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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".

Princess Chulabhorn Opens Training Course on Detection of Environmental Pollutants and Monitoring of Health Effects in Vietnam

Her Royal Highness Princess Chulabhorn, President of the Chulabhorn Research Institute, opened the training course in Hanoi on 10 May 1999 as part of the UNDP supported project: Capacity Building in Environmental Toxicology, Technology and Management to Promote Sustainable Development in Vietnam.

The training course which ran from 10 – 14 May was organized by the Vietnamese Government, Department of Science, Technology and Environment (DOSTE) in collaboration with the Chulabhorn Research Institute (CRI).

The program of the course comprised both lecture sessions and hands-on practical sessions given by faculty from the German Cancer Research

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Center, the University of Kaiserslautem in Germany, from the Chulabhorn Research Institute in Bangkok and from Vietnam National University, Hanoi.

In her opening address, Her Royal Highness Princess Chulabhorn stated that the subject of the present training course was of the greatest importance to endeavours to sustain industrial development and at the same time safeguard quality of life through adequate protection of the physical environment.

Her Royal Highness underlined the importance of effective detection of environmental pollutants as the key to successful management of toxic chemicals. The monitoring of health hazards – a major focus of the training course – was all too often overlooked by environmental specialists. But without adequate monitoring there could be no guarantee that the health of the industrial workforce would be effectively protected.

Commenting on the success of the training course, Dr. Norbert J. Frank of the German Cancer Research Center speaking on behalf of the faculty members said that the 40 course participants from all over Vietnam were eager to learn new methods and to discuss the problems of their own work with faculty members. The insights gained into new techniques and their application to solving problems would be of enormous help in addressing the environmental problems of a rapidly developing country like Vietnam.

The success of the course could be measured by the numerous requests to hold more training courses in Vietnam.

Causes of Amphibian Deformities

There has been an increasing number of reports of deformed amphibians since the early 1990s. Over the last decade, abnormalities have been reported in 36 species of amphibians from different parts of the United States. It is still uncertain, however, whether abnormalities are contributing to the globally observed trends in declines in amphibian populations or whether they are indicative of more general environmental threats.

Suggested causes of abnormal amphibians include ultraviolet-B radiation, biocide contamination, retinoids and parasite infection. None of those, however, has been decisively linked to the deformities most frequently reported in the field, namely missing, malformed or extra limbs.

In a study carried out through the Center for Conservation Biology at Stanford University, 35 ponds in Santa Clara County, California were surveyed between 1996 and 1998 to determine the prevalence of abnormal amphibians. Severely deformed frogs were observed at 4 of the 13 ponds supporting Pacific treefrogs. Intensive monitoring programs carried out at the two of the four ponds consistently recorded high frequencies of metamorphic frogs with extra limbs and other hindlimb deformities. In water tests carried out in the ponds, no pesticides, polychlorinated biphenyls (PCBs) or heavy metals were detected. Community analysis of the 35 ponds in the study revealed that the four ponds with abnormal treefrogs were the only ones to support both *Hyla regilla* and an aquatic snail, *Planorbella tenuis,* which is a first host of the trematode parasite *Ribeiroia* sp.

Upon dissection, *Ribeiroia* metacercariae were found in treefrogs from each of the four ponds. This led the researchers involved in the study to test the hypothesis that *Ribeiroia* infection is responsible for the limb abnormalities observed in the Pacific treefrogs.

The results of experiments carried out in this study show that parasite infection explains both the frequency and composition of abnormalities observed in the population of Pacific treefrogs under study. The trematode *Ribeiroia* was isolated from deformed frogs in the field, was employed at realistic concentrations in experimental exposures, and produced the same range and frequency of amphibian limb abnormalities as ob-served at the field sites.

The results of the study further suggest that trematode infection represents a considerable source of mortality in some amphibian populations since in addition to the high direct mortality caused by parasite infection, there is likely to be substantial indirect mortality resulting from increased predation on frogs with deformed or missing limbs.

