S Roy, R Rahaman, S Segers, V Slavkovich, T Islam, D Levy, A van Geen, J Graziano, H Ahsan, Y Chen, Association between arsenic exposure from drinking water and plasma levels of cardiovascular markers, *Amer J Epidemiol*, in press, 2011.

Radloff KA, Y Zheng, HA Michael, M Stute, B Bostick, I Mihajlov, M Bounds, MR Huq, I Choudhury, MW Rahman, P Schlosser, KM Ahmed, A van Geen. Arsenic adsorption protects deep groundwater from widespread contamination in Bangladesh. *Nature Geoscience* 2011;4:793-8.

Khan, K, Factor-Litvak, P, Wasserman, GA, Liu, X, Ahmed, E, Parvez, F, Slavkovich, V, Levy, D, Mey, J, van Geen, A, Graziano, JG: Manganese exposure from drinking water and children's classroom behavior in Bangladesh. *Environ Health Perspect* 2011;119:1501-6. PMID: 21493178. PMCID: in process.

Khan, K, Wasserman, G, Liu, X, Ahmed, E, Parvez, F, Slavkovic, V, Levy, D, Mey, J, van Geen, A, Graziano, J, Factor-Litvak, P: Manganese exposure from drinking water and children's academic achievement. *Neurotoxicology*, in press, 2011.

Parvez, F, Wasserman, GA, Factor-Litvak, P, Liu, X, Ahsan, H, Slavkovich, V, Sultana, Re, Sultana, Ru, Levy, D, Kline, J, Siddique, A, Islam, T, Graziano, JH: Arsenic exposure and motor function among children in Bangladesh. *Environ Health Perspect*, 2011;119(11):1665-70. PMID: 21742576 PMCID: in process.

Wasserman, GA, Liu, X, Parvez, F, Factor-Litvak, P, Ahsan, H, Levy, D, Kline, J, van Geen, A, Mey, J, Slavkovich, V, Siddique, A, Islam, T, Graziano, JH: Arsenic and manganese exposure and children's intellectual function. *Neurotoxicology* 2011;32:450-7. PMID: 21453714. PMCID: in process.

Chen Y, JH Graziano, F Parvez, M Liu, V Slavkovich, T Kalra, M Argos, T Islam, A Ahmed, M Rakibuz-Zaman, R Hasan, D Levy, A van Geen, and H Ahsan, Arsenic exposure from drinking water and cardiovascular disease mortality: A prospective cohort study in Bangladesh, *British Med J* 342:d2431, 2011.

Dhar, RK, Y Zheng, CW Saltikov, KA Radloff, B Mailloux, KM Ahmed, A van Geen, Microbes enhance mobility of arsenic in Pleistocene aquifer sand from Bangladesh, *Environ Science Technol*, 2011;45(7):2648-54. dx.doi.org/10.1021/es1022015.

van Geen A, KM Ahmed, Y Akita, MJ Alam, PJ Culligan, J Feighery, A Ferguson, M Emch, V Escamilla, P Knappett, AC Layton, BJ Mailloux, LD McKay, JL Mey, ML Serre, PK Streatfield, J Wu, M Yunus, Fecal contamination of shallow tubewells in Bangladesh inversely related to arsenic, *Environ Sci Technol*, DOI: 10.1021/es103192b, 2011; in press. PMCID: PMC3037737

Students supported in part by the Biogeochemistry Core over the past year
Ivan Mihajlov, Earth & Environmental Sciences, Columbia, PhD candidate
Jing Sun, Earth & Environmental Sciences, Columbia, PhD candidate
Christine George, Mailman School of Public Health, Columbia, PhD candidate

Core D: *Hydrogeology Support Laboratory*
PIs: Martin Stute, Peter Schlosser, Steve Chillrud, Juerg Matter

The Hydrogeology Support Core provides information on the groundwater and surface water flow and transport regime at our field sites in the US and Bangladesh, and supports projects number 5, 6, 7, and the RTC.

Notable advances for the last period:

Field efforts: During the winter of 2010/11, 24 wells were installed in area 'M' in Araihazar, our field area in Bangladesh. In January 2011, we performed a series of pumping tests and sampled the well nests for chemical and isotopic parameters. The goal of this experiment is to shed light on the hydraulic and geochemical interactions of aquitards and aquifers in Bangladesh. Results of this study will have implications for the sustainability of the deeper, low-As aquifers. Analytical fits to the hydraulic responses of the aquifer to pumping show considerable leakage through the aquitard. The geochemistry of the water below the aquitard shows evidence for Fe exchange and dissolved organic carbon leaching from the aquitard. However, it is unclear at this time if As comes with the water out of the aquitard or is mobilized in the aquifer due to increased DOC.

