CRI/ICEIT
NEWSLETTER

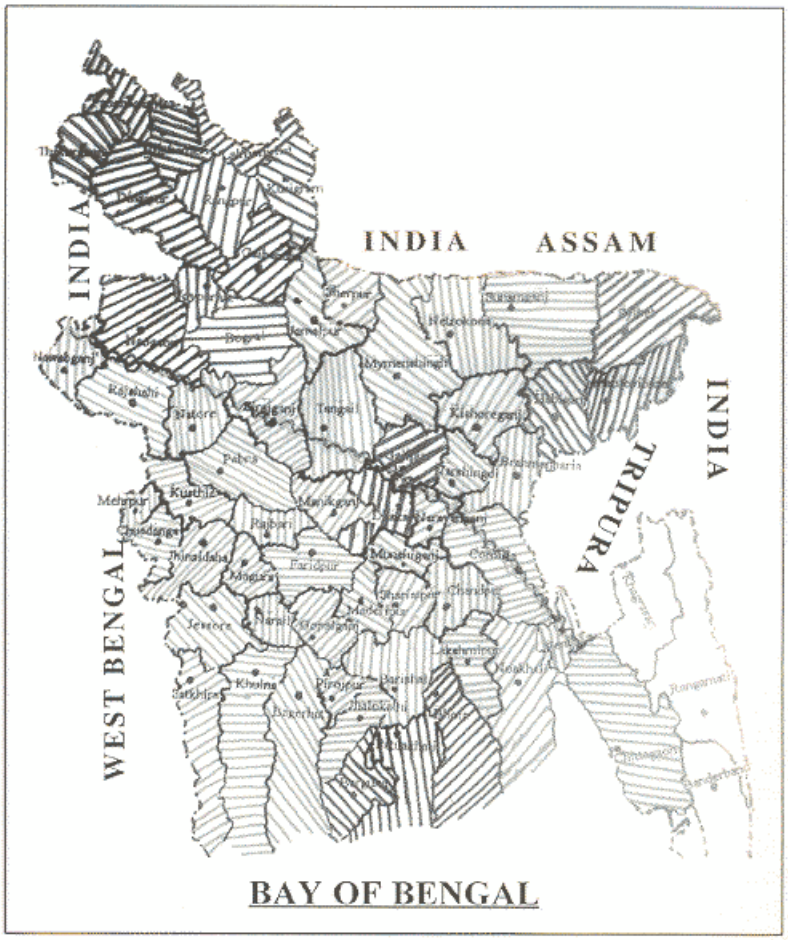
VOL. 8 NO. 2 – April 1998
ISSN 0858-2793
BANGKOK, THAILAND

Chulabhorn Research Institute

INTERNATIONAL CENTRE FOR ENVIRONMENTAL AND INDUSTRIAL TOXICOLOGY (ICEIT)

CRI's ICEIT has been designated as a
"UNEP Centre of Excellence for Environmental and Industrial Toxicology".

Arsenic Pollution of Ground Water in Bangladesh



An international conference was held in Dhaka in February 1998 to highlight the seriousness of arsenic pollution in Bangladesh and to explore the causes, effects and possible remedies.

Until recently the arsenic problem was almost unknown in Bangladesh, although in neighbouring West Bengal it became evident in the mid-eighties. Arsenic specialists in Calcutta, however, predicted that as the younger deltaic deposition stretched from West Bengal into Bangladesh, the latter might also have arsenic contamination of ground water.

In June 1996, Dhaka Community Hospital (DCH) held a health camp at Pakshi in the western part of the country

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Arsenic Pollution of Ground Water in Bangladesh

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in which several skin patients were suspected of having arsenical skin lesions. Tubewell water from that area was tested and was found to have high content of arsenic. DCH informed the local officials and issued newspaper reports. Following this, news on arsenic began flowing in from other districts. DCH felt the need to respond to the interest of the public health and send a fact-finding team consisting of 8 members including 3 skin specialists and 3 other senior doctors to that area. They collected water samples from 41 tubewells and biological samples (nail, hair, skin and urine) from 95 patients. Water samples were tested at the Bangladesh Council for Scientific and Industrial Research (BCSIR) Laboratories, Dhaka, while biological samples were tested at the School of Environmental Studies, Jadavpur University, Calcutta (SOES). 66% of the water samples and more than 90% of the biological samples were found to have higher than normal concentration of arsenic. DCH made the results public in a national seminar held in January 1997 and urged the government and other concerned organisations to take immediate steps to face the problem.

