Annual Progress Report of P42 ES 10349 "Health Effects and Geochemistry of Arsenic and Lead", Joseph H. Graziano, P.I., 12/15/2004

Section 1: Highlights for 2004

We present below two research highlights.

Highlight #1: An Association between Arsenic in Drinking Water and Cognitive Function in Children in Bangladesh.

P.I.: Joseph Graziano

In Bangladesh, approximately 30-40 million people have been chronically exposed to high concentrations of naturally occurring arsenic (As) in drinking water, supplied by approximately 10 million tube wells. Aside from carcinogenic and vascular effects, the literature contains reports of neurologic consequences of acute and chronic exposure in adults, although the dosimetry is poorly described. Given the absence of a significant research base concerning the consequences of As in children, we sought to examine the possible associations between As exposure and intellectual function. In 2000, we began a prospective study of the health effects of As in 12,000 adult residents of Araihazar, Bangladesh. The study site, a 25 square km region located approximately 30 km east of Dhaka, was chosen because of its wide range of As concentrations in drinking water. Our survey of 6,000 contiguous wells in the region revealed that 75% exceed the WHO As standard of 10 μg/L, while 53% exceed the Bangladesh standard of 50 μg/L; water As concentrations ranged from <1 to 900 μg/L. In the same region, we are examining the consequences of As exposure on children's health.

In a cross-sectional study of 201 ten year-old children, we have found a strong association between arsenic in drinking water and cognitive function (Wasserman et al, 2004. *Environ Health Perspect* 112:1329-1333). Children and mothers came to our field clinic, where children received a medical examination in which weight, height, and head circumference were measured. Children's intellectual function on tests drawn from the WISC-III was assessed by summing weighted items across domains to create Verbal, Performance and Full Scale raw scores. Children provided urine specimens for measuring urinary As and creatinine, and were asked to provide blood samples for measuring blood lead and hemoglobin concentrations. Exposure to As from drinking water was associated with reduced intellectual function after adjustment for covariates that included water manganese, as well as sociodemographic covariates such as maternal education and intelligence, housing type and access to television. Both before and after adjustment for covariates, well water arsenic concentration was associated with reduced intellectual function, in a dose-response fashion, such that children with water As > 50 μg/L achieved significantly lower Performance and Full Scale scores than children with water As < 5.5 μg/L. The association was generally stronger for well water As than for urinary As.

These findings are unique, and suggest that the recent EPA decision to lower the maximum contaminant level for arsenic in drinking water from 50 to 10 μg/L is highly justified. On the international level, our finding of a strong association between arsenic exposure and intelligence is both important and tragic, and adds urgency to the need for effective remediation in Bangladesh and other regions of south Asia where consumption of arsenic contaminated water is prevalent. The global community has been slow in responding to the public health

significance of As exposure in Bangladesh, despite the enormous scope of the problem. We hope that the present findings add a new sense of urgency to efforts aimed at alleviating and eliminating As exposure in Bangladesh

Highlight #2: Arsenite Induces Apoptosis in Malignant Melanoma Cells

P.I.: Tom K. Hei

Malignant melanoma is often a deadly disease due to the lack of effective treatment options. This cancer typically responds poorly to both chemotherapy and radiotherapy. Recent *in vitro* studies conducted in the laboratory of **Dr. Tom K. Hei**, Professor of Environmental Health Sciences in the Mailman School of Public Health at Columbia University, have shown that short term treatment with low to moderate concentrations of sodium arsenite (2-10 μM), which has little or no effects on normal melanocytes, induces apoptosis of human melanoma, including highly metastatic ones, by more than 6 fold. These data suggest that arsenic may be effective as a therapeutic regimen of an otherwise refractory and highly malignant disease.

Malignant melanoma is a cancer that responds poorly to chemotherapy and γ-irradiation. There are no effective treatments for this disease. Despite the dramatic increase in the incidence of malignant melanoma in the past decades, the molecular mechanisms of its progression and extreme resistance to treatment, which kill cells by induction of programmed cell death (apoptosis), remain largely unknown. The existence of melanoma-specific antigens, and presence of melanoma-specific immune cells in the human body, does not cause immune-mediated destruction of malignant melanomas. Furthermore, melanomas actively suppress the immune system. Melanoma cells express many different growth factors, cytokines and their receptors (including FGFβ/FGFR, EGF/EGFR and TNFα/TNFR1) for regulation of their growth. TNFα mediates a variety of biological functions such as cell proliferation, differentiation and cell death. In normal non-stress conditions, TNFα-induced death is actively suppressed by NF-κB-dependent gene expression (including BclxL, c-IAP's and FLIP proteins). The critical component of the NF-κB signaling pathway is a multi-protein catalytic complex IKK (IκB kinase) that phosphorylates the NF-κB inhibitor, IκBα at Ser 32 and 36. Phospho- IκBα is then targeted for proteasome-dependent degradation, thus liberating NF-κBp65-p50, which enters the nucleus and mediates NF-κB-dependent transcription.

Human malignant melanomas are likely to have altered and suppressed apoptotic pathways. There are several alternative mechanisms of suppression of Fas-mediated death signaling at the distinct phases of signal transduction. Down-regulation of Fas death receptor in lymphoid and solid tumors is often associated with resistance to drug- and radiation-induced cell death. Similarly, human malignant melanomas that lack surface expression of Fas have a poor prognosis. Down-regulation of Fas levels can be attributed to changes at the genomic, transcriptional and post-translational levels. Mutations in the death domain of Fas have been reported to take place in 7% of metastatic melanomas resulting in an abnormal protein that exhibits abrogated association with FADD and procaspase-8. A more common event in melanomas relates to transcriptional down-regulation of Fas expression. Silencing the Fas receptor promoter was reported to take place by cooperating transcription factors, as well as due to the hyper-methylation of its promoter. There is a profound necessity to develop alternative

approaches in the treatment of metastatic melanomas including effective induction/acceleration of apoptosis in spite of suppression of Fas-mediating death signaling.

In this regard, arsenic, an ubiquitous environmental carcinogen, has been successfully used in the treatment of acute promyelocytic leukemia through the induction of apoptosis. It seems that IKK - NF-κB suppression is one of the main targets of arsenite treatment. In our studies, we have found that low to moderate concentrations of arsenite (2-10 μM) that has little or no effect on normal melanocytes, induce high levels of apoptosis in melanomas in spite of their low surface Fas levels. The two prerequisites that dictate apoptotic response of melanomas upon arsenite treatment are low nuclear NF-κB activity and an endogenous expression of TNFα. Under these conditions, melanoma cells acquired sensitivity to TNFα-mediated killing. On the other hand, signaling pathways including those of PI3K-AKT, MEK-ERK and JNK, play a protective role against arsenite-induced oxidative stress and apoptosis. Suppression of these pathways dramatically accelerates arsenite-induced apoptosis of resistant metastatic melanomas. Taken together, these data based on combined treatment of cancer cells by arsenite and inhibitors of survival pathways could provide rational approaches to sensitize melanomas to the cytotoxic effects of arsenite.

