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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".

Chulabhorn Research Institute Hosts the Second International Conference on Environmental and Industrial Toxicology: Research and Its Application

December 9-13, 1996

The Second International Conference on Environmental and Industrial Toxicology (ICEIT II) was organized by the Chulabhorn Research Institute as part of the institute's international education and training program in environmental and industrial toxicology and was held in Bangkok from 9 to 13 December 1996. The conference attracted 319 delegates from 29 countries. The scientific program of the conference reflected the essentially multidisciplinary nature of toxicology and highlighted the following areas:

- Molecular Carcinogenesis and Epidemiology
- New Approaches to Detecting Environmental Toxicants
- Mechanisms of Epigenetic Toxicology including Oxidative Stress, Signal Transduction and Cell to Cell Communication
- Applied Environmental Toxicology
- Chemical Prevention of Cancer
- Biomarkers for Exposure and Susceptibility

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Chulabhorn Research Institute Hosts the Second International Conference on Environmental and Industrial Toxicology: Research and Its Application

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- Hazardous Waste Management
- Evaluation of Toxicity and Assessment of Risks to Human Health

The five day conference featured four plenary lectures, eight symposia, four free communication sessions and two round-table discussions.

In the report delivered at the opening of the conference, the Secretary General of the conference and Vice-President for Research of the Chulabhorn Research Institute emphasized that recent advances and major breakthroughs in disciplines such as biochemistry, molecular biology and toxicology have been achieved as a result of concerted efforts in basic research.

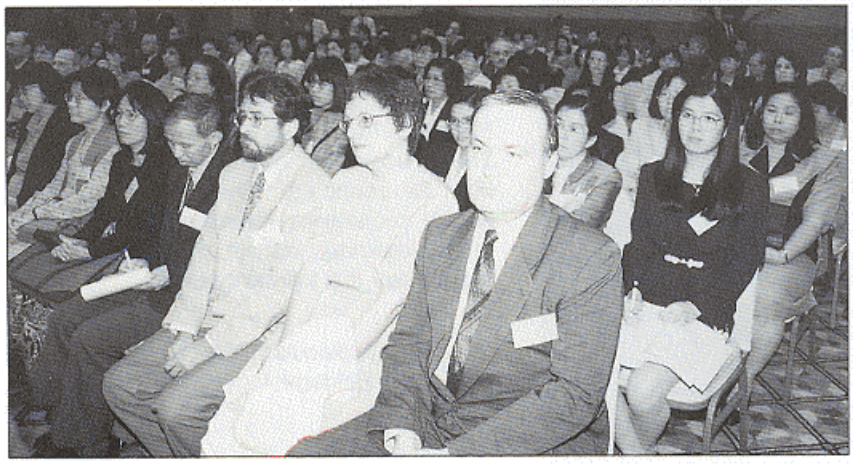
There is now a stronger foundation for applied research and for policy and regulatory decision-making to mitigate the adverse impacts of chemicals on the environment and on human health. The importance and the need for scientific research which is one of the key elements in national development cannot be overemphasized.

Reflecting the global importance of environmental and industrial toxicology, the conference featured contributions from leading scientists, government policy/decision makers, and industrial personnel from 29 nations. Within this context of global concern, the conference also addressed local and regional problems, particularly those of developing countries, which are often overlooked by major research establishments in developed countries, but which deserve priority support.

In organizing this Second International Conference, the Chulabhorn Research Institute firmly endorsed its commitment to the promotion and support of research and education in environmental and industrial toxicology locally, regionally and internationally.

ROUND-TABLE DISCUSSION

Private/Public Sector Cooperation: *Role of Toxicology in Sustainable Development*
Moderator: *Dr. Nay Htun – United Nations Development Programme (UNDP)*
Panelists: *Dr. Chokchai Aksaranan – The Federation of Thai Industries, Dr. Michel Mercier-International Programme on Chemical Safety (IPCS), Khunying Thongtip Rattanarat-The Petroleum Institute of Thailand, Dr. Somrat Yindepit-Esso (Thailand) Public Co., Ltd.*



Second Princess Chulabhorn Distinguished Lecture Series: Cancer – from Molecular Biology to Treatment

December 2, 1996

Professor Frederick F. Becker, Dr. Richard D. Klausner, Professor David Baltimore

The three lectures in the program of the Second Princess Chulabhorn Distinguished Lecture Series were delivered to an invited audience of Thai scientists at the Dusit Thani Hotel in Bangkok on 2 December 1996.

