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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".

HRH Princess Chulabhorn Opens First Executive Seminars on Environmental Toxicology in Malaysia

Her Royal Highness Princess Chulabhorn participated in two executive seminars on environmental toxicology held in Kuala Lumpur, Malaysia, on 20 June 2000 at SIRIM Environmental and Energy Technology Centre, and on 21 June 2000 at the Institute of Medical Research (IMR). These two events were organized as part of the Chulabhorn Research Institute's ongoing program of capacity building in environmental toxicology, technology and management to promote sustainable development in the Asia and Pacific region.

In her opening address, Her Royal Highness referred to the fact that rapid industrial expansion in the region in recent years had led both government and private sectors to examine more critically the effect of development on the environment and on health.

The program of human resource development in environmental toxicology has been designed to respond to the urgent need for specialized training in the management of toxic chemicals, toxic waste, and waste re-utilization.

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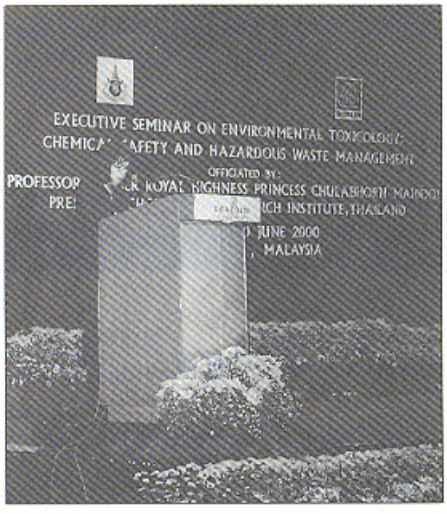

At SIRIM the emphasis of the seminar was on chemical safety and hazardous waste management, and at IMR it was on the health effects of exposure to chemicals in order to create a better understanding of the interaction between chemical and biological systems.

Faculty who taught on the seminar were from the Chulabhorn Research Institute's group of international resource persons from North America and from Europe as well as from the institute's own research team.

Agreement on Educational and Scientific Cooperation signed between the Chulabhorn Research Institute and the Hanoi Department of Science Technology and Environment

As President of the Chulabhorn Research Institute (CRI), HRH Princess Chulabhorn took part in the signing ceremony of an agreement for educational and scientific cooperation between the institute and the Hanoi Department of Science Technology and Environment (DOSTE) on 26 June 2000 in Hanoi. On the Vietnamese side, the agreement was signed by Dr. Nguyen Quoc Trieu, Vice Chairman of the Hanoi People's Committee. The Agreement sets out the terms for ongoing cooperation involving joint activities in training scientists in the area of environmental toxicology; exchange of information; and exchange of staff members for study and research.

The signing ceremony took place on the occasion of the third training course on Environmental Toxicology to be organized by the Chulabhorn Research Institute in Hanoi. The two previous courses had been held in November 1998 and May 1999.

(Continued on page 5)

IMPACT OF CYANIDE SPILL IN HUNGARY

Government officials in Hungary have warned that a cyanide spill in the Tisza River may threaten human health.

The spill occurred on 30 January 2000 at the Aural precious metals recovery plant near Baia Mare, Romania, where 100,000 m^3 of sludge contaminated with cyanide and heavy metals flowed over a 25 m length of dam and down the Szamos and Lapos rivers into the Tisza, Hungary's second longest waterway. Environment officials fear that concentrations of heavy metals – mainly lead, copper and zinc – in the beds of the affected rivers could work their way into the food chain.

The spill has wiped out practically all aquatic life in the rivers affected. In the month of February alone, 150 tonnes of dead fish had been pulled from the Tisza. Fish along one stretch of the river were found to contain 2.6 mg of cyanide per kilogram of weight. These fish include carp, catfish and pike, all commonly eaten by people in the region.

Source: British Medical Journal, Vol. 320, Feb 2000.

ARSENIC CONTAMINATION OF DRINKING WATER

Reports earlier featured in this Newsletter (Vol. 4, No.2 and Vol. 6, No. 3) have drawn attention to the problem of arsenic contamination in southern Thailand. It is of course a global problem, but it is particularly severe in Bangladesh and West Bengal, India, where over 112 million people reside in areas where ground water arsenic concentrations exceed World Health Organization's (WHO) maximum permissible level.