Arsenic is an important environmental carcinogen that affects millions of people worldwide through contaminated water supplies. Epidemiological data have shown that chronic exposure of humans to inorganic arsenical compounds is associated with liver injury, peripheral neuropathy, and an increased incidence of cancer of the lung, skin, bladder, and liver. The extent of human sufferings bestowed by arsenic exposure simply cannot be overstated. Our present study, however, indicates that arsenic can also be a double-edged sword and could, potentially, benefit thousands of melanoma patients each year who fail conventional therapeutic regimen.

Section 2: Progress Reports for Research Projects and Cores

Project 1: Bioavailability of Soil Lead and Arsenic in Humans
P.I.: Conrad Blum

The primary aims of this project are to 1) determine estimates of the bioavailability of lead in soils from a mining site, smelting site and urban site; 2) to test the hypothesis that phosphate-based soil amending agents reduce this bioavailability in adult humans; and 3) to examine the correlation between the human and *in vitro* estimates of bioavailability in these soils. This study involves the ingestion of tiny amounts of sterilized soils, which contain lead but no other contaminants of concern. The method utilizes the technique known as stable isotope dilution, and takes advantage of the fact that the presence of non-radioactive isotopes of lead in soil allow one to track tiny amounts of lead that are actually absorbed into blood.

A total of 20 volunteer subjects have completed the protocol designed to assess the bioavailability of lead in soil. The first twelve study participants were randomly assigned to ingest either the phosphate amended or non-amended soil. This soil from a former smelting site in Joplin, MO, was treated with 1% phosphate at the site, by the U.S. EPA, and sampled at 6 month intervals. We have evaluated an “amended” and “non-amended” soil specimen that was

sampled 18 months post-treatment. Final Pb isotope and bioavailability data were analyzed in the Geochemistry Core Laboratory.

The findings, discussed in last year's report, are extremely interesting and potentially important. Among the six subjects who received the non-amended soil, the mean Pb bioavailability was 34.7%. In contrast, among those who received the phosphate-amended soil, mean Pb bioavailability was 19.9%, significantly less. While there is a wide range of inter-individual variability, this represents an average reduction in bioavailability of 43%. Studies evaluating the bioavailability of these same soil samples in animals, by Casteel et al, and in an *in vitro* system, by Ruby et al, reported a 38% reduction in bioavailability, by both methods, validating the relative effect that phosphate inactivation has on soil lead bioavailability in these samples. It is particularly important to note that our work to date appears to validate the use of the *in vitro* and animal models, in that the values obtained for bioavailability in all three systems are coherent with each other.

During the past year we have been evaluating of the next set of soils which have been collected from a former mining site in Tar Creek, OK. The soils were analyzed by the EPA laboratory in Edison, NJ, for over 200 priority pollutants, and were found to be otherwise safe for human consumption. Before the soils were administered to the subjects, as in the past, they were also sterilized by gamma irradiation. Four subjects have completed this protocol, and the preliminary results indicate that Pb bioavailability from the Tar Creek mining site is surprisingly high, though we are not yet prepared to assign a numeric value to it since this work is still in progress. Thus far, a total of 64 potential study volunteers have been screened for blood Pb concentration, Pb isotope composition, and overall health. Ten of these are still potential protocol participants, and plans for admission to the General Clinical Research Center are underway.

Project 2: Genotoxic Mechanisms of Arsenic in Mammalian Cells
P.I.: Tom Hei

The overall goal of the proposed research focuses on the mechanisms of the genotoxic effects of arsenic in mammalian cells, particularly the role of mitochondrial damage and the subsequent induction of reactive oxygen and reactive nitrogen species. The specific aims of the studies remain unchanged.

During the current funding period, we succeeded in generating mitochondrial DNA deficient rho zero (ρ^o) human hamster hybrid (A_L) cells using the chemotherapeutic agent ditercalinium. Treatment of exponentially growing A_L cells with 1.5 μg/ml of the drug for 4 months and in the presence of uridine (50 μg/ml) resulted in a 95% reduction in mitochondrial DNA content. Mitochondrial DNA deficient cells showed little or no mitochondrial membrane potential based on the membrane potential sensitive fluorescent probe JC-1 stain. ρ^o A_L cells were used to further confirm the functional role of mitochondria in the genotoxicity of arsenic. Similar to our previous findings using Rhodamine 6-G treated A_L cells, which resulted in significantly higher cytotoxicity, treatment of ρ^o A_L cells with arsenic followed by rescue fusion with cytoplasts produced very few mutations. *Thus, the importance of mitochondrial function in the genotoxicity of arsenic in mammalian cells has been reaffirmed using a more conventionally accepted approach.*

We previously demonstrated that short term treatment with low concentrations of sodium arsenite (2-10 μM), which has little or no effects on normal melanocytes, induced apoptosis of human melanoma including highly metastatic ones in a process independent of binding to Fas ligands. There is evidence that epidermal growth factor receptor (EGFR) is expressed in human melanomas at different stages of tumor progression. Furthermore, specific inhibitors of EGFR-mediated signaling may reduce anti-apoptotic properties of cancer cells, including melanomas. Since EGFR signaling operates via activation of the PI3K-AKT and MEK-ERK pathways, we suggested that the combination of arsenite and EGFR inhibitors might also effectively induce apoptosis in melanoma. During the current funding period, we showed that a moderate concentration of arsenite (5-10 μM) indeed up-regulated apoptosis induced by EGFR inhibitors in EGFR-positive melanomas. In contrast, induction of apoptosis in melanomas with negligible surface expression of EGFR or with defective EGFR signaling required direct suppression of the PI3K-AKT and MAPK pathways by specific pharmacological inhibitors in the presence of arsenite. Taken together, these data provide additional approaches in sensitizing melanomas to the cytotoxic effects of arsenic in melanomas, an often deadly disease due to the lack of effective treatment options.

Arsenic is an important environmental carcinogen that affects millions of people worldwide through contaminated water supplies. For decades, arsenic was considered a non-genotoxic carcinogen. Using the highly sensitive A_L mutation assay, we showed previously that arsenic is indeed a potent gene and chromosomal mutagen and that its effects are mediated through the induction of reactive oxygen species. However, the origin of these radicals and the pathways involved are not known. Our studies illustrate that mitochondria are a primary target in arsenic-induced genotoxic response and that a better understanding of the mutagenic/carcinogenic mechanism of arsenic should provide a basis for better interventional approach in both treatment and prevention of arsenic induced cancer.

In the coming year, we will use multiplex PCR and primers for the various genes located on both the short and long arm of human chromosome 11 to compare the types of mutations generated in both ρ^o and wild type A_L cells. We will further examine the role of *Ras* signaling pathways in arsenic induced apoptosis of human melanoma cells.

Project 3: A Cohort Study Of Health Effects Of Arsenic Exposure In Bangladesh
P.I.: Habibul Ahsan

In Bangladesh, nearly 40 million people have been chronically exposed to elevated concentrations of arsenic in drinking water for the past several decades, resulting in an epidemic of arsenical skin lesions. This situation arose as a result of the well-intentioned efforts of UNICEF, which installed a million tube wells in an effort to shift the population away from microbially-contaminated surface water, not realizing that the groundwater is naturally enriched in arsenic. Three of our seven SBRP projects take place in Bangladesh, in an effort to learn about health and geochemistry issues that are of importance in the U.S., while at the same time trying to help the people of Bangladesh reduce their exposure to arsenic.