At present the role of trematodes in the abnormalities in other amphibian species and the wider issue of amphibian decline is largely unexplored. There is an urgent need for increased research focus on parasite infection and its effects on amphibian host populations.

Source: Science, Vol. 284, April 1999.

Declines in Frog Population: An Early Warning of Environmental Problems or a Lethal Fungus?

In the last decade it has been asserted by herpetologists and ecologists that frog declines were symptomatic of larger environmental problems on the plants. Now, however, there is mounting evidence that both declines in frog populations and the disturbing limb deformities that have been observed may be due, at least in part, to pathogens, specifically to a lethal chytrid fungus.

The disease was first identified by scientists at the National Zoo in Washington D.C. In a recent study, researchers isolated the chytrid from poison dart frogs killed by the disease. This was used to inoculate healthy frogs. All infected frogs died, whereas frogs inoculated with a placebo did not. The chytrid from the second batch of dead frogs was then reisolated in a sequence of experiments that fulfills Koch's postulates, the gold standard for proving that an organism causes a disease.

The chytrid apparently uses the keratin in the frog's skin as a nutrient. Its motile, water-borne spores invade surface skin cells and grow and divide there asexually.

The chytrids favor wet conditions and cool temperatures and this may well explain dramatic frog deaths in both the United States and in Australia in recent years. However, proponents of the chytrid hypothesis do not claim that this pathogen is responsible. Herpetologists generally agree that the biggest problem for frogs worldwide is habitat loss; a species with only a few small, fragmented populations is likely to be much more vulnerable to the chytrid or another disease. Most fungal infections in amphibians are opportunistic, moving in when animals are already stressed or injured from other sources.

Source: Science, Vol. 284, April 1999.

The Threat of Biological Warfare

Although 140 nations have ratified the 1972 Biological Weapons Convention in which signatories agreed never to develop, produce or stockpile agents used in biological weapons, the threat of their use still exists. Indeed, it is a threat that has gained increasing attention in recent years.

In 1995, at least 17 countries (including several signatories of the 1972 convention) had been identified as nations harbouring biological weapons according to the US Office of Technology Assessment.

Biological warfare (BW) agents can cause large numbers of casualties with minimal logistical requirements. Perpetrators can escape long before BW agents incubate and cause casualties. Weapons are easy and relatively inexpensive to produce and can be used to selectively target humans, animals, or plants.

Agents can be easily procured from the environment, universities, biological supply houses, and clinical specimens. Common fermentation techniques used for producing antibiotics, vaccines, foods, and beverages can be adapted to grow large quantities of biological agents. Sample aerosol-generating devices mounted on planes or trucks, like those used for crop dusting, can be adapted to generate 1 – to 5 µm particles ideal for lodging in alveoli. Such aerosols would be undetectable by our senses, and an attack might not be noted until people became ill. Panic could result as medical capabilities become quickly overwhelmed. Aerosolization of biological agents often results in different clinical features of disease than those observed following natural infection. For instance, anthrax is usually a cutaneous disease in nature, but a rapidly fatal hemorrhagic mediastinitis ensues after inhaling spores.

Biological attacks could be attempted by contaminating water supplies, although modern water purification and the dilution effects of large water volumes would negate the effectiveness of such an attack. While intact skin provides a barrier to most BW agents, the trichothecene mycotoxins can penetrate the skin and cause systemic effects. Ingestion and cutaneous penetration are currently considered as unimportant potential routes of exposure. Agents could be dispersed by releasing them in their natural arthropod vectors. Person-to-person aerosol transmission of several agents (notably plague and smallpox) could perpetrate an epidemic. Last, nosocomial transmission could also cause casualties following exposure to contaminated blood, body fluids, or respiratory secretions.