Arsenic exposure is associated with health effects such as skin lesions and cancer of the lung, liver and bladder.

A recent report of surveys undertaken by researchers from the School of Environmental Studies at Jadavpur University, Calcutta, the Dhaka Community Hospital Trust in Bangladesh, and the Calcutta Medical College and Hospital finds that arsenic contamination of drinking water is more severe in Bangladesh than in West Bengal, but that some of the preliminary health effects can be reversed with a healthy diet and uncontaminated water.

Forty-two districts in Bangladesh, with a population of 79.9 million, have groundwater with arsenic concentrations in excess of 50 µg/L. Nine districts in West Bengal, with a population of 42.7 million, have concentrations in excess of the WHO maximum permissible level. Over 90% of the residents in Bangladesh and West Bengal use groundwater for drinking and cooking. To determine the extent of drinking water contamination, the researchers collected nearly 11,000 water samples over a four-year period from districts in Bangladesh and discovered that 59% of those samples exceeded 50 µg/L. Of 58,166 samples from West Bengal, 34% exceeded 50 µg/L.

The levels of contamination also run higher in Bangladesh. Of the samples from Bangladesh exceeding the WHO maximum permissible level, nearly one-quarter were contaminated with concentrations of 100-299 µg/L. Nearly 11% of the samples contained concentrations of 300-499 µg/L, while 8.7% contained concentrations of 500-1,000 µg/L. Only 14% of the samples from West Bengal contained 100-299 µg/L, and only 3.9% had concentrations of 300-1,000 µg/L.

Similarly, the researchers found that a higher percentage of villagers in Bangladesh suffer from skin lesions than in West Bengal. Nearly one-quarter of the 11,000 villagers surveyed in Bangladesh suffered skin lesions, compared to slightly more than 15% of the 29,000 villagers surveyed in West Bengal. During 10 years of field surveys in West Bengal and 5 years in Bangladesh, the researchers observed that concentrations in excess of 300 µg/L were associated with arsenical lesions, although lesions also occur at lower concentrations when nutrition is poor, the volume of water consumed is high, or contaminated water is consumed for an extended period.

The group also observed that concentrations as high as 400 µg/L may not produce lesions if those exposed eat a nutritious diet. Arsenical skin lesions in their earliest stages can be reversed with safe drinking water and proper nutrition. Keratosis, a skin condition that accompanies more severe toxicity, may not disappear, but it can be reduced with safe water and nutritious food. More severe keratosis may, however, lead to skin cancers.

Source: Environmental Health Perspectives, Vol. 108, No. 5, May 2000.

LAUNCH OF JOINT TEACHING PROGRAM IN BIOENGINEERING AND ENVIRONMENTAL HEALTH

A joint teaching program has been launched between the Massachusetts Institute of Technology (MIT) and the Chulabhorn Research Institute (CRI) in collaboration with the Asian Institute of Technology (AIT).

The program opened in May 2000 with the teaching of two month course by a team of biologists and chemists dedicated to solving health and environmental problems. The course has been designed to combine the strengths of traditional disciplines, such as engineering or chemistry, with the realization that solving complex world problems requires a cross disciplinary approach made possible by a broader educational perspective involving the collaborative effort of scientists of many disciplines.

This is the first time the course has been taught in Thailand. The faculty comprises two course instructors from MIT, Professor John Essigmann, from the Department of Chemistry, and Associate Professor Ram Sasisekharan, from the Division of Bioengineering and Environmental Health, as well as three teaching assistants, Dr. Ganesh Venkataraman of the Division of Health Sciences and Technology, Harvard University and MIT, Dr. Maria Kartalou, of the Department of Chemistry, MIT, and Dr. Suvit Loprasert of the Laboratory of Biotechnology at CRI.

The main teaching method is through case studies, and the topic of the present course is the problem of AIDS. On the first day of class, students are divided into four groups: Clinical, Marketing, Engineering and Ethics. The Marketing group attempts to determine how many people in a given population have the target disease. They must also determine the quantity of respective drugs needed. The Production group uses engineering methodology to design an industrial plant locally in Asia to produce the

volume of drugs requested by the Marketing group.

The Clinical group has the task of describing the biological basis of the target disease, identifying clinical options that could cut into the market and define methods of drugs delivery. The Ethics group probes the various ethical issues that exist in relation to the use of the drug.