This project is our largest biomedical project. It has established a prospective cohort study that has recruited 11,746 men and women in Araihazar, Bangladesh, to investigate the health effects of arsenic exposure with an initial focus on skin lesions and skin cancers, and also to establish a biorepository for future studies. 99% of the eligible participants who were approached agreed to be in the study and were recruited over an 18-month recruitment period from October 1, 2000 to April 2002. In order to set the stage for the cohort study, especially to build a sampling frame, we tested all 5,966 contiguous tube wells for arsenic within a well-defined area of approximately 26 square kilometers in collaboration with our hydrology and geochemistry colleagues. We also enumerated all 65,876 people in the study area who were drinking water from these 5,966 wells. Findings from this pre-cohort study survey are published in a series of papers [van Geen et al., 2002 and 2003; Parvez et al., Submitted].

The biological samples have been processed and baseline questionnaire data have been processed and stored for all 11,746 cohort members. We have completed the analysis of total urinary arsenic of all these individuals at baseline, and also arsenic metabolites in a subset of 1,200 individuals (skin lesion cases and controls). Using baseline cross-sectional data on arsenic exposure and prevalent skin lesion cases we have conducted full dose-response analyses of the relationship between arsenic exposure and risk of skin lesions. These novel results, with major public health significance, are being written up for publication. We have also collected and analyzed full dietary data from all 11,746 cohort members using a modified meal-based dietary questionnaire. In addition, we completed a dietary validation study by collecting complete records of a seven-day food diary on a randomly selected sample of 200 cohort participants, during two different seasons of the year. The results of this validation study showed very good agreement with the questionnaire data collected from the entire cohort, confirming the reliability of that data. These results were recently published [Chen et al., 2004]. Thus, this dietary information will enable us to examine possible nutritional effects on arsenic metabolism and disease.

Between October 2002 and May 2004, we completed our first bi-annual follow-up visit of the entire cohort. The follow-up of the cohort members was done through in-person home visits, in addition to the passive follow-up through the participants' visits to a field clinic established to provide primary care to study participants and their families. We collected questionnaire and clinical data as well as a urine sample (for monitoring the changes in arsenic exposure) during the follow-up visits. We were able to collect follow-up data on nearly 100% (11,686 of the total 11,746) of the baseline cohort. A total of 11,328 individuals completed the follow-up interview and clinical evaluations: 254 migrated, 104 died and 60 were not found. A total of 11,109 individuals (of 11,328 completed interview and clinical evaluations) provided urine samples. The follow-up data on all 11,746 individuals have been computerized. All 11,109 follow-up urine samples have also been analyzed for total urinary arsenic.

Our second bi-annual follow-up visit started in October, 2004; to date, we have completed in-person follow-up home visits and have collected questionnaire data, clinical data and biological samples from 1,000 of our cohort members.

Almost all published epidemiological studies have used either retrospective assessments of arsenic exposure or examined ecological associations without individual exposure assessments. Our ongoing cohort study is the first to prospectively examine the dose-response relationship between arsenic exposure and skin lesions using individual-level exposure data.

Results of our prospective analyses will undoubtedly shed light on the health effects of arsenic at dose ranges that are relevant for both Bangladesh and the U.S.A.

Project 4: Environmental Arsenic, Pregnancy and Children's Health
P.I.: Joseph Graziano

Substantial progress has been made with each of the four specific aims of this project, two of which involved cross-sectional studies of 10- and 6-year old children, respectively. This report focuses on one aim, i.e., our effort to determine whether arsenic exposure from the consumption of groundwater is associated with diminished intellectual function in 10-year old children. Sadly, the answer is yes. (Note that above, in Highlight #1, some of this was described.)

Exposure to arsenic has long been known to have neurologic consequences in the occupational setting, but to date there have been no well controlled studies in children. We therefore recently completed two cross-sectional studies in Araihazar, Bangladesh. In the first, a cross-sectional study of 201 ten year-old children, we have found a strong association between arsenic in drinking water and cognitive function (Wasserman et al, Environ Health Perspect, 112: 1329-1333, 2004). Children and mothers came to our field clinic, where children received a medical examination in which weight, height, and head circumference were measured. Children's intellectual function on tests drawn from the WISC-III was assessed by summing weighted items across domains to create Verbal, Performance and Full Scale raw scores. Children provided urine specimens for measuring urinary As and creatinine, and were asked to provide blood samples for measuring blood lead and hemoglobin concentrations. Exposure to As from drinking water was associated with reduced intellectual function after adjustment for covariates that included water manganese, as well as sociodemographic covariates such as maternal education and intelligence, housing type and access to television. Both before and after adjustment for covariates, well water arsenic concentration was associated with reduced intellectual function, in a dose-response fashion, such that children with water As > 50 μg/L achieved significantly lower Performance and Full Scale scores than children with water As < 5.5 μg/L. The association was generally stronger for well water As than for urinary As.

The field work of a second cross-sectional study of 235 six year-old children was recently completed, and statistical analyses are under way. An interim analysis was presented in poster format at the 2004 annual SBRP meeting in Seattle. In general, it appears that the association between water arsenic and cognitive function exists in younger children, but the finding is less robust than in 10 year old children. The reason(s) for this likely includes the fact that the assessment of cognitive function in younger children – in the case using the WPSSI- is somewhat less precise than that in older children. In any case, with IRB permission (for a sample size of 300), we have gone back into the field to recruit additional children to bolster this finding.

Finally, we have made another highly significant and, we believe, landmark finding concerning children's' environmental health. In our original cross-sectional study of 10 year-old children, described above, we noted that both water arsenic and *water manganese* are elevated in Bangladesh. Indeed, 80% of the wells in Araihazar – our study area – have manganese concentrations in excess of 500 μg/L, the WHO drinking water standard. Water As and water

Mn were significantly associated with each other, but weakly so (Spearman r = 0.34). Since occupational exposure to Mn is associated with neurotoxicity, we examined the possible effects of both water arsenic and water manganese on cognitive function. When both were included in the regression model predicting child intelligence, Mn dropped out of the model, while As was adversely associated with intelligence; there was no significant interaction either. However, in the discussion of the publication (Wasserman et al, EHP, 2004), we noted that that study was not designed to examine possible effects of water Mn on intelligence. Rather, such a study would select only children with very low water As, e.g., < 10 μg/L. Since our study region included a low arsenic area (with variable Mn), we went back into the field (with IRB approval) and recruited 150 ten year-old children *who had been consuming tube well water with arsenic < 10 μg/L, but with water Mn concentrations of Mn that ranged 4 to 3900 μg/L*. In this study, now being prepared for publication, after control for sociodemographic covariates and urinary arsenic**, *water Mn was highly associated with total raw score on the WISC-R (p = 0.0014), Performance Raw Score (p = 0.0008), and Verbal Raw Score (p = 0.0656).*** We believe this to be a landmark finding and will be further pursuing this line of investigation in the competitive renewal of our SBRP.