We also collected samples for isotopic tracer and geochemical analyses (noble gases, ^{14}C, ^{13}C, ^{18}O, ^{2}H, major and trace elements) from the wells at site M and from 13 community wells in Araihazar to better

characterize the deeper aquifer. While geochemical correction models need to be refined – the preliminary evidence suggests that much of the water in the deeper, low As aquifers contain water recharged in late glacial/Holocene transition.

Laboratory efforts: We purchased (with non NIEHS funds) a cavity ring-down spectrometer which will allow us to measure samples for ^{18}O and ^{2}H at a precision exceeding that of commercial mass spectrometry. The instrument has been successfully tested, and laboratory protocols have been established (P5,6,7).

Sample Measurements: We performed 71 ^{3}H and 43 ^{14}C analyses on samples from wells in Bangladesh (P5,7) and 10 ^{14}C analyses on organic matter (soil/wood).

Modeling: Thus far, analytical models have been used to derive leakage rates and hydraulic conductivities from the pumping tests discussed above (P5,7). The Core supported groundwater flow modeling activities (MODFLOW, MT3D) at site 'X' in Bangladesh (P5&7) in order to quantify the groundwater/surface water interactions. (Aziz et al., 2011) and the incorporation of results of our push-pull experiments related to As adsorption in a regional groundwater transport model (Radloff et al., 2011).

All publications listed in Projects 5, 6, 7 and RTC have been supported by the Hydrogeology Core. Of particular relevance are the following:

Aziz, Z. et al. Distribution of As in shallow aquifers of Bangladesh controlled by desorption and flushing: An evaluation at the village-scale using a 3-D groundwater flow model. *Water Resources Research*, under revision, Nov. 2011.

Radloff KA, Y Zheng, HA Michael, M Stute, B Bostick, I Mihajlov, M Bounds, MR Huq, I Choudhury, MW Rahman, P Schlosser, KM Ahmed, A van Geen. Arsenic adsorption protects deep groundwater from widespread contamination in Bangladesh. *Nature Geoscience* 2011;4:793-8.

Research Translation Core: *Collaborating with Government & the Public: Arsenic & Manganese Exposure via Groundwater*
Co-PI's: Steve Chillrud, Meredith L. Golden
Co-investigators: Joseph Graziano, Martin Stute, Stuart Braman

The Columbia SRP RTC continues to focus its efforts on groundwater issues in general and arsenic contamination in particular. We describe below some of our government and community engagement activities.

Columbia RTC continues to partner with government agencies at the county, state, and federal levels in NJ, NY, NH, and ME. At the Vineland Superfund Site, RTC and Project 6 scientists have worked closely with the Remedial Program Manager to determine the most cost effective and expedient way to remove arsenic contamination from the area's groundwater. We have provided feedback to key parts of the external review of this EPA Superfund site based on our work exploring new arsenic remediation techniques. We are currently planning additional field and laboratory work in conjunction with EPA and USACE. In 2011 Columbia RTC established new partnerships with two offices in NJDEP to begin addressing the problem of arsenic in private wells in several NJ counties, In a new partnership with the Hunterdon County Dept. of Health RTC has engaged a Barnard Sustainable Development workshop class in developing videos and web resources for private well owners. In NY, Columbia RTC has continued its collaboration with the Rockland County Department of Health and the United Water company focusing this year on laying the foundation for the analysis of alternative water conservation plans in Rockland County, an effort emerging directly from RTC Rockland water outreach in previous years. In addition, over 3000 people attended the annual open house on Columbia's Lamont Campus where we organized hands-on activities highlighting issues of water use and

arsenic contamination in the US and Bangladesh. Project scientists working in Maine continue to engage educators, parents, and the local media to promote community involvement in arsenic issues. Projects scientists have been interviewed for many articles in regional and national popular press, such as Dr. Graziano's interview for the recent Consumer Reports article on arsenic and lead in commercial juice.