Of all the means of mass destruction, biological warfare is the most alarming and most feared. The US government has funded the training of emergency response teams so that by the year 2001, more than 100 American cities will have personnel trained to recognise and contain a biological warfare attack. Dermatologists play a key role in disaster prevention and reduction. Many potential agents have cutaneous manifestations that a dermatologist can identify and thus through early recognition of an attack, dermatologists and trained paramedics can aid public health authorities in diagnosing symptoms so that preventitive and containment measures can promptly instituted to mitigate morbidity and mortality.

Source: Arch Dematol/Vol. 135, March 1999.

Organic Solvents and Pregnancy

In a study carried out by researchers at the Hospital for Sick Children in Toronto, Canada, it was found that women who are occupationally exposed to organic solvents, such as toluene and ethers, during pregnancy are at risk of giving birth to a baby with serious congenital malformations.

The study documented 125 pregnant women who were exposed to organic solvents in their place of work and seen at the hospital during the first trimester between 1987 and 1996. For the purpose of the study, each pregnant woman who was exposed to organic solvents was matched to a pregnant woman who was exposed to a nonteratogenic agent on age (± 4 years), gravidity (+ 1) and smoking and drinking status.

The study revealed that significantly more major malformations occurred among fetuses of women exposed to organic solvents than among controls. Twelve malformations occurred among the 75 women in the study who had symptoms temporally associated with exposure, while none occurred among 43 asymptomatic exposure women. More of these exposed women had previous miscarriages while working with organic solvents than women in the control group. However, exposed women who had a previous miscarriage had rates of major malformation of the fetus that were similar to exposed women who had no previous miscarriage.

The study supports the recommendation that women's exposure to organic solvents should be minimized during pregnancy.

Source: JAMA, Vol. 281, No. 12, March 1999.

Dioxin Exposure and Tooth Development in Children

Recent research has found an association between dioxin exposure in children and developmental dental defects.

This finding has led a group of researchers in the Institute of Dentistry, University of Helsinki, Finland, to explore whether teeth could be used as a biomarker of exposure to polychlorinated aromatic hydrocarbons. These are environmental contaminants to which breast fed infants are at risk.

The researchers examined dentitions of 102 children aged 6-7 years, who were from a normal breast fed population in Finland, for the presence of hypomineralised enamel defects.

Source: The Lancet, Vol. 353, January 1999.

STRATEGIES FOR REDUCING BLOOD LEAD LEVELS

Available data suggest that subtle health effects, such as lower IQ scores in children may result from elevated blood lead levels. While not as well studied, an association between blood lead levels in the range ≥ 0.483 µmol/L and the cognitive function of the middle-aged and elderly has also been reported.

Studies have found that irregular food intake, high dietary fat, low dietary calcium, and iron deficiency can increase the risk of lead toxicology of populations of all ages in a contaminated environment.

However, intake of ascorbic acid can have a beneficial effect on reducing lead toxicology. A recent report from a small-scale randomized trial in adult smokers supports the efficaciousness of ascorbic acid supplements. More evidence from controlled intervention studies is needed, however, to demonstrate potential value, if any, of increased ascorbic acid intake, especially in young children.

Even if a nutritional manipulation is proven effective in reducing blood lead levels, reliance on such an intervention places most of the burden for prevention on those most affected and least responsible for the underlying environmental causes of lead toxicity. Nutritional interventions, therefore, must never substitute for efforts to reduce lead exposure to safe levels. On the other hand, when used as an adjunct to environmental measures, some nutritional changes may prove to have benefits beyond any impact on lead toxicology. For example, studies have suggested benefits of higher ascorbic acid intake on blood pressure, blood lipid profiles, and respiratory symptoms.

What needs to be done to hasten the reduction of lead exposure, especially for the populations most affected? While existing efforts, such as screening and responding to lead-poisoned children, need to continue, it would seem reasonable to propose expanded activity on two fronts in particular.