Project 5: Arsenic mobilization in Bangladesh Groundwater
P.I.s: Yan Zheng and Martin Stute

The goal of project 5 is to document the spatial and temporal variability of groundwater As concentrations in the region of Bangladesh where biomedical Projects 3 and 4 are being conducted and to gain a better understanding of the geophysical, hydrological, and geochemical processes that regulate As levels in groundwater.

There have been several notable advances during the past year:

Flushing rate controls As inventory in Bangladesh Aquifer:

We used the $^{3}H/^{3}He$ dating technique to determine groundwater ages at our 6 multi level well nest sites in Araihazar. ^{3}H (tritium), primarily produced in the atmospheric atomic bomb tests in the early 1960s, was found up to a depth of 20 m suggesting that the residence time of the deeper groundwater in shallow aquifer is more than 50 years. Recharge rates derived from vertical $^{3}H/^{3}He$ age profiles in the shallow aquifer range from 10 to 70 cm/year. These rates exceed withdrawal rates (<2 cm/year) and therefore appear to be dominated by natural processes, perhaps controlled by the downward hydraulic gradient between the shallow and deep aquifer. Recharge rates are highest in areas with a sandy surface geology and lower average As concentrations. On a timescale of 30 years, As increases as a function of $^{3}H/^{3}He$ age in the shallow aquifer at a rate ranging from 6 to 20 μg/L/year. In areas with the highest recharge rate and overall low As concentrations, the As accumulation rate is only about a factor of 3 lower than in areas with low recharge rates. *This work suggests that the contact time between water and sediment is an important factor in controlling As concentrations*.

Hydrological modeling of the shallow Holocene aquifer calibrated by transient tracers:

Ph.D. candidate Allan Horneman developed a 3-dimensional groundwater flow model for the western section of our area of investigation in Araihazar. The model incorporates the geology

of the area, our long-term hydraulic head time series from the local rivers and monitoring wells, and meteorological data. Besides hydraulic data, $^{3}H/^{3}He$ data in combination with flow path calculations were used as calibration targets. In addition to $^{3}H/^{3}He$, CFCs and SF_6 were explored as tracers for groundwater flow and transport. CFCs were found to degrade in less than 3 years under the reducing conditions in the aquifer. SF_6 appears to have a small natural source in the deeper aquifer. At one of our work sites (site F), SF_6 derived ages are consistent with $^{3}H/^{3}He$ ages, but at another site (site A), SF_6 ages appear to be considerably higher than $^{3}H/^{3}He$ ages suggesting loss into gas phases or retardation of SF_6.

Limited temporal variability of groundwater As in shallow and deep aquifers:

Ph.D. candidate Ratan Dhar has carefully evaluated the temporal variability of groundwater As using a series of samples from Araihazar, Bangladesh that were collected biweekly or monthly between 2001 and 2004. High-resolution inductively-coupled-plasma mass-spectrometry, which has better than 5% long-term reproducibility for As, was employed to generate dissolved As data together with several other elements (Fe, Mn, S, P) to investigate various issues including seasonal variations in As. Groundwater samples were from six nests of monitoring wells installed in an area where the hydrology and geochemistry have been carefully studied. Dissolved As concentrations range from < 1 μg/L to ~ 600 μg/L in the shallow Holocene aquifer (upper 30 m) and mostly < 1 μg/L (As <1-6.6 μg/L) in the deep Pleistocene aquifer (> 30 m depth). Dating of shallow aquifer water showed tritium-helium ages ranging from < 1 yr to > 40 yr. Deep Pleistocene aquifer water was ^{14}C-dated and found to be up to thousands of years old. *In the shallow aquifers, variations in groundwater As concentrations in all but 2 out of 27 wells did not display any discernable pattern linked to seasonal water table fluctuations. In addition, As concentration fluctuations were limited (4-12%) in all 27 wells.* The two wells that displayed a seasonal pattern of As variations (10%-15%) were particularly shallow (depths 6 m and 9 m). Redox-sensitive indicators such as Fe and Mn also displayed seasonal pattern in these two wells. In contrast to As, most of the wells with tritium-helium ages less than 21 years showed much larger variations in dissolved Cl- concentrations (10-43%) and total dissolved cations (5-31%) concentrations. Temporal variability was considerably reduced for groundwater >21 years old: 6-7 % and 10-14 % major cations and anions, respectively. This suggests that despite the apparent influence of recharge on major ion concentrations, dissolved As concentrations in most shallow aquifers are relatively well buffered. No notable variability (<2%) in As concentrations was observed in groundwaters from the Pleistocene aquifer.

Bioaccessibility of As in rice samples:

Ph.D. candidate Yi He (now at John Jay College as an assistance professor of chemistry) used *in vitro* gastric fluid and small intestinal (GFSI) incubation, which mimic the digestion process occurring inside the human body, to investigate arsenic bioaccessibility during the digestion process. Arsenic in rice was chosen for investigation because rice is a staple food in many areas of the world, including the US. In Bangladesh and India, the normal daily adult rice consumption level is measured in kilograms. Bulk As concentrations in rice samples obtained from rice fields in Araihazar, Bangladesh and from US supermarkets were determined after acid dissolution and displayed a range of As levels from ~ 70 to ~ 600 μg/kg. When rice samples were subjected to GFSI incubation, ~ 40% of the As is dissolved, suggesting a 40% bioaccessibility during digestion. About 50% of the GFSI-dissolved As is speciated to be

inorganic As by IC-ICPMS. More significantly, when rice is cooked with inorganic As-spiked water, only ~ 40% of the inorganic As spiked to cooking water is later re-dissolved by GFSI incubation, suggesting that As in water used for cooking has lower bioaccessibility than As used for drinking.

Development of undergraduate curriculum:

In 2003, Dr. Yan Zheng taught a capstone course for Environmental Science and Studies seniors at Queens College using the As problem in Bangladesh Groundwater as a case study. Consequently, she was invited to speak at an NSF Cutting Edge Workshop series on Geology and Human Health held in May, 2004 and at the Geological Society of America Fall annual meeting in Nov. 2004. Two innovative pedagogical approaches were used in this course: a) peer review, and b) proposal writing. Additionally, Drs. Stute and Becker developed an educational module applying GIS (Geographical Information System) technology to the Bangladesh data set for their undergraduate Environmental Data Analysis course.

Project 6: Redistribution of arsenic (As) and other contaminants at sites in New Jersey and Maine

P.I.s: Harry J. Simpson, Martin Stute, and Steven Chillrud

Arsenic mobilization in surface and groundwaters presents major challenges for minimizing chronic human As exposure in drinking water and other pathways. We are currently working at two Superfund sites, both of which have elevated As concentrations. The Superfund site which has been the focus of our field efforts during the past year is Vineland, NJ, the location of a former manufacturing facility for arsenical biocides which operated for more than three decades beginning in the late 1940s. Hundreds of tons of arsenic from this facility were dispersed in local soils, groundwaters, streams and sediments, extending many 10's of km "downstream" of the site.