At present several departments of the government with assistance from international donor agencies, some NGOs, university departments and private organisations are working on the arsenic problem and although there is lack of standardisation in their work (for example, some are using laboratory methods, others are using kits for testing water) and exchange of information among themselves, an overall gloomy picture has emerged. To date 8065 tubewells from 60 districts have been tested for the presence of arsenic in underground water by the above-mentioned organisations. In 41 districts, water samples were found to have arsenic above 0.05 mg/1, the maximum permissible limit recommended by WHO, and in 52 districts the arsenic concentration was more than 0.01 mg/1, the WHO recommended value for safe water. In those 41 districts where arsenic concentration crossed the 0.05 mg/1 limit, 51% of the samples were found to have crossed that border. The surface area of these 41 districts is 89,186 sq. km. with a population of 76.9 million. Given the present state of knowledge, it can be safely concluded that although not all tubewells are contaminated, there are thousands of pockets of contaminated underground water in at least two thirds of the districts of Bangladesh, and the people living there are at real risk of developing arsenic toxicosis.

DCH and SOES conducted surveys for arsenicosis patients in 22 districts and found patients with arsenical skin lesions in 21 of them. They examined 5664 people in the affected villages and 33.6% of them were diagnosed as patients with arsenical skin manifestations. A total of 2167 hair samples, 2165 nail samples, 220 skin samples and 830 urine samples were analysed and an average of 94% of them were found to have arsenic concentration above the normal limit.

The Dhaka Community Hospital and the School of Environmental, Studies, Jadavpur University Calcutta were joint organizers of the Dhaka conference and have been the prime movers in raising national and international awareness of the gravity of the arsenic problem in Bangladesh.

Source: Programme of the International Conference on Arsenic Pollution of Ground Water in Bangladesh: Causes, Effects and Remedies, 1998.

Growing Concern Over Nutrient Pollution of Coastal Waters

In August 1997 some 30,000 fish died in Maryland's Pocomoke River on the Chesapeake Bay. Moreover, fishermen, waterskiers and field researchers who came into contact with the nutrient-rich water of the shallow estuary suffered symptoms that included memory loss, shortness of breath, and skin rashes.

A panel of scientists investigating the outbreak concluded that it was caused by toxic dinoflagellates similar to *Pfiesteria*, which had earlier been cited in fish kills in North Carolina.

Pfiesteria-like organisms can assume several life forms, only some of which are toxic. They have complex life cycles that are not fully understood.

Pfiesteria is only one of many harmful algae species whose blooms have increased in size and frequency worldwide over the past twenty years. Although many scientists have suggested that the recent explosion of blooms is due to nutrient pollution, not all researchers agree on the causes of this expansion. Circumstantial evidence would certainly appear to implicate nutrient pollution as a cause of the blooms, but a firm link has proved difficult to establish, due to the complex nature of *Pfiesteria*-like dinoflagellates.

Although *Pfiesteria*-like species have probably existed for millions of years, *Pfiesteria piscicida,* the only currently described *Pfiesteria* species, was not identified until 1991.

Pfiesteria piscicida is a heterotroph – it cannot make its own food through photosynthesis – and feeds on other phytoplankton, bacteria, and zooplankton. *Pfiesteria's* nontoxic forms included cysts that remain dormant in sediments, amoebae, and flagellated zoospores. However, unknown substances excreted by schools of fish can stimulate these nontoxic stages to transform into toxic zoospores. The zoospores release toxins that drug fish and cause open, bleeding sores. *Pfiesteria* then feeds on fish tissue and blood. Within hours of the fish kill, *Pfiesteria* reverts to a nontoxic amobae or cyst form.