In order to facilitate good communication between students and faculty, a dedicated website for the course was developed. This website served as the central communication mode between the different student groups and also with the MIT faculty. This remote interaction was in addition to class attendance. Student presentations were made available to the MIT faculty through the website for their active participation during the course.

A teleconference meeting was held by course participants at the Communications Authority of Thailand (CAT) on 24 July at 19:00 hrs. with 5 committee members from MIT in Boston where the local time was approximately 8:00 hrs. In this teleconference the **clinical group** gave presentations on the biology of HIV infection, the mechanism of reverse transcriptase inhibitors and protease inhibitors, and combination therapy and resistance; the **marketing group** on the Asian and Thai market for HIV drugs, cost analysis, and health insurance laws and intellectual laws in Thailand; the **production group** on design of new protease inhibitor and ritonavir synthesis, production plant design and pollution control strategies, purification strategies, and production cost analysis; and the **ethics group** on education, religion and HIV, "Is HIV still a death sentence in Asia?", animal testing and clinical trials, a pregnant woman's right to choose to have an abortion when she has HIV infection, and the role of law in HIV.

Agreement on Educational and Scientific Cooperation signed between the Chulabhorn Research Institute...

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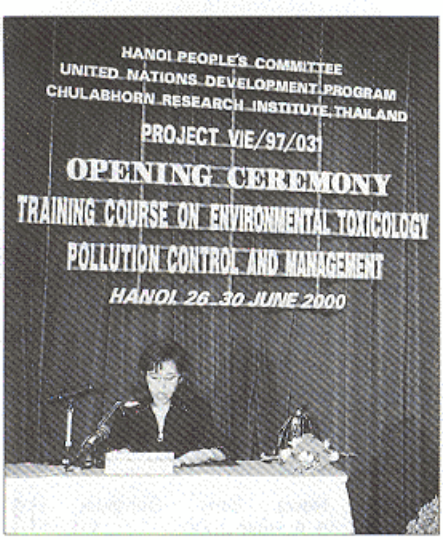

The present training course provided the opportunity for indepth studies of areas of critical importance to sustainable development.

In her opening address, HRH Princess Chulabhorn stated that in Vietnam, as elsewhere in the Southeast Asia region, the rapid expansion of new industries that had occurred in recent years had caused industrial planners to reassess the effects of this expansion on the environment in terms of both control and management of pollution.

The training course, part of CRI's ongoing program in human resource development, was held from 26 to 30 June 2000.

The link between dietary bioflavonoids and infant leukemia

A new report suggests that nutrients called flavonoids may occasionally trigger a deadly form of infant leukemia which starts before birth.

Chromosomal translocations involving the *MLL* gene occur in about 80% of infant leukemia. In the search for possible agents inducing infant leukemia, a recent research study has identified bioflavonoids, natural substances in food as well as in dietary supplements, that cause site-specific DNA cleavage in the *MLL* breakpoint cluster region (BCR) *in vivo*. The *MLL* BCR DNA cleavage was shown in primary progenitor hematopoietic cells from healthy newborns and adults as well as in cell lines; it colocalized with the *MLL* BCR cleavage site induced by chemotherapeutic agents, such as etoposide (VP16) and doxorubicin (Dox). Both *in vivo* and additional *in vitro* experiments demonstrated topoisomerase II (topo II) as the target of bioflavonoids similar to VP16 and Dox. Based on 20 bioflavonoids tested, researchers have identified a common structure essential for topo II-induced DNA cleavage. Reversibility experiments demonstrated a religation of the bioflavonoid as well as the VP16-induced *MLL* cleavage site. Observations support a two-stage model of cellular processing of topo II inhibitors: the first and reversible stage of topo II-induced DNA cleavage results in DNA repair, but also rarely in chromosome translocations; whereas the second, nonreversible stage, leads to cell death because of an accumulation of DNA damage. These results suggest that maternal ingestion of bioflavonoids may induce *MLL* breaks and potentially translocations *in utero* leading to infant and early childhood leukemia.

Source: Proceedings of the National Academy of Sciences, Vol. 197, No. 9, April 2000.

THE EFFECT OF AEROSOLS ON CLIMATE

Submicrometer-sized particles suspended in the atmosphere may have as great an impact on Earth's climate as the greenhouse gases that have accumulated in the atmosphere over the past century. Aerosols affect climate directly by scattering sunlight back to space and indirectly by augmenting the numbers of droplets within clouds. These effects cool Earth, counteracting the greenhouse effect.

