Capacity Building in Environmental Health Research in India and Nepal

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The Fogarty International Training and Research Program in Environmental and Occupational Health at UC Berkeley concentrates on two major environmental health issues in the Indian subcontinent: arsenic in drinking water in West Bengal, India, and indoor air pollution in India and Nepal. Local trainees and researchers have had the opportunity to work on related research. Concerning arsenic in drinking water, projects included studies of skin lesions, pulmonary effects, reproductive outcomes, and child development, as well as mitigation approaches to reduce exposures. Activities in the indoor air pollution project have emphasized quantifying exposures to smoke from cooking and heating as well as their associations with tuberculosis and eye disease. Training has focused on developing skills necessary to address these problems. The training emphasizes in-country mentoring of trainees related to their research projects, and intensive short courses at partner institutions. The focus of capacity building in environmental health research in countries in economic and environmental transition should be on country-based research projects with embedded training efforts. *Key words*: Fogarty International Program; research; training; arsenic; water pollution; indoor air pollution.

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The South Asian region faces social, industrial, and economic transitions and related environmental health problems but still suffers from the hazards associated with poverty and traditional living conditions. The UC Berkeley Fogarty International Training and Research Program in Environmental and Occupational Health (ITREOH) concentrates on two main areas: indoor air pollution, a traditional hazard principally associated with rural poverty, and the more recent widespread arsenic contamination of drinking well water, a tragic side effect of attempts to address another traditional hazard, bacteriologic contamination of surface water. Trainees in the program have had the opportunity to develop new skills while working on a variety of related mentored research projects in several centers throughout India and Nepal. We present an overview of the ongoing research and training activities of the UC Berkeley ITREOH program (Table 1). Separate funding has been obtained for most of the research activities in which trainees have been involved.

ARSENIC IN DRINKING WATER IN WEST BENGAL

Millions of people worldwide are exposed to drinking water containing naturally occurring arsenic.[1–4] West Bengal in India and Bangladesh constitute the largest population in the world exposed to health-damaging levels of arsenic from drinking water. These exposures may cause a variety of health effects, including skin lesions, skin and internal cancers, and cardiovascular diseases.[5–7] Recently, developmental impairments of children[8] and adverse pregnancy outcomes have been suggested.[9,10] Trainees in the UCB ITREOH program have had opportunities to work on research projects of the arsenic research program in India, addressing health effects in relation to arsenic ingestion that have included studies of 1) skin lesions, 2) respiratory effects, 3) reproductive outcomes and child development, and 4) methods to reduce arsenic exposure. All research studies were conducted in close collaboration with our Fogarty institutions in Kolkata, West Bengal, and several trainees were involved in the individual projects.

Arsenic-induced Skin Lesions

Dose–response relationship. Prior studies of skin lesions and arsenic in drinking water have been cross-sectional, focusing only on recent or current exposures.[11–14] To characterize the dose–response relation between long-term consumption of arsenic and related skin lesions, a nested case–control study was con-

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ducted, including a detailed assessment of arsenic exposures covering at least 20 years, in collaboration with our Fogarty partners at the Institute of Postgraduate Medical Education and Research, Kolkata (IPGMER). Cases with arsenic-induced keratoses or hyperpigmentation and matched controls (192 pairs) were selected from over 7,000 participants of a 1995–1996 survey in West Bengal.[15] A strong dose–response gradient with arsenic water concentrations, and an average latency for skin lesions of 23 years, were found. Intensive longitudinal exposure assessment provides the basis for this detailed dose–response evaluation of arsenic-induced skin lesions.[16] Trainees involved in the skin lesion studies in Kolkata were Soma Mitra (PhD student at Kolkata University), Dr. Santra, and Dr. Sambit Samanta (post doctoral researchers, IPGMER).

Nutritional factors and susceptibility. Earlier studies suggested that the prevalences of arsenic-induced skin lesions and other arsenic-caused diseases might be increased by malnutrition.[17] The association between nutritional deficiencies and arsenic-induced skin lesions was investigated in the above-mentioned case–control study.[16] Food tables were used to estimate intakes of nutrients and micronutrients based on a detailed dietary assessment. Modest increases in risk were related to low intakes of animal protein (RR = 1.94; 95% CI: 1.05, 3.59), calcium (1.89; 1.04, 3.43), fiber (2.20; 1.15, 4.21), and folate (1.67; 0.87, 3.2) suggesting that low intakes of these nutrients may increase susceptibility to arsenic-induced skin lesions.[18] This project was the doctoral research project of Soma Mitra at the University of Kolkata, who is also lead author on the related publication.[18]