First, efforts should be made to increase the testing and remediation of residential lead hazards from deteriorated paint and contaminated dust before children develop lead toxic effects. Interior dust lead measurements, available at relatively low cost, can now be used to help identify the most immediately hazardous dwellings, and interventions are available to substantially reduce residential lead exposure. The use of this relatively inexpensive test should be expanded, thus decreasing the reliance on elevated blood lead levels in children to identify hazardous home environments.

Second, additional research is needed regarding the sources, fate, and remediation of contaminated exterior dust and soil, which can have major effects on blood lead levels. Lead levels in some urban communities may be comparable to those found in communities contaminated by smelting and mining operations. Practical interventions and the resources to implement them in large urban areas are currently lacking.

Source: JAMA, Vol. 281, June 1999.

TEA CONSUMPTION AND THE SUPPRESSION OF ANGIOGENESIS

Drinking tea, especially green tea, has been associated with a lower incidence of human cancer. Several different hypotheses have been proposed to explain the mechanisms of cancer inhibition. A recent study investigated whether drinking green tea could suppress angiogenesis, a process of blood-vessel growth required for tumor growth and metastasis.

The study examined the effect of oral consumption by mice of green tea as the sole drinking fluid on the inhibition of corneal neovascularization stimulated by vascular endothelial growth factor (VEGF). The amount of green tea in the drinking water was 1.25% containing 708 µg ml-1 of epigallocatechin-3-gallate (EGCG) a component of green tea. The concentration of EGCG in the plasma was previously reported to be in the range of 0.1 - 0.3 µM, which is similar to levels in humans after drinking two or three cups of tea.

Compared with the control mice that drank water alone, drinking tea significantly prevented VEGF–induced corneal neovascularization. Blood-vessel length, clock-hours of corneal neovascularization and area of neovascularization in seven corneas from four mice in the tea-drinking group were inhibited by approximately 55, 35 and 70% respectively. Drinking green tea significantly prevents corneal neovascularization induced by one of the most potent angiogenic factors, VEGF. Because the growth of all solid tumors is dependent on angiogenesis, the finding of this study may explain why drinking green tea prevents the growth of a variety of different types of tumor.

Source: Nature, Vol. 398, April 1999.

Ascorbic Acid Intake and the Control of Lead Toxicity

Lead exposure is an important public health problem in many countries. Among children it is seen as a probable cause of low educational performance and among adults, work-related lead exposure has been targeted as an area of particular concern by public and occupational health authorities. Recently, some animal studies have suggested that orally administered ascorbic acid may chelate lead and decrease the risk of the toxic effects of the metal. However, results from several small-scale studies in humans have yielded inconclusive evidence of a beneficial effect of ascorbic acid on lead toxicity.

A recent study of the relationship of ascorbic acid to blood lead levels has used data previously collected in the Third National and Nutrition Examination Survey carried out between 1998 and 1994 that included data about serum ascorbic acid levels and blood lead levels in more than 19,000 Americans.

The principal finding of the study is that serum ascorbic acid level was inversely related to blood lead level among adults and youths enrolled in the survey. No significant relationship was observed, however, between dietary ascorbic acid intake and blood lead levels suggesting either that dietary estimates derived from the survey data were too imprecise to allow the detection of an association, or that elevated blood lead levels may increase the turnover of ascorbic acid levels.

However, prior evidence from animal studies is consistent with the hypothesis that ascorbic acid may lower blood lead levels. If a causal relationship is confirmed in human populations, higher intakes of ascorbic acid may have important public health implications for the prevention of lead toxicity.

Source: JAMA, Vol. 281, No. 24, 1999.