It remains unclear whether aerosols offset the greenhouse effect only slightly or cancel it entirely. This uncertainty stems from inherent difficulties in quantifying the impacts of aerosols on climate. In contrast to greenhouse gases, which remain in the atmosphere for a long time and are nearly uniformly distributed, aerosols tend to be concentrated near their sources and are highly variable in space and time.

Our albeit limited understanding of how aerosols modify cloud properties suggests that pollution greatly augments the number of particles in the atmosphere.

Each cloud droplet originates on a preexisting particle, and increasing the number of particles thus increases the number of cloud droplets. However, the temperature and the atmospheric motions driving cloud formation, rather than the number of droplets, control the mass of water condensing in the cloud. Therefore, if there are more cloud droplets, they will on average be smaller in size. A cloud containing smaller particles has a larger droplet surface area than a cloud with big particles for the same amount of condensed water. The optical depth of the cloud, a measure of the reflectivity of the cloud, is directly proportional to the surface area, and therefore pollution should lead to more reflective clouds.

Climate modelers have made estimates of the magnitude of the indirect effect of aerosols on cloud reflectivity. However, much still remains to be learned about how aerosols modulate different types of clouds, alter the area covered by clouds, change their lifetimes, and modify their precipitation rates. Decreases in precipitation rates would alter the amount of surface moisture that might be used by humans. They will also induce changes in cloud reflectivity, lifetime, and area that may be as important for climate as the changes in reflectivity caused by the increased numbers of cloud droplets as a result of added aerosols.

Source: Science, Vol. 287, No. 5459, March 2000.

PLANT CLOSURE FAILS TO EFFECT A REDUCTION IN LEAD BLOOD LEVEL OF VILLAGERS

High levels of lead have been detected in blood samples from villagers living near Klity creek in Kanchanaburi, Thailand, despite the closure of a lead floating plant that had contaminated the area.

Analysis of recent blood tests show that the lead content in blood samples taken from local villagers has not decreased appreciably two years after the factory of Lead Concentrate Thailand was shut down in 1998. Indeed, among certain groups, lead blood levels are higher than those formerly recorded. Blood tests conducted in March this year found the lead content in villagers' blood ranged between 12.56 and 48.80 microgrammes per decilitre, as compared with 4.92 microgrammes across the whole population. According to the government Pollution Control Department, the lead content in Klity creek is 10 times higher than the safety standard. Persistant high lead blood levels may be due to the fact that some villagers were still using water from the contaminated creek, although tap water was available in Lower Klity village.

Source: News Item, Bangkok Post, 3 August 2000.

ATTACKING COCAINE PRODUCTION AT SOURCE

As part of a new strategy in its war against illicit drugs, the UN International Drug Control Programme is currently negotiating with the government of Colombia to carry out open field trials of a strain of the fungus *Fusarium oxysporum* that attacks coca plants, the source of cocaine.

Fusarium species are common in many parts of the world. Different strains attack different plant root systems, causing a variety of diseases in crops. The coca-attacking strain was discovered at a US government research station in Hawaii after it infected an experimental coca plot.

However, the strain has never been field tested outside Hawaii, and last year plans to use a similar fungus to kill marijuana plants in Florida raised strong protest from environmentalists. They pointed out that the fungus might attack other plants in addition to their targets.

Thus the aim of the proposed trials in Colombia is to make sure that the fungus affects only coca plants and to find an easy way to distribute it. However agreement to procede with the trails is still under consideration.

Source: New Scientist, Vol. 165, No. 2229, March 2000.

Identification of a new marine pathogen

Disease-related mortalities of sea urchin populations have occurred globally over the past 20 years, although the causative agents have rarely been identified. However, researchers have now discovered a potent new marine pathogen that caused a sudden die-off of the sea urchin *Meoma ventricosa* in Curacao, Netherlands Antilles, in January of 1997, and which also has implications for human health. This turns out to be a neurotoxin-producing bacterium that is closely related to the deadly *Pseudoalteromonas halophanktis tetraodonis*, which is responsible for numerous deaths each year in Japan resulting from the consumption of pufferfish.