A major treatment facility at the site has been in operation for more than three years to remove both organic and inorganic As from groundwaters beneath the site. A large new soil washing treatment plant is now also in operation. One of the primary goals and design criteria for the extraction wells and soil washing was to eliminate off-site migration of dissolved As via groundwater discharge to the Blackwater Branch, which flows along the northern perimeter of the site. We have used environmental samples of sediment, pore waters and surface waters along this stream to establish the extent of ongoing dispersal of As from the plant site during full operation of the treatment facilities. During July 2003, concentrations of dissolved As increased by an order of magnitude (2.5 to 24 ppb) in the Blackwater Branch as it transited about 1.4 km around the property. Our results from detailed pore water sample composition profiles indicate that the dominant source of dissolved As to the stream was on-going inflows to the stream of contaminated groundwaters, rather than diffusion of highly contaminated pore waters from the stream sediments.

Another significant difficulty associated with remediation of the Vineland site, which is projected to have cumulative costs on the order of $100 million over the next several decades, is

rapid clogging of a number of the extraction well screens. This decreases groundwater extraction rates, contributes to continued outflow of groundwaters into surface waters, and makes treatment plant operations less efficient due to frequent interruptions for chemical flushing of the wells. We conducted experiments that allowed us to exclude the hypothesis that entrainment of atmospheric O_2 through the wells by rapid pumping was responsible for the clogging. This may imply that mixing of water derived from multiple aquifer zones with different redox characteristics could contribute to the clogging of well screens. Review of recent literature suggests that the chemical used at Vineland for clearing well screens, sulfamic acid, is substantially less effective when compared to Na-dithionite and oxalic acid.

Field testing at Vineland of an experimental system for removing both organic and inorganic As was quite promising. The concept of this remediation approach is based on using zero-valent iron (metallic iron filings) as a medium for extraction of dissolved As. One advantage of this approach is that it doesn't require oxidizing inflowing water to achieve removal from solution of iron. If this approach can be further refined, it could offer an alternative strategy to further decrease dissolved As levels beyond those provided by the treatment facilities in operation at Vineland.

The second Superfund site at which we are working (Winthrop, ME) is a closed landfill that has undergone extensive remediation, including operation of pump and treat facilities for about seven years, but continues to have high dissolved As concentrations in ground waters (200-400 ppb). These elevated As groundwater levels appear to be derived from "natural" sediment As, present at average abundances (~3-30 mg/kg) typical of soils and other unconsolidated crustal materials, which is mobilized by strongly reducing conditions ultimately derived from landfill leachate. Results from both field and laboratory experiments concerning mobilizaton of As in reducing conditions at Winthrop are currently in press in Applied Geochemistry (Keimowitz et al, 2004). *Our findings suggest that As mobilization associated with landfills could be a widespread problem at locations not currently designated as national priority sites*, since it appears as if natural abundances of As in sediment are sufficient to generate quite elevated dissolved arsenic when reducing conditions are induced.

Laboratory progressive oxidation experiments with aquifer solids and reducing groundwaters from Winthrop indicate that dissolved iron [Fe(II)] represents the dominant buffer against increasing Eh. Once oxidized, there is a large excess of amorphous Fe(III) precipitates available for removal of all initially dissolved As onto strong sorption sites for either As(III) or As(V) species. Laboratory experiments and field data demonstrate differential removal of these elements, consistent with appreciable different precipitation and sorption pathways for these two redox sensitive elements. These results are reported in a manuscript currently in press in an ACS symposium volume on Advances in Arsenic Research (Keimowitz et al, 2004). Work involving incubation experiments over the last year has also focused on investigating the potential for sequestering arsenic via formation of insoluble sulfide minerals by stimulation of the microbial community involved in sulfate reduction. Preliminary results from those enhanced reducing condition experiments were presented at the 32nd International Geological Congress in Florence in August, 2004 and further results will be presented at the American Geophysical Union national meeting in December, 2004 (Keimowitz et al, 2004).

Project 7 Assessment and Remediation of Arsenic in Groundwater
P.I.: Alexander van Geen

The objective of this project is to translate fundamental knowledge of arsenic behavior into improved mitigation for the US and Bangladesh. Close collaboration with health and social scientists has become increasingly important to determine quantitatively the effectiveness of mitigation efforts in Bangladesh. After leading the effort to collect and analyze groundwater analyze from over 6000 tube wells within a 25 km^2 area (van Geen et al., 2003a), the project has focused on two approaches to mitigation: (1) promotion of well-switching (van Geen et al., 2002; Gelman et al., 2004) and (2) the installation community wells in the most affected villages where existing safe wells is not a viable option (van Geen et al., 2003b). One measure of the effectiveness of mitigation was recently obtained by asking a representative user of each of the 6500 wells inventoried in the study area some simple questions, as part of an effort to place new placards on each tested well to re-confirm its status. Results from the survey indicate that two-thirds of the households that were drawing their water from a well that tested unsafe for arsenic in 2000-01 had switched to another well by 2004 (Opar et al., in review). On average, 200 villagers drew their water from each of the 50 community wells installed by the project. Most households, however, had switched to a nearby private well. The impact of well switching was confirmed by a remarkable drop in urinary arsenic levels for members of the cohort recruited in the same area under Projects 3 and 4 (unpublished data, J. Graziano).

Project 7 contributed to the fundamental understanding of the mechanisms of As mobilization by demonstrating the key role of micro-organisms through incubations of Bangladesh sediment (van Geen et al., 2004a) and by developing new approaches to measuring sediment and groundwater properties (Horneman et al., 2004). The fortunate lack of a direct impact on the As content of rice from irrigation with groundwater containing elevated As was also demonstrated (van Geen et al., in review). On the analytical side, Project 7 contributed significantly to the improvement of an entirely different field method for arsenic (Dhar et al., 2004). This work resulted in two US and international patent applications based on related chemistry and the prototype of an inexpensive double-beam infra-red colorimeter developed with colleagues at Caltech. The signing of a licensing agreement between Columbia University and SpectraSensors of San Dimas, CA, (http://www.spectrasensors.com/), is imminent. Under an unusual agreement between the parties involved, the licensing revenue accruing from sales of the new field kit in rich countries will subsidize the distribution of the kit to developing countries such as Bangladesh. A rapid and sensitive method for analyzing groundwater for a wide suite of elements including arsenic (detection limit of 0.1 µg/L) was also developed in collaboration with Core B (Cheng et al., 2004a).

Two types of household-scale arsenic removal systems were also tested in Bangladesh and found to be effective technically (Cheng et al., 2004b, Nikolaidis et al., in press). These options were not pursued further, however, because they turned out to be logistically more complex to maintain than using existing safe wells or installing new safe wells. From a practical perspective, the project devised a new inexpensive method for sampling groundwater and sediment by relying on the manual drilling method used by small teams throughout Bangladesh to deploy a device called the "needle-sampler (van Geen et al., 2004b, van Geen et al., under review). Besides making it possible to collect samples at a much reduced cost for research purposes, the device allows drillers to test an aquifer for a household before installing a well. By

comparing field kit results and laboratory tests, the team has also shown that the kit used to test millions of wells throughout Bangladesh, the Hach kit, is considerably better than preceding kits (van Geen et al, 2004c). This particular study also resulted in a recommendation to increase the reaction time from 20 to 40 min to obtain consistent results.