Blood Lead Levels and Dental Caries

Experiments have shown that dental caries rates are higher among lead-exposed animals, but this association has not been established in humans. A recent analysis was made, however, to examine the association between blood lead level and dental caries status using data collected in the United States in the Third National Health and Nutrition Examination Survey (NHANES III). This cross-sectional survey, conducted from 1988 to 1994, included personal household interviews and health examinations of approximately 40,000 persons aged 2 months and older. Results from the dental examination used in the survey for coronal caries have now been analyzed. Children aged 10 to 23 months only had a brief inspection for the presence of early childhood caries and were excluded from the analysis. A total of 24,901 individuals had both an oral examination and a blood lead assay. For the purposes of the present analysis they were divided into three groups viz. 2-5 year olds, 6-11 year olds, and those over 12. There were 3,547 subjects in the first group, 2,894 in the second, and 18,460 in the third.

The primary independent variable was environmental lead exposure. Blood specimens were collected during the examination component of the survey from examinees aged 1 year and older and lead levels were determined. Blood lead levels below the detection limit were assigned a value of 0.03 µmol/L. Lead levels were log transformed to normalize the distribution of blood lead levels.

Other potential independent associations with dental caries were analyzed. Demographic characteristics included age, sex, race, family poverty level, region of the country, educational level of head of household, and exposure to cigarette smoke in the home. Family poverty level was defined as the poverty income ratio (PIR), calculated as the total family income divided by the poverty threshold for the year of the interview. A PIR of 1 represents a family at 100% of the federal poverty level. As family income increases the PIR increases. Carbohydrate and calcium intakes from a 24-hour dietary recall interview were also included in the analysis. Use of oral health services was determined by time since the last visit to a dentist and how often person visited a dentist or dental hygienist.

There were statistically significant associations between log of blood lead level and caries status among all age groups.

The results of the present analysis suggest that environmental lead exposure may explain, at least in part, the disproportionately high rate of dental caries among disadvantaged children and adolescents. Without the lead exposure variable in the statistical model, the PIR shows that the odds of having a decayed, filled, or missing permanent tooth decrease as income level increases. Statistical adjustment for lead exposure reduced the strength of the association between income level and caries status. This suggests that the association between poverty and dental caries is partially explained by lead exposure.

The present analysis supports the hypothesis that environment lead exposure is a risk factor for dental caries. Nonetheless, a mechanistic role to explain differences in caries prevalence has not been clearly established for lead. In support of a causal role for lead in dental caries, there are compelling experimental data from well-controlled animal studies that support the biologic plausibility of the hypothesis. Still, to satisfy the criteria for causality, further prospective investigations will be needed to demonstrate that lead exposure precedes the development of caries in humans after adequate control of potential confounders and that these findings are consistent across different populations and with different study designs.

Source: JAMA, June 1999.

A Field Kit for Testing for Arsenic in Drinking Water

In a previous issue of the Newsletter (Vol. 8 No. 2, April 1998 issue) we reported on the seriousness of problem of arsenic contamination of drinking water in Bangladesh.

In an effort to find a sustainable mitigation procedure, the Asian Arsenic Network of Japan has developed a kit for determining the presence of arsenic in water through chemical reactions.

It is currently being trialled in Bangladesh as a method for large-scale, field-level arsenic testing by village-based community health workers.

The kit works by reducing the arsenate (As-V) in groundwater to arsenite (As-III) by potassium iodide and stannous chloride. The As-III is then reacted with zinc hydrochloric acid to produce arsenic gas. A color change from light yellow to reddish brown on bromide paper indicates the presence of arsenic in the water.

Forty community health workers in a sub district previously known to be arsenic-affected were trained to use the kit. They then tested water from all 11,954 hand-pumps in 156 villages. Results showed that water from 93% of the hand-pumps was contaminated. A subsample of the water samples simultaneously tested in a government laboratory using a spectrophotometer confirmed the field testing in 92% of the cases. The cost of the testing was less than 50 cents per water sample, which is only a fraction of what it costs in a laboratory. This mass testing at the field level also aroused enormous awareness among the villagers about the arsenic problem.

Source: Science, Vol. 284, June 1999.