Pfiesteria piscicida and look-alikes are difficult to study in the field and are even hard to identify under a scanning electron microscope. Moreover, toxic forms can disappear within a few hours after a fish kill. However, scientists say, field research on *Pfiesteria* and other harmful algae is on the brink of a breakthrough, thanks to biotechnology and remote sensing.

Source: Environmental Science and Technology/News, Jan. 1, 1998.

METHYL BROMIDE AND OZONE DEPLETION

Methyl bromide is an effective pesticide used to fumigate soils before the planting of high-value crops such as tomatoes, strawberries, grapes and flowers. Once the gas escapes into the atmosphere, it breaks down to release bromide compounds that destroy the ozone layer.

However, the precise importance of methyl bromide in ozone destruction is less clear cut than for other ozone destroyers. There are many natural sources of methyl bromide, and its short survival time in the atmosphere means that only a fraction of the 75 million tonnes used annually ever reaches the stratosphere.

Through the Montreal Protocol, strict controls on other ozone-depleting chemicals such as CFCs and halons are already coming into force. A proposed ban on methyl bromide by the year 2001 has, however, met with opposition mainly from European countries such as Italy and Spain, which are major users of the pesticide. At the meeting of signatories to the Montreal Protocol in September 1997, politicians were under heavy pressure from lobbyists employed by manufacturers and users of the chemical, who argue that there are no practical alternatives for many users.

However, similar complaints were made about proposed controls on CFCs a decade ago, when reductions in use were mandated with the full knowledge that alternatives were not available.

Source: New Scientist, September 1997.

THE USE OF POPLAR TREES IN PHYTOREMEDIATION

Phytoremediation is an approach to using plants to remove toxic substances from contaminated soil and water. Plants have proved effective at extracting heavy metals, including isotopes of uranium, cesium and strontium. Now, researchers from the University of Washington are experimenting with the planting of hybrid poplar trees to handle organic solvents.

The experiment is being carried out near the town of Central Point in Oregon, U.S.A. where, in 1984, a truck accident resulted in a spill of hundreds of gallons of 1, 1, 1-trichloroethane. Despite many cleanup efforts, the chemical still leaches from the soil, feeding a pool of contaminated groundwater that infiltrates nearby drinking wells.

The researchers have planted some 800 hybrid poplars downstream from the original spill and are monitoring the effects.

There are good reasons to suppose that this use of poplars for phytoremediation will be successful.

The same group of researchers from the University of Washington have carried out experiments using poplars to fight pollutants for the last three growing seasons. They have fed 30-foot potted plants a regular amount of organic solvents, mimicking the situation at chemical spills where contaminants travel in moving water.

One of these toxic compounds is trichloroethane (TCE), a dry-cleaning and degreasing solvent that is a suspected carcinogen.

In these experiments, plots bearing trees have been removing more than 97 percent of the TCE piped in.

If the poplars work well in the field, they should be especially useful for cleaning spills in densely populated areas since, unlike conventional mechanical pump-and-strip systems of decontamination, the poplars do not release appreciable amounts of solvent into the atmosphere.

Source: Scientific American, December 1997.

Health Effects of Cadmium in Sunflower Kernels

Cadmium intake in relatively high amounts can cause adverse health effects. Over a long period of regular intake, cadmium may accumulate in the kidney and liver and, because of its long biological half-life, may result in kidney damage.

Because of inherent genetic and physiological characteristics, sunflowers have a propensity to take up cadmium from the soil and deposit it in the kernels. Thus, the sunflower kernel has a higher natural concentration of cadmium than most other grains, even when grown in uncontaminated soils.

Tests carried out by the United States Department of Agriculture found that the concentration of cadmium in confectionery sunflower kernels may range from 0.2 to 2.5 µg/g fresh weight, depending on the genotype, the seasonal conditions, and the local soil conditions where the sunflowers are grown.