The three eminent scientists invited to deliver the lectures on this occasion were *Professor David Baltimore,* Nobel Laureate and Professor of Molecular Biology and Immunology at the Massachusetts Institute of Technology, U.S.A.; *Professor Frederick F. Becker,* Vice-President for Research at the University of Texas, M.D. Anderson Cancer Center, U.S.A.; and *Dr. Richard D. Klausner,* Director of the National Cancer Institute, U.S.A.

The theme of cancer for the Second Distinguished Lecture Series was chosen by Her Royal Highness Princess Chulabhorn because of the Chulabhorn Research Institute's long-standing research interests in cancer. Moreover, CRI is now in the process of establishing a Cancer Centre to undertake treatment and provide information to the public about cancer. The establishment of the Centre will augment existing resources in Thailand in areas of research and treatment.

The Second Princess Chulabhorn Distinguished Lecture Series attracted an audience of Thai scientists and medical personnel in all fields relating to cancer and to the treatment of cancer patients.

FEATURE

One highly successful feature of the Second ICEIT Conference was the display of 130 poster sessions that attracted much attention during the five days of the conference. The high quality of the visual display of research findings was complemented by the informative summaries provided of ongoing research in the areas of Heavy Metals, Pesticides, Mechanisms of Toxicity, Cancer Risks by Environmental Factors, Detection and Detoxification of Chemicals in the Environment, Risk Assessment and Risk Management.

The Editor took this opportunity to speak with presenters of research in areas that form the subject of articles regularly featured in this Newsletter.

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Marjan Najafi of the Division of Environmental Health and Sanitation of the Ministry of Health, Palau, presented research findings on *Childhood Lead* Poisoning in the Republic of Palau.

The Palau Lead Poisoning Prevention Program is a Rural Health Outreach initiative based in Koror, Republic of Palau. Palau, previously a Trust Territory of the US, is a small island nation of approximately 17,000 people located in the Western Pacific. The country is designated as rural and a medically underserved area. The Ministry of Health, concerned about the potential for lead poisoning in the Palauan community, initiated a collaborative effort by creating a consortium of government and semi-government agencies to determine the prevalence of lead poisoning in all sixteen states of the Republic. The target groups are children aged 0-72 months and prenatal patients. The consortium organizations offer services that include blood testing, water testing, pottery testing, and community awareness. Outreach trips are an important component of the program as they ensure that rural populations are equally informed on lead poisoning and its prevention. Approximately 5% of children have been found to have elevated blood lead levels. Determining the sources of lead and preventing exposure will result in improved health outcomes for not only the children but all residents of Palau.

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Tippawan Prapamontol of the Research Institute for Health Sciences, Faculty of Medicine, Chiang Mai University, Thailand, presented a study of the *Health Status of Chiang Mai Traffic Policemen.*

Air pollution in Chiang Mai City in recent years has been a cause of public health concern. In April 1995 we launched a study to examine the health of Chiang Mai traffic policemen. One hundred and seventy two traffic policemen were enrolled. Mean±SD and range of age were 35.2±5.6 and 23-55 years old, respectively. Tests of blood lead, liver and kidney function, complete blood count, pulmonary function, chest x-rays and also hearing function were performed. Blood lead levels in median, mean±SD and range were 8.1, 8.3±3.4, 2.3-32.9 µg/dl, respectively. Of 172 policemen, 36 cases (20.9%) had blood lead level ≥10 µg/dl with one case having lead level of 32.9 µg/dl. Of 138 policemen who had pulmonary function tests, 7 cases (5.1%) had small airways disease and 4 of 7 cases never smoked. We concluded that the cause of these 4 cases with small airways disease was probably from breathing in mineral dusts. Other problems included 13.0% with abnormal serum glutamic oxalacetic transaminase (SGOT), 4.1% with abnormal serum glutamic pyruvic tramsaminase (SGPT), 1.2 % with abnormal serum creatinine and 4.1% with anemic blood. Since it was the first time that they had a hearing function test, we obtained the baseline data for further follow-up study. 9.4% had lost their hearing capacity in either left or right ears. In order to assess their health risk from breathing of air pollutants, we measured airborne lead and dust that deposited on the mask filters they used. We estimated that,

without using masks, Chiang Mai traffic policemen could take up lead and dust via breathing of about 0.17 µg and 0.66 mg per hour dry season and 0.12 µg and 0.53 mg per hour during the rainy season, respectively. The present study showed that airborne lead and dust pollution in Chiang Mai City poses a health problem for Chiang Mai traffic policemen.