Our RTC plays a leadership role in advancing the interactions among SRP-funded universities, federal agencies, and communities concerned with Superfund sites. For example, Meredith Golden, is an active member of the Dartmouth SRP External Advisory Committee. She also participated in the Northeastern SRP Consortium meeting on 25 April 2011 and carried out several of the group's action items. Ms. Golden has also served on RTC working groups including those focused on geospatial technologies, data sharing, and partnering with state and federal government agencies. She led a webinar discussion on data-sharing and a break-out session and computer demonstration on GIS at the annual meeting. The CU RTC has been in touch with researchers at EPA, CDC/ATSDR, and other data providers to integrate existing data on vulnerable populations near Superfund sites. It has developed an online mapping tool (currently in alpha) for agencies and other stakeholders concerned with the impact of Superfund sites on nearby communities.

Ongoing communications are facilitated by monthly seminars (available as webinars for remote audiences), the project website, and participation in agency and SRP sponsored webinars and forums.

Students and Postdocs involved in RTC activities in 2010:
Jing Sun, Ph.D student, Columbia University
Qiang, Yan, PhD received in 2011, Queens College
Karen Wovkulich, PhD received in 2011, Columbia University

Governmental agency contacts:
Vineland Superfund Site: Ron Naman, Nica Klaber, John Frisko, Jon Josephs, Michael Sivak from EPA Region 2; Steve Creighton and Laura Bittner from USACE- Philadelphia Office;
Craig Wallace and Chad Vansciver from NJDEP.

NJDEP Arsenic in Private Wells: Judy Louis, Office of Science; Steve Spayd, NJGS; Greg Herman, NJGS

Hunterdon County Dept. of Health: John Beckley, Carla Hobbs, Debbie Vacarella

NYS Landfills: Steve Parisio, NYSDEC.

Rockland County Drinking Water Issues: Dan Miller, RCDOH; Hon. Harriet Cornell, Hon. Connie Coker, and Hon. Alden Wolfe, Rockland County Legislature.

Vulnerable Populations Supplemental: Andrew Dent, ATSDR, GRASP; Olivia Harris, ATSDR, Office of Science; Scott Parris, EPA Office of Environmental Justice

General Superfund issues: Nigel Fields, EPA Office of Science Policy; Ronald Landy, EPA Region 3

Maine research on exposures to arsenic in groundwater:
Charles Culbertson, Charles Schalk, Martha Nielsen from USGS Maine Water Science Center; Carole Johnson from USGS Office of Groundwater;
Robert Marvinney, Robert Johnston, Marc Loiselle, Daniel Locke from Maine Geological Survey; Andrew Smith, Diane Silverman, Deborah Rice, and Eric Frohmberg from Maine Department of Health and Human Services Office of Environmental and Occupational Health Programs;
Marcel Belaval from EPA Region I, Drinking Water Program

RTC Core-Supported Publications and presentations:

Braman S, S Gruber, Hurdles to incorporating conservation into long-term water supply planning: a Rockland County NY case study, published in the AWWA Symposium Showcase Conference *Proceedings, 2011,Tuesday 2C-2: 1-15. Papers selected from the AWWA Water Conservation Symposium, March 2011, Orlando, Fl.*

Bostick BC, J Sun, K Wovkulich, M Stute, B Mailloux, SN Chillrud. Evaluation of Potential Strategies for the Effective Remediation of Arsenic- Contaminated Superfund Sites. Presented at the 12th annual Research & Industrial Collaboration Conference (RICC) at Northeastern University on October 13, 2011, Boston, MA (invited).

Chai-Onn T, G Yetman, and M Golden (presenter). 2011. Interactive Mapping Service: Superfund Sites and Vulnerable Populations: Computer Demonstration of Work in Progress. Superfund Research Program Annual Meeting. Lexington, KY, 23 October 2011.

Golden M. 2011. Breakout Session 1: GIS Applications for SRP . Discussion Leader. Superfund Research Program RTC Annual Meeting. Lexington, KY, 26 October 2011.

Wovkulich K, Stute M, Protus TJ, Mailloux BJ and Chillrud SN. (2011), Injection System for Multiwell Injection Using a Single Pump. Ground Water Monitoring & Remediation, 31: 79–85. doi: 10.1111/j.1745-6592.2011.01325.x

Example of popular press article citing SRP Director Joe Graziano:
Consumer Reports Magazine: Jan. 2012. Arsenic in your juice. How much is too much? Federal limits don't exist. Accessed on Nov 30, 2011 at http://www.consumerreports.org/cro/consumer-reports-magazine-january-2012/arsenic-in-your-juice/index.htm.

Website urls:
Columbia SRP Program website: http://superfund.ciesin.columbia.edu
Columbia SRP Water Resources in Rockland County: Planning in a Changing World: http://superfund.ciesin.columbia.edu/Rocklandwater/