Blood micronutrients. Susceptibility to arsenic toxicity may be influenced by micronutrients, in particular selenium, methionine, and beta-carotene.[19,20] We investigated whether differences in blood levels of micronutrients and metabolic indicators contribute to the susceptibility of developing arsenic-induced skin lesions.[16] The distributions of nutrient concentrations were similar between cases and controls. For decreasing quartiles of selenium, the odds ratio (OR) estimates were 1.00, 0.67, 0.99, 0.80; $p = 0.81$; for methionine, OR were 1.00, 0.83, 0.78, 0.72; $p = 0.29$, and ORs for beta-carotene were 1.00, 0.53, 0.51, 0.96. The findings suggest that the measured micronutrients and metabolic indicators do not modify the risk of developing arsenic-induced skin lesions, which has important implications for proposed therapeutic interventions.[21] Several trainees were involved, particularly in the field work and data analyses of this project.

Arsenic methylation. Higher methylation capacity of inorganic arsenic (InAs) to monomethylarsonous acid (MMA) and dimethylarsinic acid (DMA) has also been linked to increased risks for arsenic-related diseases.[22,23] In a separate analysis based on the same case–control study,[16] the association between arsenic-induced skin lesions and methylation capacity was examined. Preliminary findings indicate that cases with skin lesions had lower concentrations of InAs and higher concentrations of MMA and DMA in urine compared with controls, supporting the notion that higher methylation capacity increases the risk for arsenic-induced diseases. Further ongoing investigations concern the relationships between dietary variables, serum micronutrients, and methylation of InAs. This project serves as the doctoral research of Arin Basu, MD, who is based in Kolkata and completing his PhD at the University in St. Louis, USA. Part of his training was also a six-month visit to UC Berkeley for in-depth training in specific epidemiologic methods in 2005–2006; since then he has continued his work in Kolkata.

TABLE 1 Overview of Research Projects Related to the UC Berkeley ITREOH Program

Arsenic in drinking water projects
Skin lesions related to arsenic
Dose–response relationship
Nutritional susceptibility
Blood micronutrients
Methylation capacity
Pulmonary effects
Lung function
Bronchiectasis
Reproduction and child development
Pregnancy outcomes
Fertility
Intellectual function testing
School achievements
Mitigation related
Dug well program
Seasonal variation
Indoor air pollution projects
Air pollution atlas for India
Global database for national exposure
Respirable particle exposure
Quantification of household-based exposure
Health impact assessment
National household survey based
Health effects studies
Cataracts
Tuberculosis
Biomarkers of exposure
Photographs of eye opacity

Pulmonary Effects of Arsenic

Lung function. Very few studies have assessed nonmalignant chronic respiratory effects in arsenic-exposed populations, although limited evidence supports increased risks.[24–30] The relation between lung function, respiratory symptoms, and arsenic ingestion

Tube well in West Bengal, India.

was studied in 287 adult participants (>20 years old) involved in the case-control study.[16] Respiratory symptoms were increased among men with skin lesions, smokers, and non-smokers. In men with skin lesions the average adjusted forced expiratory volume in 1 second (FEV_1) was reduced by 256 mL (95%CI: 114, 398; $p < 0.001$), and the average adjusted forced vital capacity (FVC) by 288 mL (135, 441; $p < 0.001$), compared with men without skin lesions. An increase of 100 µg/L arsenic was associated with a decrease in FEV_1 of 45 mL ($p = 0.02$) and FVC of 41.4 mL ($p = 0.053$) in men. Women showed little evidence of respiratory effects.[31]

Bronchiectasis. For the first time, radiographic findings of nonmalignant pulmonary disease in a population exposed to arsenic in drinking water were investigated. Subjects with (n = 108) and without arsenic-caused skin lesions (n = 150) were selected from the source population of over 7,000.[15] Thirty-eight study participants with chronic cough underwent high-resolution computed tomography with readings by investigators in India and the United States blinded to the presence or absence of skin lesions. Overall, subjects with skin lesions had a tenfold increased risk of bronchiectasis compared with subjects without skin lesions (OR: 10.1, 95% CI 2.7, 37.1), suggesting that consumption of arsenic also causes severe nonmalignant lung disease.[32] Several local medical doctors who worked in the clinic of the IPGMER as well as in the field project collaborately developed and conducted the pulmonary studies.