ß-Carotene Supplementation and Increased Risk of Lung Cancer in Smokers

Chemoprevention trials have shown that ß-carotene either alone or in combination with vitamin A or vitamin E increases incidence and mortality from lung cancer in heavy smokers. This finding has caused some degree of surprise since epidemiological and animal studies on vitamin A and its analogies give support to the hypothesis that ß-carotene can indeed prevent cancer in humans.

In research aimed at explaining this apparent paradox, it was found that ß-carotene in rat lung produces a powerful booster effect on phase I carcinogen-bioactivating enzymes, including activators of polycyclic aromatic hydrocarbons (PAHs) and that this induction is associated with the generation of oxidative stress.

A highly significant increase was found in certain carcinogen-metabolizing enzymes, or CYPs, in the lungs of rats supplemented with high doses of ß-carotene.

In humans, correspondingly high levels of CYPs would predispose an individual to cancer risk from the widely bioactivated tobacco-smoke procarcinogens.

Moreover, many of these could act synergistically with ß-carotene as CYP inducers to impose a co-carcinogenic effect, particularly in genetically predisposed individuals who inherit the 'at risk' genotypes of xenobiotic metabolizing enzymes.

It has thus been postulated that the co-carcinogenic properties of carotene and its abilities to generate oxidative stress account for the paradoxical effect of increased morbidity and mortality observed in the clinical chemoprevention trials.

Source: Nature, Vol. 398, April 1999.

ANNOUNCEMENT

MASTERS AND DOCTORAL DEGREE PROGRAMS IN ENVIRONMENTAL TOXICOLOGY TECHNOLOGY AND MANAGEMENT (ETT & M)

This joint degree program is offered by Asian Institute of Technology (AIT), Chulabhorn Research Institute (CRI) and Mahidol University (MU).

The design of the program is based on the recognition that in developing countries there is a shortage of qualified personnel for policy/decision making, management and research on toxic chemicals and hazardous waste treatment.

Master's degree program Students can either complete a program of coursework (55 credits) and independent research study (12 credits), or a program of coursework (minimum 30 credits) and a research thesis.

Entry to the five-term Master's degree program is normally in January.

Doctoral program Students are required to complete a minimum of 18 credits of coursework of which not more than 6 credits are earned from special studies. Entry timing is flexible.

Curriculum The curriculum consists of three types of course: prerequisite, core and elective. The courses include a combination of toxicology and related health sciences, biotechnology and environmental engineering, industrial toxicology, hazardous waste treatment and environmental management.

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Notice of Forthcoming Workshops and Meetings

The following program of satellite workshops/meetings has been organized to coincide with the Fourth Princess Chulabhorn International Science Congress.

This program includes:

1. *SETAC Asia/Pacific Metals in the Environment Workshop*
   3 December 1999
   Registration fee US$50

The workshop is designed to provide practical information on the currently accepted international practices for sampling, analysing and assessing the ecotoxicology of heavy metals in waters, sediments and soil samples for compliance with appropriate environmental quality guidelines. It will include presentations by key international experts in metal ecotoxicology and chemistry and will provide ample opportunity for discussion on methodology and standards appropriate for developing countries.

2. *IOCD International Symposium on Chemistry and Pharmacology of Asian Plants and Validation of Phytopharmaceuticals*
   1-2 December 1999
   No additional registration fee

An update on different aspects of research concerning the phytochemistry and pharmacology of Asian plants will be presented. Special lectures are planned on the current state and future trends of phytomedicine in Asia and elsewhere in the world. The symposium will feature 2 – 3 plenary lectures from Asian or overseas speakers working on plants of Asia. One half day will be devoted to the validation of phytopharmaceuticals, with special emphasis on quality control, standardisation, safety and efficacy, including clinical trials. In addition, there will be contributions in the forms of oral presentations and poster sessions.

3. *ICEIT Training Workshop on Risk Assessment and Management in Biotechnology*
   3-9 December 1999
   Registration fee US$400

For further information please contact the CRI web site http://www.cri.or.th

To register for any part of the program please contact:

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