Because of this relatively high cadmium content, regular consumption of the kernels could substantially increase the daily intake of cadmium with potentially harmful long-term health effects.

As a consequence of these findings, a study was carried out by the Agricultural Research Service of the United States Department of Agriculture to determine whether regular consumption of sunflower kernels will increase the body burden and health effects of cadmium in humans.

Sixty-six men and women who reported consuming various amounts of sunflower kernels were recruited and divided by sex and kernel consumption: those who consumed less than or equal to 1 ounce (oz)/ week and those who consumed more than 1 oz/ week. Cadmium intake was assessed by calculation from 7-day food diaries, cadmium burden by whole blood cadmium, red blood cell (RBC) cadmium and urine cadmium concentrations, and health effects by urinary excretion of *N*-acetyl-β-D-glucosaminidase (NAG) activity and β2-microglobulin (β2MG). The results showed that high intakes of sunflower kernels (>1 oz/day) significantly increased the intake of cadmium ($p<0.004$). However, the amount of cadmium in whole blood or RBCs was not affected by cadmium intake. Urinary excretion of cadmium also was not affected by cadmium intake. Urine NAG activity and the amount of urinary β2MG were significantly elevated in the urine of high sunflower kernel consumers when the values were expressed on a urine volume basis ($p<0.03$), but not when expressed on a creatinine basis ($p>0.05$). Because normal ranges for the excretion of these protein markers have not been established, it was not possible to determine if these elevated values were meaningful. However, given the knowledge that habitual consumption of sunflower kernels with natural cadmium concentrations higher than most other food products will increase the average intake of dietary cadmium, the potential exists for an increased body burden of cadmium. Controlled feeding studies in humans should be pursued in order to determine if the body burden does indeed increase and, if so, whether it is a cause for concern.

Source: Environmental Health Perspectives, Vol. 105, No. 10, October 1997.

The Role of Metallothioneins in the Detoxification of Heavy Metals

Metallothioneins are small, low-molecular-weight, cysteine-rich proteins that have a very high metal binding capacity.

The widespread occurrence of metallothioneins suggests that these proteins play a fundamental physiological role in every organism. One widely accepted role is to provide protection against toxic heavy metals such as cadmium. However, despite intensive research efforts, the physiological functions of metallothioneins remain only partially understood.

Studies of the health effects of cadmium have attracted great interest because it is a ubiquitous environmental contaminant. Cigarette smoke, a major human health concern, is the most common non-industrial source. While chronic exposure to low doses of cadmium results mainly in nephrotoxicity, acute exposure to large doses can result in damage to a number of tissues.

Thus, a better understanding of the defense mechanisms available to counteract heavy metal toxicity is needed. As part of this ongoing investigation, researchers from the University of Texas Health Science Center at San Antonio, in the United States, carried out an important study of cadmium toxicity and distribution in metallothionein deficient transgenic mice.

Cadmium-binding proteins (metallothionein equivalents), cadmium acute toxicity, and cadmium distribution in tissues and subcellular fractions were compared in metallothionein-I and -II deficient (MT-/-) mice and the parental strain carrying intact metallothionein genes (MT+/+) to determine if the absence of metallothionein altered any of these parameters. In an uninduced state, MT-/- mice expressed lower levels of cadmium-binding proteins relative to MT+/+ mice in several tissues. Administration of zinc enhanced the levels of cadmium-binding proteins in liver, small intestine, kidney, pancreas, and male sex organs, but not in cecum or brain of MT+/+ mice compared to zinc pretreated MT-/- mice. The cadmium LD50 was similar for MT-/-, MT+/+, and zinc-pretreated MT-/- mice (15-17 µmol $CdCl_2$/kg body weight delivered ip). However, zinc-pretreated MT+/+ mice had a cadmium LD50 of 58-63 µmol $CdCl_2$kg body weight. Over two-thirds of cadmium was found in liver cecum, small intestine, and kidney in both MT+/+ and MT-/- mice; therefore, metallothionein levels do not appear to play a major role in the tissue distribution of cadmium. However, after zinc pretreatment, MT+/+ mice accumulated more cadmium in the liver and less in other tissues, whereas the amount of cadmium in the liver was not altered by zinc pretreatment in MT-/- mice.