Effects of Arsenic on Reproductive Outcomes and Child Development

The following studies were conducted with involvement of local investigators from the department of Psychology at Kolakata University as well as the IPGMER, and trainees worked on different study aspects.

Pregnancy outcomes and infant mortality. Though recently more attention has been focused on reproductive health effects of arsenic, the findings are still inconclusive.[9,33–37] Pregnancy outcomes and infant mortality were studied among 202 married women. Reproductive histories were ascertained by structured interviews and arsenic exposure during each pregnancy was assessed. High concentrations of arsenic (>200 µg/L) during pregnancy were associated with a sixfold increased risk for stillbirth (OR: 6.07; 95% CI 1.54, 24.0, $p < 0.01$). The OR for neonatal death was 2.81 (95% CI: 0.73, 10.8). This study adds to the limited evidence that exposures to high concentrations of arsenic during pregnancy increase the risk of stillbirth, but there was no indication of increased rates of spontaneous abortion and overall infant mortality.[38]

Fertility. Data on arsenic exposure and effects on fertility are largely lacking. Currently under way is the investigation of fertility-related indicators and arsenic in drinking water consumed.

Children's intellectual function. Only little evidence exists concerning the possible impairment of children's intellectual function in relation to arsenic ingestion. We conducted a cross-sectional study among 351 children aged 5 to 15 years who were linked to the pregnancy study.[38] Intellectual function was assessed with culturally appropriate testing methods.[39–41] Arsenic was measured in urine and lifetime water sources.[42]

Children's school performance. A subgroup of over 300 children who were attending school was selected from the child study[42] to investigate the impact of arsenic on achievements in school. Currently under way are analyses of school marks in relation to arsenic in water and urine.[43] This project was also part of a doctoral research project of the trainee Shalini Poddar, a graduate in psychology from Kolkata University.

Mitigation Methods to Reduce Arsenic Exposure

A dug well program to provide arsenic-safe water. Today, more than 20 years after arsenic-induced skin lesions were first identified in West Bengal, a large number of people are still drinking arsenic-contaminated water in this region. "Projectwellusa," together with its sister organization in West Bengal, is a program that promotes arsenic-safe drinking water by implementing shallow, concrete dug wells that tap the water of the unconfined aquifer, with funding from donors who adopt wells. The project includes community awareness programs, and training in monitoring and chlorination of dug-well water. The aim is to make the system sustainable at the village level using local labor and materials.[44]

Seasonal variation of arsenic concentration in tube wells. Mitigation programs may also involve installing deep tube wells, or the use of shallow tube wells producing water concentrations low in arsenic. One issue in these alternatives concerns the stability of the arsenic concentrations over time. Seasonal variation of arsenic concentration was measured in water from 74 selected tube wells during the winter, the summer, the monsoon season, and the following winter in the years 2002 to 2003. A GPS was used to locate the tube wells, and a GIS was used for mapping. From the winter of 2002 to the winter of 2003, concentrations increased irrespective of the depths of the tube wells from an average of 464 μg/L to 820 μg/L ($p < 0.001$). This extent of variation in arsenic concentrations, if confirmed, has important implications for both epidemiologic research and mitigation programs.[45] This project was conducted with Fogarty trainee Xavier Savarimuthu, who successfully completed his PhD in Kolkata based on the project, and is also the lead author on the related publication.[45]

Intensive training course 2005. An intensive training course, "Basic and Molecular Epidemiology, Environmental Health, Arsenic, Exposure and Risk Assessment," was conducted jointly with the Indian Institute of Chemical Biology, Kolkata, India, in December 2005. The training involved participants from Institutions in seven Asian countries, including other Fogarty ITREOH program sites: India, Bangladesh, Nepal, Vietnam, Pakistan, Iran, and Sri Lanka. Twenty-eight participants were selected among over 70 applicants based on a scoring system considering prior experience in environmental health as well as future goals for research in environmental epidemiology. The faculty came from the School of Public Health, University of California, Berkeley, the University of Washington, Seattle, and the Indian Institute for Chemical Biology, Kolkata. Areas covered included epidemiologic study design, arsenic exposure assessment and laboratory analyses, molecular epidemiology, and environmental health risk assessment. The training focused on small mentored group projects in which the participants developed their own epidemiologic studies, which they presented at the end of the course. A web site and an e-mail list-serve have been set up. One outcome of the training was that several participants have been selected as trainees for longer-term training within the ITREOH program jointly with the Indian Institute of Chemical Biology, Kolkata.