M. ventricosa inhabits sandy sediment adjacent to and within sea-grass beds and patch reefs throughout the Florida reef tract and the Caribbean. The die-off in Curacao extended from the Curacao harbour to an area 3.5 km downcurrent along the coast. Necropsy of infected animals revealed a progressive loss of spines associated with the disease. Microscopic comparison of the base of the spines and the catch apparatus (where the spine is connected to the skeleton) from affected and healthy animals revealed Gram-negative bacteria in diseased tissue. Researchers have now isolated these bacteria using a non-selective artificial seawater medium: in all, 249 bacterial strains were found in various tissues associated with affected and unaffected urchins.

DNA-sequence analysis of small ribosomal RNA (16S rDNA) identified VL-1 as a new bacterium closely related to *Pseudoalteromonas halophanktis* subsp. *tetraodonis*, which produces tetrodotoxin (GenBank accession number, AF154414). Tetrodotoxin has been isolated from various marine organisms, but is best known for its association with pufferfish (order Tetraodontiformes): poisoning by pufferfish (fugu) consumption remains a major health concern, primarily in Japan, where fugu is a delicacy.

Source: Nature, Vol. 404, No. 6776, March 2000.

THE ROLE OF BENZENE IN SMOKING-INDUCED LEUKEMIA

Based on the results of several large cohort studies, cigarette smoking is associated with an increased risk of leukemia. The relative risks range from 1.5 to 2.0. Although cigarette smoke contains a multitude of toxic chemical compounds, reseachers have not yet established which chemicals are responsible for the leukemogenicity of this complex mixture.

Benzene is present in mainstream cigarette smoke at concentrations of approximately 45 µg/cigarette, and in sidestream smoke at concentrations about 10 times higher. Personal exposure assessment research has indicated that the average cigarette smoker inhales 6-10 times the benzene inhaled by the average nonsmoker, and that approximately 90% of a smoker's benzene exposure is from smoking. For nonsmokers, most benzene exposure comes from automobile exhaust, environmental tobacco smoke, and exposure to consumer products. Benzene induces leukemia both in humans with occupational exposures and in experimental animals. Some research indicates the strongest association of benzene to be with acute myeloid leukemia (AML), but effects on other types of leukemia have not been ruled out.

A new investigation has now been carried out to determine what proportion of smoking-induced leukemia is likely to be caused by the benzene in cigarette smoke.

In the study, five steps were used to estimate the proportion of smoking-induced leukemia caused by benzene:

a) A calculation of the lifetime risk of leukemia due to smoking; *b)* a determination of the leukemogenic potency of benzene; *c)* the quantification of benzene dose for smokers at two levels of smoking; *d)* the characterization of the low-dose risk of leukemia due to the benzene in cigarette smoke [using the results of *b)* and *c)*]; and *e)* a comparison of the predicted life-time leukemia risk due to benzene in cigarette smoke [from *d)*] to the observed lifetime leukemia risk due to smoking. [from *a)*]

By combining epidemiologic data on the health effects of smoking with risk assessment techniques for low-dose extrapolation, researchers assessed the proportion of smoking-induced total leukemia and acute myeloid leukemia (AML) attributable to the benzene in cigarette smoke, fitting both linear and quadratic models to data from two benzene-exposed occupational cohorts to estimate the leukemogenic potency of benzene. Using multiple-decrement life tables, lifetime risks of total leukemia and AML deaths for never, light, and heavy smokers were calculated. These calculations were then repeated, removing the effect of benzene in cigarettes based on the estimated potencies. From these life tables smoking-attributable risks and benzene-attributable risks were determined. The ratio of the latter to the former constitutes the proportion of smoking-induced cases attributable to benzene. Based on linear potency models, the benzene in cigarette smoke contributed from 8 to 48% of smoking-induced total leukemia deaths [95% upper confidence limit (UCL), 20-66%], and from 12 to 58% of smoking-induced AML deaths (95% UCL, 19-121%). The inclusion of a quadratic term yielded results that were comparable; however, potency models with only quadratic terms resulted in much lower attributable fractions–all < 1%. Thus, benzene is estimated to be responsible for approximately one-tenth to one-half of smoking-induced total leukemia mortality and up to three-fifths of smoking-related AML mortality. In contrast to theoretical arguments that linear models substantially overestimate low-dose risk, linear extrapolations from empirical data over a dose range of 10- to 100-fold resulted in plausible predictions.

Source: Environmental Health Perspectives, Vol. 108, No. 4, April 2000.

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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