Core A: Trace Metals Research Core Laboratory
P.I.: Joseph Graziano

The Trace Metals Research Support Core currently provides analytical support to three of the biomedical research projects under this SBRP, i.e., Projects 1, 3 and 4. The Core has the capability of measuring a broad range of metals and metalloids in biological samples, including Pb, Hg, As, Cd, Mn, Fe, Cu, Zn, Cr, Co, Pt, K and others. In addition, a number of simple biochemical assays are performed so as to allow for the interpretation of the metal concentration data.

To address one of the major aims of the Core, measuring urinary metabolites in urine, during the past year, a newly acquired Perkin-Elmer Elan II DRC Mass Spectrometer has been installed and is fully operational. This has led to the successful adaptation of an assay established in the Core to measure arsenic metabolites in urine. An HPLC is coupled to the ICP-MS enabling the highly sensitive detection of inorganic and organic arsenic species without on-line digestion of organic forms. The data is fed directly into a computer where data quantification and calibration are achieved via TotalChrom 6.2, after converting the ELAN.nsf data files to TotalChrom.raw files through ChromLink. TotalChrom offers powerful and flexible data review. Throughput of arsenic metabolite measurements has been increased from 1-2 samples per day (by graphite furnace atomic absorption) to 40 samples per day.

Urinary arsenic metabolite data derived from this Core Laboratory is being used to test the general hypothesis that people who are poor metabolizers of arsenic may be at highest risk for disease. For example, 1200 samples analyzed for Dr. Habibul Ahsan (Project 3) will test the hypothesis that cohort participants who have skin lesions are more likely to be poor metabolizers than those without skin lesions. Indeed, our analyses indicate that individuals who are less able to efficiently convert monomethyl arsenic (MMA) to dimethylarsenic (DMA) are at increased risk for skin lesions. In addition, 300 samples analyzed for Dr. Mary Gamble have helped establish that folate deficiency is associated with poor methylation of arsenic. Finally, in Dr. Graziano's studies (Project 4) evaluating the effect of arsenic exposure on child intelligence, urine samples were analyzed to determine if children who are poor metabolizers of arsenic are at increased risk for cognitive deficits; in this case, methylation status did not predict poor cognitive outcome.

In summary, the Trace Metals Core Laboratory has proven to be an extraordinary resource to many investigators in both our SBRP and our NIEHS Center. The number and type of biological samples analyzed during the past grant period are outlined below:

Type of Analysis	Number of Samples Analyzed
Total urinary arsenic	6,092
Urinary arsenic metabolites	1,300

Urinary creatinine	6,092
Blood Lead GFAA	242
Total hemoglobin	2,100
As in cell lysate	40
Blood lead, manganese, selenium and arsenic, by ICP MS	1,450

Core B: Geochemistry Core
PIs: Steven N. Chillrud and Alexander van Geen

This 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 (biomedical projects 1, 3 and 4 and earth science projects 5, 6 and 7) and trains students and post-docs. Sample preparation and analyses are carried out for water, soil, sediment, leachates, plant materials and pre-ashed blood.

The number of total analyses carried out by the core over the last 4.5 years is shown in Table 1. More than 25,000 samples and QA/QC samples have been analyzed for a total of over 200,000 analyses in support of these six projects of the Columbia Superfund Basic Research Program.

Notable advances for this analytical core, discussed below, include: renovation of our sample preparation laboratory; increased efficiency and quantities of information obtained on environmental samples, by switching from single element analyses by atomic absorption spectrometry (AAS) to multiple element analyses on a high resolution inductively coupled mass spectrometry (HR-ICP-MS); and the development of a method for rapid sample preparation and analysis of blood samples for lead concentrations and lead isotope ratios via multi-collector ICP-MS. Furthermore, since no standard reference material for a blood matrix existed for stable lead isotope analyses, we created an internal blood standard for stable lead isotope analysis using out-dated units of banked red cells. Similar to current values for human blood, the blood standard has a low Pb concentration of 1.5 µg/dL and was made by adding saline to packed red cells to simulate blood without coagulants, generating 155 aliquots which are stored in 7 ml vials in a freezer. Validation of the MC-ICP-MS method has been done by analyzing the blood standard and a small number of samples by TIMS (thermal ionization mass spectrometry), with ratios agreeing within measurement errors.

The renovation of the sample preparation laboratory of Dr. Chillrud is just being completed with funds from LDEO and includes setting up a clean lab area with HEPA filtration for preparation of the chemically-ashed blood samples for lead isotopes as well as purchase of a climate controlled glove box and microbalance (the latter with NIEHS Center funds) for accurate gravimetric determinations of small masses of suspended particulate matter collected onto filters.

Switching to HR-ICP-MS analysis has allowed routine analysis of 33 major and trace elements including As in groundwater samples and has been significant for the projects in two direct ways. First , this method has reduced the detection limit for As to 0.1 µg/L (from 5 µg/L by GFAA). This proved to be significant, for example, for the interpretation of biomedical data

collected under Projects 3 and 4, allowing them to have concentration values for all samples, with no "non-detects"; this allows them to treat the data as a continuous variable, rather than having to use categorical statistical methods for study interpretation. In addition, the collection of quality control data under the recent well re-sampling effort has shown a reduction of the standard deviation for replicate measurements from ±10 µg/L by GFAA (n=353) to ±4 µg/L by HR ICP-MS (n=42) and a reduction of the standard deviation for recovery of a 500 µg/L spike added in the field from ±56 by GFAA (n=341) to ±17 µg/L (n=42). Second, this ability to quickly collect data on a wide range of elements "simultaneously" enabled a quick examination of overall water quality for a large number of samples. As an example, in a survey of 630 groundwater samples from Northeast Araihazar in Bangladesh about 80% of the samples were found to contain Mn levels above the World Health Organization's guideline value of 500-µg/L. These improvements are significant enough that we have not used the graphite furnace AA at all in the last year.

Fig 1. Comparison of stable lead isotope results by MC-ICP-MS and TIMS. Line shown is drawn for 1:1 agreement.