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Ravi Gooneratne of the Animal and Veterinary Sciences Group, Lincoln University, Canterbury, New Zealand, presented a study on *Cytochrome P-450 Enzyme Activities in the Possum, Rat, Sheep, Rabbit and Chicken.*

Possum is a pest in New Zealand. This study was conducted to probe for potential biochemical weaknesses that may be exploited for designing a possum-specific toxin. Liver microsomal enzyme content and kinetics of *in-vitro* biotransformation reactions (aromatic and aliphatic hydroxylations, O-dealkylation, N-dealkylation) in the possum were quantified and compared with the values for the chicken, rabbit, rat, and sheep. There was a significant ($P<0.05$) species variation in the liver microsomal enzyme content. All mammals including the possum had higher levels than the chicken. The chicken had the highest phase I biotransformation activity (V_{max}) for almost all xenobiotics tested. Among mammals, P-450 V_{max} values in the possum were similar or tended to be higher than in the rabbit, rat or sheep. The K_m values varied significantly ($P<0.05$) between species. The K_m for 7-hydroxylation of coumarin was highest in the rat. In comparison with other species, the possum tended to have a lower K_m for aromatic hydroxylation of aniline, N-demethylation of N, N-dimethyl aniline and N-dimethyl aniline, but a higher K_m for 7-hydroxylation of coumarin, and O-demethylation of acetaphenetidin and 7-methoxycoumarin. Plasma pharmacokinetics of antipyrine ($t½$ = 1.25±0.4h; C_{max} = 419±111 µg/l; AUC = 81.3±25.2h) in the possum was similar to the values published for other species. It is concluded that phase I biotransformation of xenobiotics in the possum is similar to or more efficient than in other animals tested.

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Chantana Padungtod of the Occupational Health Program, Harvard School of Public Health, Boston, U.S.A., gave a presentation on an epidemiological approach to *Occupational Exposure to Pesticides and Reproductive Toxicity.*

Based on the hypothesis that pesticides disrupt reproductive hormones causing subsequent abnormal spermatogenesis, we conducted a series of epidemiological studies to assess reproductive toxicity of pesticides. In 1994, a cross-sectional pilot study was conducted among 60 Chinese farmers. Classified by qualitative exposure to pesticides, analysis revealed a significant increase in the serum level of FSH, LH and a significant decrease in sperm density among the exposed. In February 1996, a cross-sectional study was conducted to establish baseline sperm parameters of normal Chinese men. Starting in April 1996, a one-year prospective study has been initiated to investigate the occupational exposure to pesticides among workers in an organophosphate pesticide manufacturing factory. The specific adverse outcomes, which will be assessed quarterly, are elevation of FSH and LH, reduction of testosterone, decreased sperm count, decreased normal motility, decreased normal morphology and increased mutation. Exposure to pesticides is estimated over one full shift by means of personal sampling: pump and skin patch together with the measurement of pesticide level in end-of-shift blood and its metabolite in 24-hour urine. Measurement of red blood cell acetylcholine esterase and paraoxonase genotyping are also included since the latter determines individual genetic susceptibility to pesticide toxicity. All subjects donate one blood sample and three first void urine samples for reproductive hormone analysis. Semen analysis consists of two stages; first, immediate manual analysis for such parameters as count and liquefaction time; second, CASA videotape and semen smears are prepared for standardized analysis of morphology, motility and mutation. With careful study design, objective measurement and integration of toxicological knowledge, epidemiological study can serve as a powerful tool to better understand human toxicology.

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Ali R. Shalaby of the Food Technology and Dairy Science Department, National Research Centre, Dokki, Cairo, Egypt reported the *Significance of Biogenic Amines to Food Safety and Human Health.*

Biogenic amines are natural antinutrition factors important from a hygienic point of view, since they have been implicated as the causative agents in a number of food poisoning episodes, and they are able to initiate various pharmacological reactions. Histamine, putrescine, cadaverine, tyramine, tryptamine, ß-phenylethylamine, spermine, and spermidine are considered to be the most important biogenic amines occurring in foods. These

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amines are designated as biogenic because they are formed by the action of living organisms. Histamine, has been implicated as the causative agent in several outbreaks of food poisoning, while tyramine and ß-phenylethylamine, have been proposed as the initiators of hypertensive crisis. The toxicity of biogenic amines to chicks in terms of loss of weight and mortality was also reported. The toxicity of histamine appeared to be enhanced by the presence of other amines such as cadaverine, putrescine, and tyramine. Biogenic amines may, also, be considered as carcinogens because of their ability to react with nitrites to form potentially carcinogenic nitrosamines. The biogenic amines content of various foods and feed has been widely studied and found in cheese, fish and meat products, eggs and mushrooms. Food substances that have been prepared by a fermentative process, or have been exposed to microbial contamination during aging or storage, are likely to contain amines. Alcoholic beverages such as beers can contain biogenic amines, as can some other fermented foods such as sauerkraut and soy bean products. Amines were also considered as endogenous to plant substances that is commonly used for food where some fruits and vegetables were found to contain high concentrations of various amines.