A major finding of this study was that the cadmium LD50 values were similar for MT-/- and non-pretreated MT+/+ mice using an acute toxicity test. Because metallothionein levels were shown to be induced in cadmium-treated MT+/+ mice, but not in MT-/- mice, it was concluded that induction of metallothionein following a single cadmium exposure is an inadequate response to ameliorate acute toxicity. In contrast, MT+/+ mice pretreated with zinc, such that metallothionein was maximally elevated prior to cadmium challenge, required three to fourfold higher doses of cadmium to produce acute toxicity. These results indicate that induced levels of metallothionein, due to zinc pretreatment, can reduce the acute toxicity induced by cadmium. However, basal levels of metallothionein do not appear to afford protection from a single ip, acute dose of cadmium in the absence of prior induction. The theory that induced levels of metallothionein mediate protection is consistent with numerous reports documenting that animals pretreated with zinc develop a tolerance to subsequent challenges of cadmium.

Source: Journal of Toxicology and Environmental Health, Vol. 52, No. 6, December 26, 1997.

Cervical Cancer and Tobacco Smoking

Cervical cancer is the leading cause of cancer deaths and the most common cancer among women in developing countries.

In a recent international study, human papillomavirus DNA was found in more than 90% of cervical tumor specimens examined, irrespective of the nationality of the patients from whom the samples were obtained. Although infection with human papillomavirus is the major known risk factor for the development of cervical cancer, it alone is not sufficient. Other etiologic factors that have been associated with this disease include deficiencies in micronutrients, lower socioeconomic status, oral contraceptive use, and cigarette smoking. Several compounds from cigarette smoke (nicotine and its major metabolite, cotinine) have been identified in cervical mucus, and the occurrence of smoking-related DNA damage in the cervical epithelium has been documented.

The mechanisms by which tobacco smoke constituents could induce a genotoxic effect in the cervical epithelium are not known. The presence of nicotine and cotinine in the cervical mucus of smokers may indicate that inhaled tobacco-specific carcinogens could likewise become blood-borne and transported to the cervix, where they may damage cellular DNA. There are at least 60 toxic and/or carcinogenic compounds among the 4000 chemical constituents identified in tobacco smoke; seven of these compounds are known human carcinogens. Two major classes of carcinogens are the tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons. One of the tobacco-specific nitrosamines, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), is relatively abundant in tobacco products and is the most active tobacco-specific carcinogen in animal model assays.

A study carried out by researchers from the American Health Foundation to determine if NNK could be detected in the cervical mucus of smokers produced findings that the researchers claim provide the first unequivocal evidence of the presence of a tobacco-specific carcinogen in the cervical mucus specimens of women who smoke cigarettes. The study identified lower levels of NNK in the cervical mucus from non-smokers, which may relate to exposure to environmental tobacco smoke. Since NNK was not detected in wet blank control specimens and blank analyses, it is unlikely that sample contamination during collection or sample carry-over throughout the assay occurred. Significant differences in the amount of mucus collected from smokers and non smokers were not observed and thus cannot account for the variation in levels of NNK in specimens of cervical mucus. It is known that NNK induces tumors in the lung, liver and nasal mucosa of rodents independent of route of administration. When administered in drinking water, NNK also induced tumors of the exocrine pancreas in rats. Animal models to study the induction of cervical carcinoma by NNK or other tobacco-specific nitrosamines have not yet been developed, and suggest an important area for future research.

Source: Journal of the National Cancer Institute, Vol. 89, No. 12, June 1997.

Alcohol Sensitivity: The Role of the Fyn Kinase Gene

Experiments on genetically altered mice at the RIKEN Brain Science Institute in Wako City, Japan, provide new insights into how alcohol affects brain neurons.