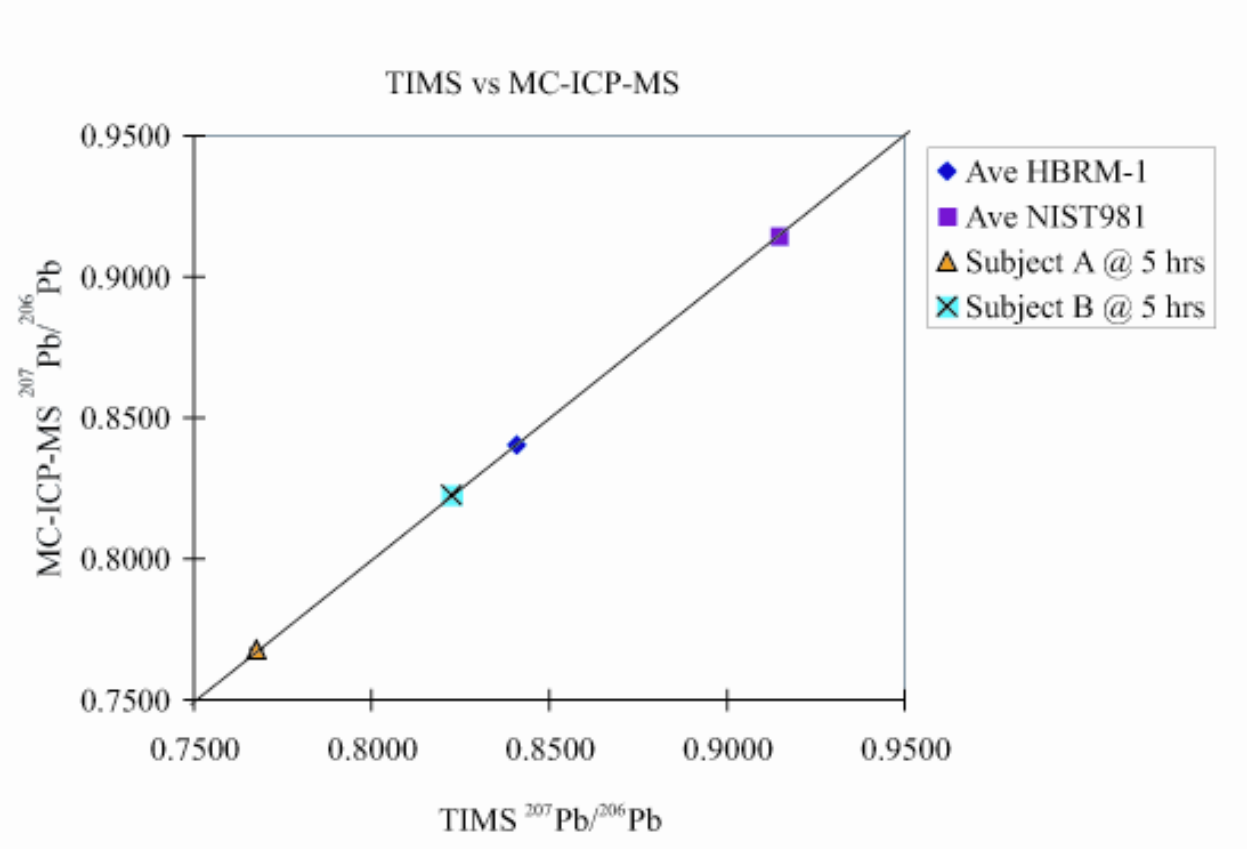

Table 1. Summary of total analyses by Geochemistry Core over the last 4.5 years.

Analysis	Analyte	Samples	QA/QC	Total	# of analytes	Total Analyses
GFAAS	As	6,750	5,230	11,980	1	11,980
FAAS	Fe	985	595	1,580	1	1,580
HR-ICP-MS	As (sp. columns)	470	121	591	1	591
HR-ICP-MS	multi	1,745	350	2,095	2	4,190
HR-ICP-MS	multi	357	77	434	4	1,736
HR-ICP-MS	multi	211	41	252	5	1,260
HR-ICP-MS	multi	878	472	1,350	6	8,100
HR-ICP-MS	multi	73	74	147	16	2,352
HR-ICP-MS	multi	31	16	47	22	1,034
HR-ICP-MS	multi	11	23	34	25	850
HR-ICP-MS	multi	91	54	145	27	3,915
HR-ICP-MS	multi	3,831	1,100	4,931	32	157,792
HR-ICP-MS	Pb or Fe	0	45	45	1	45
MC-ICP-MS	lead isotopes	403	806	1,209	4	4,836
TIMS	lead isotopes	2	14	16	4	64
COD	COD	79	19	98	1	98
GC	TC& TN	94	19	113	2	226
Colorimetry	As & PO4				2	
Colorimetry	Si	45	18	63	1	63
GC	SF6	100	35	135	1	135
Gamma	Cs-137, Be-7, K-40	80	8	88	3	264
Totals		**16,156**	**9,109**	**25,265**		**201,111**

Core C: Hydrogeology Research Support Core Laboratory
P.I.s: M. Stute, M. Steckler, R. Versteeg, and P. Schlosser

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, and 7.

Notable advances for the last period

Our continued focus this past year has been on hydraulic and tracer studies as well as groundwater flow and transport modeling in Bangladesh. We have continued to collect hydraulic head time series data from our well nests and a series of private wells. We installed automatic pressure transducers in two well nests in Bangladesh that gave us one water level record for an entire rainy season and allow us a better evaluation of the importance of irrigation for the water budget in our area of investigation. We have been measuring high precision vertical relative hydraulic heads at 6 multi level well nests at bi-weekly intervals for one year. The vertical gradients show complicated patterns that indicate recharge from precipitation and surface waters. The annual average vertical hydraulic gradient is pointed downward at all well nests. During our

fieldtrip in the spring of '04 we performed hydraulic conductivity measurements on all monitoring wells and surveyed irrigation wells in our study area. Recharge rates derived from vertical hydraulic gradients and conductivities were found to be consistent with tracer ($^3H/^3He$) based estimates. Hydraulic data were used in an expanded groundwater flow model that uses hydraulic head distributions and environmental tracer data as calibration targets. We have also been collecting time series of the stable isotopic composition (^2H, ^{18}O) of precipitation, surface waters and groundwater in Bangladesh. Preliminary results show a large variability in the groundwater isotopic composition suggesting that this tracer might be helpful to differentiate the origin of water feeding the aquifers in Bangladesh.

At the Vineland, N.J., Superfund site, we collected several sediment cores from the stream and the lake that have been affected by As from the Superfund site. The pore water profiles indicate that As transport into surface waters through the pore fluids was very small. The dominating As transport mechanism is likely transport of sediment particles during storm events.

We built a reaction chamber for incubation experiments for Winthrop, M.E., Superfund landfill sediments that allows for the monitoring of pH, Eh, conductivity, oxygen concentration, and temperature, as well as the collection of samples during incubation experiments while introducing practically no oxygen.

The following analyses were performed over the past year:

a) Ca 500 hydraulic head time series observations in Bangladesh
b) 30 and 10 hydraulic conductivity measurements in Bangladesh and at the Winthrop site, respectively
c) 4 Stream discharge measurements at Vineland site
d) 20 environmental SF_6 measurements in Bangladesh
e) 12 mass spectrometric measurements of ^3H and ^3He, respectively,
f) 68 mass spectrometric $\delta^{18}O$ and δ^2H analyses for Bangladesh samples,
g) Collection of one monthly averaged precipitation and 11 surface water samples for stable isotopic composition determination
h) Handheld GPS position measurements at all field locations.

Administrative Core
P.I.: Joseph Graziano

The Administrative Core, which includes the information dissemination program that is discussed below, has directed this SBRP program rather smoothly. Dr. Graziano, the Program Director, and Dr. van Geen, the Associate Director, communicate virtually every working day with regard to the integration of our biomedical and non-biomedical research programs. 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. Our monthly two-hour seminars (one hour biomedical and one hour non-biomedical) are exceptionally well attended. We believe that our SBRP is unique with regard to the extent that these two dimensions of the program are highly integrated. This integration and joint

leadership led to an unusually strong representation at the 2004 annual SBRP meeting in Seattle, with a total of eight poster presentations of our work.