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The above reports reflect the wide range of topics covered by the poster displays that provided a forum for much of the informal discussion and exchange of views amongst scientists and researchers who attended the five-day ICEIT II Conference.

Pesticides and Dioxin Body Burden

***A** research study co-ordinated by the Department of Preventive Medicine at the State University of New York has been undertaken to determine dioxin levels in human tissue samples of populations exposed to large amounts of the powerful pesticide sodium pentachlorophenol salt (Na-PCP). Dioxins, a class of toxic persistent compounds, are found as impurities in commercial Na-PCP products. These contaminants are released into the environment and significantly contribute to human exposure.*

Since the 1960s large amounts of Na-PCP have been sprayed over vast areas of central China to control schistozomiasis, a parasitic disease that had reached epidemic proportions. The official government policy for controlling schistosomiasis has been the elimination of the carrier snails by spraying Na-PCP over vast agricultural areas. This action was undertaken as an important preventive measure to reduce the number of persons exposed to schistosomiasis. Na-PCP, which is contaminated with the higher chlorinated dioxins and closely related dibenzofurans, was used since it is a powerful and relatively inexpensive pesticide. However, its adverse health effects may outweigh its benefit by causing dioxin contamination in the environment, and the Chinese government has now implemented plans to replace Na-PCP with a new molluscicide. In the meantime, dioxin contamination and the effects on human health of pentachlorophenol and dioxin exposure in schistosomiasis regions are being investigated. In the present study, a region in Jiangxi province was selected for analysis because it is a typical problem area. Agricultural workers living in sprayed areas traditionally wear open sandals or walk barefoot when working in the fields. They eat food grown in contaminated soil and consume water from contaminated streams or lakes.

Individual human whole-blood and breast-milk samples from the schistosomiasis area where Na-PCP had been used for more than 30 years were collected and then pooled for analysis.

Also, general population blood and milk samples were collected from control regions in the same province where no Na-PCP was used.

Results show that dioxin levels in blood and breast-milk samples from residents who live or work in sprayed areas are about two or three times higher than those from non-sprayed areas. For the most part, the levels of dibenzofurans from samples collected from sprayed and non-sprayed areas are similar. Concern in China about dioxin contamination resulted in the plan to replace Na-PCP as a molluscicide. Further study of the food chain and individual blood analyses would lead to a better characterization of environmental contamination from Na-PCP.

Adapted from Journal of Occupational and Environmental Medicine, Vol. 38, No. 9, Sept. 1996.

ASSESSING THE POTENTIAL FOR EXPOSURE TO BENOMYL AMONG AGRICULTURAL WORKERS

Benomyl is one of the most widely used members of a family of fungicides known as benzimidazoles. It is used on more that 70 crops including cotton, fruits, sugar, soybeans and tobacco, and is also widely used in the ornamental plant industry.

With its use, there is potential for dermal, respiratory, and oral exposure by agricultural workers, which may occur during the application of the fungicide, or the post application tending of crops and plants.

Animal experiments have shown that benomyl is well absorbed after oral and inhalation exposure, but less well absorbed after dermal exposure. There is no Occupational and Safety and Health Administration (OSHA) permissible exposure limit (PEL) specifically for benomyl; however, the OSHA PEL of 15,000 $\mu g/m^3$ for total nuisance dust is used in the United States for enforcement purposes.

During the 26 years in which benomyl has been used commercially, localized effects from handling benomyl fungicide products have been reported. Effects most commonly noted on exposed skin of the hands and forearms, and eye irritation may occur when benomyl is used in enclosed areas. Although there is no evidence of carcinogenesis in humans as a result of benomyl exposure, in animal studies, benomyl caused a decrease in testis and epididymis weight of male rats and at high doses caused hypospermatogenesis. Benomyl has been shown to cause an increase of hepatocellular tumors in one strain of laboratory mice; however, this effect was not found in rats or other strains of mice.