The mice lack a functional gene for an enzyme called Fyn tyrosine kinase, which previous work had linked to memory and learning. Five years ago, researchers at Columbia University College of Physicians and Surgeons in New York City had shown that the enzyme is needed for spatial learning and long-term potentiation, a long-lasting alteration in nerve-cell excitability thought to underlie memory.

Now the research collaborators at RIKEN are studying how the mice respond to various drugs, including sedatives such as ethanol. To assess alcohol sensitivity, ethanol was injected into the mice, which were put on their backs in V-shaped troughs, and the time it took for the inebriated mice to stand upright was measured.

It was found that while mice not given alcohol stand up immediately, normal injected mice take between 3 to 40 minutes depending on the amount of alcohol administered.

However, for each blood level of alcohol tested, the mice lacking Fyn kinase took twice as long as the mice with a functioning Fyn kinase gene.

This study may provide some insight into why some people are more susceptible to alcoholic addiction than others. In the past, one theory was that sensitive individuals simply break down alcohol more slowly, but the Japanese study suggests that sensitivity to alcohol is determined at least in part by levels of Fyn tyrosine kinase. Thus, individual differences in enzyme levels could account for different degrees of sensitivity to alcohol. If this is so, the Fyn kinase gene may be a target for researchers identifying genes that might predispose individuals to alcoholism.

Source: Science, Vol. 278, October 1997.

Pesticides and the Risk of Childhood Cancers

Investigations of environmental factors and childhood cancers carried out in the United States in recent years have mainly focused on parental occupational exposures. These studies have pointed to increased risks of cancers in children of workers exposed to electromagnetic fields, paints, solvents, radiation, hydrocarbons, and agricultural chemicals.

Agricultural exposures may encompass a variety of chemicals, but pesticides are usually of greatest interest. These include herbicides, insecticides, fungicides, rodenticides, and other biocides.

The relationship between pesticide exposures and the risk of childhood cancer has been investigated in a number of epidemiological studies. However, there is still considerable speculation as to the mechanisms by which pesticide exposure may lead to cancer in children.

Potential mechanisms for childhood cancer include preconceptional exposure causing mutation of parental germ cells or epigenetic effects such as alteration of imprinting patterns, or transplacental exposure causing somatic cell mutations in the embryo or alterations in hormonal or immunological function.

Laboratory studies have not yet provided insight on how pesticides might act through these pathways. However, animal studies of other environmental agents such as metals, alkylating agents, and radiation, have provided direct evidence for some mechanisms leading to some childhood cancers (e.g. germ cell mutation). Other carcinogenic mechanisms for environmental exposures, including pesticides, have not been thoroughly studied. Thus, linking potential mechanisms of perinatal carcinogenesis to specific exposures remains an important challenge.

This is highlighted in the analysis of the epidemiological studies carried out in the United States and published between 1970 and 1996.

Collectively, these studies suggest an increase in risk of brain cancer, leukemia, Wilms' tumor, Ewing's sarcoma, and germ cell tumors associated with paternal occupational exposure to pesticides prior to and during pregnancy. Maternal occupational exposure during pregnancy was studied less frequently, but was also associated with leukemia, Wilms' tumor, and germ cell tumors. Most of these cancers were only evaluated in one or two studies, and the number of exposed cases was often small. Childhood brain cancer and leukemia were the most studied, with fairly consistent, moderate increases in risk. Farm residence was associated with brain cancers, neuroblastoma, retinoblastoma, non-Hodgkin's lymphoma, and Wilms' tumor to varying degrees. However, inference of individual-level exposure from the aggregate pesticide exposure for all farm residents limits conclusions about risk from these studies.

Few studies distinguished between herbicides, insecticides, fungicides, or other types of pesticides, which are not always mutually exclusive categories. It is possible that differences in the chemical properties of various pesticides, the methods of application, and consequently the exposure pathways (dermal, ingestion, or inhalation) may be partially responsible for the reported differences in risk of childhood cancer associated with pesticide exposure. The magnitude of the relative risks reported in these studies also appears to vary by the timing and frequency of exposure, as well as by the heterogeneity of study groups and other aspects of study design. Drawing conclusions from these studies requires careful consideration of possible methodological limitations. Exposure misclassification, insufficient sample size, biases in control selection, and uncontrolled confounding factors are among the primary limitations of case-control studies of pesticides and childhood cancers.