Since August, the administrative core has directed numerous scientific planning meetings for the competitive renewal application that will be submitted in April, 2005. We have visited new sites, interacted with government and academic scientists, and have set out our new research agenda accordingly. Our scientific research plan for the coming five years is already set, and the integrative writing of our proposal has begun. Along those lines, this year, the annual meeting of our External Advisory Committee, which includes Dr. C.J. Chen, now Minister of Health of Taiwan, has been set for March 4, 2005, so that the advisory committee can provide constructive input into our upcoming five year research plan.

Information Dissemination and Transfer, Government Liaison, and Outreach Activities, directed by Meredith Golden

Information Dissemination and Transfer, Government Liaison, and Outreach Activities continue to be valuable components of the Columbia Superfund Basic Research Program. As part of the Administrative Core, Columbia has succeeded in integrating these tasks into its research, administrative, and training activities. The overriding objective has been to make available the scientific findings and products generated from Columbia's interdisciplinary suite of projects related to the bioavailability of soil lead in humans and the bioavailability, health effects, and geochemistry of arsenic. The communication of new knowledge among scientists, policymakers, and the private and public sectors is essential to stimulate pioneering research, highlight the most urgent priorities, generate innovative products, and ensure effective policies.

The Columbia SBRP distributes online information regarding its projects and seminars to a diverse audience of students, educators, researchers, policymakers, private entrepreneurs, non-profit advocates, and the general public. Over 200 Columbia University faculty, staff, and graduate students receive e-mail announcements on an ongoing basis for SBRP program activities. In addition, Columbia SBRP announcements are posted on the Columbia Earth Institute Website reaching an interdisciplinary group of scientists and students at the Lamont-Doherty Earth Observatory, the Center for Environmental Research and Conservation, the Earth Engineering Center, the International Research Center, the Laboratory of Populations, CIESIN, and the Goddard Institute for Space Studies at Columbia University. Another 150 individuals from other universities, government agencies, private organizations, and public interest groups in the United States regularly receive Columbia SBRP notices. The announcements are also distributed to the Arsenic Crisis Newsletter whose readership includes over 1,100 subscribers from more than 30 countries. The extensive network established by the Columbia SBRP has facilitated frequent correspondence among researchers both in the United States and around the world.

The Columbia SBRP Monthly Seminars serve as an open forum for both the program scientists and others concerned with the geochemistry and health effects of lead and arsenic. Each seminar includes two or more presentations highlighting biomedical and geoscience topics. The monthly meetings provide investigators with the opportunity to share their research with a diverse group of researchers, policymakers, and the public. In turn, the participants have a chance to learn first hand about ongoing research and preliminary findings. The informal discussions that follow the presentations help enhance the quality and usefulness of these studies.

This year Columbia will have hosted eight SBRP Seminars. In addition to the Columbia SBRP researchers and graduate students, guest speakers included Andrew Lent from the New York State Department of Environmental Conservation, George Breit with the U.S. Geological Survey, David Christiani with the Harvard School of Public Health and Department of Medicine, Richard Wilson from Harvard University, Benjamin Bostick from Dartmouth College, and John Stolz from Duquesne University. Attendance at the seminars have ranged from about 25 to 45 with an average of 31 participants including faculty and students from a variety of Columbia programs, the larger Metro New York academic community, city, county, state, and federal officials, and the general public. In response to the widely distributed seminar announcements, the program has received many online requests for more information about the presentations from individuals not able to attend. In addition, some attendees have specifically scheduled other meetings in the NYC vicinity in order to participate in the seminars as well.

Columbia SBRP continues to enhance its website (www.superfund.ciesin.columbia.edu) for the seven individual projects, three research laboratories, and administrative and training cores. The purpose of the website is to facilitate communications and promote opportunities for meaningful interactions among project scientists and individuals concerned with lead and arsenic exposures. In addition to the new entries for the Calendar of Events, the Publications section has been both updated and expanded. The searchable database allows users to identify Columbia SBRP publications by author, title, project, or other keywords. The list includes the citation, associated projects, the paper abstract, and, when permissible, direct access to the full text. The website also provides Project descriptions and updates, the Columbia Research Briefs, its Annual Progress Reports, and Staff Contact information.

Information Dissemination and Outreach activities are often an ongoing offshoot of the individual research projects and lab cores. Several faculty have presented their SBRP research as part of college courses. Consequently, more students attend the SBRP seminars, become involved in SBRP projects, and incorporate related research into theses and publications. These students not only have shared their findings at the Columbia seminars, but have also presented them at national and international meetings. As part of its annual workshop series, the Columbia SBRP Training Core hosted in August 2004 an intensive weeklong workshop on "Endocrine, Reproductive, and Development Toxicology". Announcements for the workshop via Columbia's extensive online distribution list drew participants from both federal and state government and as far away as Arizona. Given the demand and promise of incorporating SBRP research into the curriculum of interdisciplinary programs, initial steps have been taken to explore the feasibility and effectiveness of developing online educational modules based on the Columbia SBRP research. Outside the classroom, Columbia scientists have also interacted in many forums with policymakers, private stakeholders, commercial firms, and non-profit groups.

Finally, about a dozen Columbia SBRP scientists, students, and Administrative Core staff participated in the 2004 SBRP Annual Meeting in Seattle—contributing seven exhibits to the Poster Session. Columbia's active participation has helped to renew old networks, strengthen ongoing collaborations, and initiate future partnerships with other SBRP scientists and outreach coordinators. As a result of discussions at this year's Annual Meeting, several other SBRP grantees from the NYC Metro area are now regularly attending the Columbia SBRP seminars.

SBRP Training Core
P.I.: Paul Brandt-Rauf

The Training Core continued its Summer Workshop Program with a week-long workshop from August 30-September 2 on Endocrine, Reproductive and Developmental Toxicology given by Dr. Donald Mattison of NIH, an expert in this area. The workshop was well attended by trainees, faculty, members of other SBRPs and representatives of government agencies, and the feedback was very positive. Besides the monthly Superfund Seminar Series, the Training Core also participated in the Annual Granville H. Sewell Distinguished Lecture in Environmental Health Sciences which this year featured Professor Mario Molina of M.I.T., 1995 Nobel Laureate in Chemistry, speaking on *The Impact of Human Activities on the Atmosphere*; trainees had the opportunity to meet with Dr. Molina over breakfast to discuss scientific and policy issues and career paths related to environmental studies. In addition, the Training Core continued to offer trainees participation in the web-based, case study-oriented course on Hazardous Waste and Public Health during the summer semester. The Training Core also participated in the recently established field trip program to introduce trainees to non-academic career opportunities in environmental health sciences. Last semester the site visit was to the Region II EPA Laboratory and Field facility in New Jersey. This semester the site visit is to Exxon Mobil Biomedical Sciences research facility in New Jersey.

Section 3: Patent Updates

Colorimetric device and procedure to measure Arsenic in natural water and waste waters

U.S. Patent application 60/404,964 filed August 21, 2003

Serial # PCT/US03/26484—International patent application based on U.S. Patent application 60/404,964 filed August 21, 2003, entitled "An Arsenic Meter"

Inventors: Alexander van Geen (Columbia University), Pietro Perona, Dmitri Psaltis, Christophe Moser (California Institute of Technology)

Section 4: Superfund Site Updates

None

Section 5: Contact Information Updates

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