INDOOR AIR POLLUTION IN INDIA AND NEPAL

Indoor air pollution from combustion of solid fuels (such as wood, crop residues, animal dung, grasses, and coal) for cooking and space heating has been identified as one of the ten most important risk factors in the global burden of disease (measured as disability-adjusted life years [DALYs]). It accounts for an estimated 2–3% of the global disease burden and some 1–2 million premature deaths annually. In poor developing countries, indoor smoke from solid fuels ranks fourth among risk factors for disease, behind only undernutrition, unsafe sex, and unsafe water/sanitation/hygiene, accounting for an estimated 3.7% of the total disease burden.[46] In India, approximately 80% of the population uses biomass fuel for cooking and heating.

Woman wearing personal monitor to measure exposure to wood smoke in Chennai, India.

There is strong evidence that high exposures to smoke from solid fuels can cause serious respiratory diseases in children and adult women. But for other health outcomes, such as adverse pregnancy outcomes, cataract, lung cancer, heart disease, and tuberculosis (TB), the links are less well established, even though smoke from combustion of solid fuels contains some of the same pollutants that are found in ambient air pollution and tobacco smoke, both of which have been linked with many of these health outcomes.[47–51] More carefully controlled studies are needed to confirm these associations and identify solutions.

The research and training activities in the indoor air pollution program have emphasized the development of skills necessary to address environmental health problems in India and Nepal resulting from exposure to indoor air pollution. Over the course of the Fogarty grant, researchers from India and Nepal have attended Fogarty-sponsored training sessions in India, and some have been selected to spend a semester or more at the UC Berkeley, working with faculty members in the School of Public Health to received specialized training in exposure assessment and advanced epidemiologic methods.

Air pollution exposure atlas for India. There have been several publications and activities to help set the stage for development of a national air pollution exposure atlas for India. First, a global database of indoor air pollution studies was jointly published with the WHO.[52] Second, studies were initiated along with the World Bank office in Delhi to field test measurement and modeling techniques in Andhra Pradesh that might be used for a national atlas.[53] Finally, UCB Fogarty collaborators in India have been piloting specific simplified indoor air quality measurement methods in four

Indian states that might be used as part of a planned national household survey.[54] This work involves several Indian collaborators.

Exposures to respirable particulate matter associated with household fuel use. This study, part of the activities pursuant to creating a national exposure atlas, quantified the daily average concentrations of respirable particulates (50% cut-off at 4 mm) in 412 rural homes selected through stratified random sampling from three districts of Andhra Pradesh, India, and recorded time activity data from 1,400 individuals to reconstruct 24-hour average exposures. Mean 24-hour average concentrations ranged from 73 to 732 mg/m^3 in gas-using and solid fuel–using households, respectively. Concentrations were significantly correlated with fuel type, kitchen type, and fuel quantity. Mean 24-hour average exposures ranged from 80 to 573 mg/m^3. Among solid fuel users, the mean 24-hour average exposures were the highest for women cooks and were significantly different from those for men and children. Among women, exposures were the highest in the age group 15–40 years (most likely to be involved in cooking or helping in cooking), while among men, exposures were highest in the age group 65–80 years (most likely to be indoors).[55]

Health impacts of indoor air pollution evaluated via national household-survey databases. Conducted jointly with Indian collaborators and the East–West Center in Honolulu, this analysis examined the association between indoor air pollution from combustion of unprocessed solid fuels (wood, animal dung, crop residues, shrubs/grass, coal) for cooking and heating and selected health outcomes in five countries—China, Georgia, India, Indonesia, and Nigeria—in which the WHO had conducted large household surveys. Data from 18 indicators of respiratory, vision, cardiovascular, and tumor/cancer morbidity were analyzed. Results from the analysis were inconclusive regarding the association between cooking and heating fuels and health. Unfortunately, important variables regarding indoor smoke exposure and tobacco smoke were not included in the surveys, and several quality-control problems with the datasets were found, which limited the scope of the analysis.[56,57]