Although many of these studies suggest an association between certain exposures and certain cancers, an etiologic relationship between pesticide exposure and childhood cancer is far from proven. Future studies should carefully classify exposure with regard to chemical type and timing, and more narrowly define cancer type based on histology. Laboratory investigations are also needed to provide the critical data for understanding these mechanistic relationships.

Source: Environmental Health Perspectives, Vol. 105, No. 10, October 1997.

Chulabhorn Research Institute
CAPACITY BUILDING PROJECT ACTIVITIES
for Southeast Asian Countries

In the January 1998 issue of the Newsletter we highlighted the launch of CRI's regional capacity building project. We are now pleased to announce the following schedule of project activities for 1998.

Date	*Course*	*City/Country*
May 18-19	Environmental Toxicology/ Executive Seminar	Hochiminh City/ VIETNAM
May 21-22	Environmental Toxicology/ Executive Seminar	Hanoi/VIETNAM
May 25	Environmental Toxicology/ Executive Seminar	Jakarta/INDONESIA
May 26 – June 5	Environmental Toxicology Pollution Control and Management/Core Course	Jakarta/INDONESIA
June 24 – July 2	Environmental Biotechnology/ Practical Training Course	Bangkok/THAILAND
October 26-30	Detection of Environmental Pollutants and Monitoring of Health Effects/Practical Training Course	Bangkok/THAILAND
November 9-21	Environmental Toxicology Pollution Control and Management/Core Course	Hochiminh City/ VIETNAM
November 23 – December 4	Environmental Toxicology Pollution Control and Management/Core Course	Hanoi/VIETNAM

The ICEIT NEWSLETTER is published quarterly by the International Centre for Environmental and Industrial Toxicology of the Chulabhorn Research Institute. It is intended to be a source of information to create awareness of the problems caused by chemicals. However, the contents and views expressed in this newsletter do not necessarily represent the policies of ICEIT.

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Advance Notice

Symposium on the Epidemiology and Prevention of Cancer
November 2-4, 1998
Bangkok, Thailand

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Organized by

International Union Against Cancer (UICC) in collaboration with Bender Foundation, Munich, Germany and The Chulabhorn Research Institute

The Symposium will be followed by a one day educational workshop on subjects discussed during the Symposium.

The Symposium and Workshop will be co-chaired by:

Professor Dr. HRH Princess Chulabhorn (CRI)
Dr. S. Tominaga (UICC)
Dr. K. Zanker (Witten University)

The program will include discussions of Molecular Epidemiology with emphasis on cancer in Southeast Asia, risk factors, concepts germane to molecular epidemiology approaches with focus on the expression of markers during the etiology of Barrett's disease, colon cancer and cervical cancer. A session will be devoted to the role of genetic and environmental factors in the etiology of cancer in defined populations. Other discussions will concern cancer prevention from the medicinal chemistry, biochemical and clinical points of view and the potentiality of cellular and genetic markers as endpoints (surrogate markers) for clinical studies of chemoprevention. Finally, clinical intervention studies will be discussed focussing on head and neck, lung and gastrointestinal cancers as examples of intensive study.

The Educational Workshop will be concerned with two very important areas, namely, the problem of protocol design and field applications, and the opportunities, approaches and problems in transferring knowledge acquired in the laboratory to clinical applications.

It is expected that many opportunities for interactions with the invited speakers will be open to registered attendees and that much progress in individual advanced education and in the development of new ideas will derive from these opportunities. For registration details, please write directly to Dr. Mathuros Ruchirawat, Office of Academic Affairs, Chulabhorn Research Institute, Vipavadee Rangsit Highway, Bangkok 10210, Thailand, Fax: (66-2) 247-1222, 574-0616.