In a study conducted in 1994 by the U.S. National Institute for Occupational Safety and Health

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HEALTH EFFECTS OF AIR POLLUTION

In the early 1950s the major source of air pollution was the domestic and industrial burning of fossil fuels. Although coal fired power stations continue to emit sulfur dioxide at the same general rate, the ambient level of this pollutant has fallen in many countries and at present it is the effect of photochemical pollution on health that attracts greater concern. Photochemical pollution arises from a mixture of nitrogen oxides, hydrocarbons and small particles, the major source of which are vehicle exhausts. Diesel engines, notably trucks, buses and taxis, are the main source of particles, thus countries with the highest number of diesel engines have the largest problem with particle pollution.

Lead and carbon monoxide are also important pollutants derived from vehicle exhausts, while volatile organic compounds, apart from acting as a substrate for ozone formation, also carry carcinogenic potential. For a detrimental health effect to occur, many factors can be involved. The dose and exposure time of the pollutant is important, and also the existence of "co-exposures" such as viral infection, exercise and allergen exposure. In addition, individual host characteristics may play a part, as patients with asthma and pre-existing lung and heart disease are more susceptible to the effects of air pollution. A series of studies carried out recently in the United States shows that hospital admissions and mortality are positively associated with higher levels of ambient particle exposure in various American cities.

Lead exposure has long been associated with a reduced IQ in children and this is usually accepted as a causal association. This has led to the introduction of unleaded fuels in many countries. However, there is evidence that the major contribution to blood lead comes from diet rather than inhalation. Very high levels of carbon monoxide may cause an increase in symptoms of patients with severe coronary heart disease, but no panel studies have been performed in patients with coronary heart disease which might confirm whether this is likely to be a real effect.

The fact that an increased level of a pollutant can be associated with a health effect does not, however, necessarily mean that the association is causal. The current belief is that particles do have an effect on lung and cardiac health, although only to a small degree and only affecting those who already have a severe disease.

Adapted from Chemistry and Industry, No. 21, 4 Nov. 1996.

Occupational Exposure to Aromatic Amines and Incidence of Bladder Cancer

A study reported in the Journal of the National Cancer Institute was undertaken to characterize current exposure to 0-toluidine and aniline at a chemical plant in Niagara Falls, New York, where an excess risk of bladder cancer had been observed.

This excess was primarily confined to 708 workers who had been employed in the rubber chemicals manufacturing area of the plant, where the aromatic amines aniline and *0*-toluidine have historically been used.

An environmental and biological monitoring survey was conducted to evaluate current exposures to aniline and *0*-toluidine in the rubber chemicals department. A total of 73 workers, including 46 of 64 exposed workers who were employed in this department and had the potential for exposure to aniline and *0*-toluidine and 27 of 52 unexposed workers in other departments where aniline and *0*-toluidine were not used or produced, had data available for both aniline and *0*-toluidine and Hb adducts; 28 of the workers in the former group had personal air-sampling data. Personal air sample measurements showed that airborne concentrations of aniline and *0*-toluidine were well within the Occupational Safety and Health Administration (OSHA) limits in the workplace. Urinary aniline and *0*-toluidine levels, however, were substantially higher among exposed workers than among unexposed control subjects.

The adduct data collected in the study suggest that, among current workers, *0*-toluidine exposure substantially exceeds aniline exposure and that 4-aminobiphenyl (4-ABP) exposure, if it occurs at all, is not widespread. These data support the conclusion that occupational exposure to *0*-toluidine is the most likely causal agent of the bladder cancer excess observed among workers in the rubber chemicals department of the plant under study, although exposures to aniline and 4-ABP cannot be ruled out.

Source: Journal of the National Cancer Institute, Vol. 88, No. 15, August 7, 1996.

ASSESSING THE POTENTIAL FOR EXPOSURE TO BENOMYL AMONG AGRICULTURAL WORKERS

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(NIOSH) to assess the potential for worker exposure to benomyl in commercial nurseries in Florida, worker inhalation and dermal exposure to benomyl and its known degradation products carbendazim, n-butyl isocyanate (BIC), and butyl amine were assessed. In conjunction with the environmental exposure assessment, a new noninvasive method of biological monitoring of benomyl exposure via the urinary metabolite methyl-5-hydroxy-2-benzimidazole carbamate (5-HBC) was conducted.

This new method has potential applications in many agricultural settings worldwide.

Source: Journal of Occupational and Environmental Medicine, Vol. 38, No. 8, August 1996.

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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