Indoor air pollution and cataracts. The prevalence of cataract is higher in developing countries, and in both developed and developing countries more females than males are blind from cataracts. To explore the relationship between indoor air pollution and cataracts a hospital-based case–control study was conducted on the Nepal–India border. Cases (n = 206) were women patients, aged 35–75 years with confirmed cataracts. Controls (n = 203), frequency matched by age, were patients attending the refractive error clinic at the same hospital. A standardized questionnaire was administered to all participants. Logistic regression analysis involved adjustment for age, literacy, residential area, ventilation, type of lighting, incense use, and working outside.[58] Compared with using a clean-burning-fuel stove (biogas, LPG, or kerosene), the adjusted OR for using a flued solid-fuel stove was 1.23 (95% CI: 0.44-3.42), whereas use of an unflued solid-fuel stove had an OR of 1.90 (95% CI: 1.00-3.61). Lack of kitchen ventilation was an independent risk factor for cataract (OR 1.96; 95% CI 1.25-3.07). This study provides conclusive evidence that use of solid fuel in unflued indoor stoves is associated with increased risk of cataract in women who do the cooking.

Indoor air pollution and tuberculosis. Worldwide, TB kills about 2 million people per year. In South Asia, India carries the world's largest burden of TB cases, with approximately 2 million people developing the disease each year. In Nepal, about 45% of the total population is thought to be infected with TB, and of that, approximately 60% are of reproductive age. Though there is an association between indoor air pollution and acute respiratory infections, the relationship between indoor air pollution and tuberculosis is not well understood.

An analysis of India's National Family Health Survey, co-funded by the Fogarty program, showed an association between exposures to smoke from biomass fuels and prevalence of tuberculosis.[59] The analysis involved 260,000 people aged 20 and over, and the adjusted effect size was an OR of 2.58 (95% CI 1.98–3.37). The attributable risk was estimated to be about 50%. This study was limited by its cross-sectional design, and both exposures and the outcome were self-reported. An independent follow-up case–control study in Mexico estimated the OR to be 2.4 (95% CI 1.04–5.6), adjusted for age, sex, education, crowding, smoking, socioeconomic status, and residence. In this study, TB was diagnosed using smear/culture. Exposure ascertainment, however, was done by questionnaires.[60]

To further elucidate the relationship between indoor air pollution and TB, a multisite proposal was collaboratively developed by UCB Fogarty institutions. Proposals were developed during a two-week environmental and occupational epidemiology workshop held in December 2003. The first week focused on principles of epidemiology while the second week was spent designing protocols and study instruments for the multisite indoor air pollution and TB case–control study. After review and revision, four proposals were chosen for the multi-center project, three in India and one in Nepal.[61]

Cases are restricted to women 20 years old or older to minimize confounding due to tobacco smoke and because their exposure to indoor smoke is likely higher. Approximately 200 cases are being recruited at each site based on diagnosis of active pulmonary tuberculosis at the hospital during a specified period of time. Controls are selected from women who present to the medical, surgical, or gynecology departments of the participating medical facilities for conditions unrelated to tuberculosis, are sputum-negative, and have no recent history of tuberculosis. Exposure to indoor air pollution will be determined by an extensive questionnaire that has a particular focus on cooking history, including types of stoves and fuels used before and after marriage. Indoor particulate air monitoring using the newly developed UCB PM Monitor is being conducted in case and control households at two sites.[62] Investigators visit a sample of the houses to measure the levels of smoke that occur. These measurements will be used to validate smoke exposure estimates based on the responses to the questionnaire.

Biomarkers of exposure. In conjunction with the Nepal TB study, work is being undertaken with the optometry department of a major teaching hospital in Pokhara and the School of Optometry at Berkeley to explore the use of digital photographs of eye opacity as a long-term biomarker of exposure to indoor air pollution. This work is suggested by the several-times-documented association with cataracts, which are the clinical manifestation of a spectrum of changes in the eye.

CONCLUSIONS

Several kinds of mentored research projects related to the two environmental hazards, arsenic in drinking water and indoor air pollution, have been conducted in India and Nepal as part of the Berkeley ITREOH program. Related to these research projects, training activities were targeted at the specific needs of the involved country-based researchers. The main activity involved mentored in-country research, supplemented by occasional intensive training workshops and visits of selected trainees to UC Berkeley. We believe that the key focus of capacity building in environmental health research in India and other countries in environmental, economic, and social transition should concentrate on in-country training within high-quality research projects. An important outcome to assess the success of the program is publications in international peer reviewed journals authored and co-authored by local Fogarty investigators and trainees. This approach is in step with the objectives of the Global Health goal of the proposed draft of the NIEHS strategic plan for the period 2006 to 2011, aiming to "develop a program in global environmental health" by following the objective of "building capacity to pursue research in global environmental health."

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