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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".

The Seventh Princess Chulabhorn International Science Congress
Cancer: From Basic Research to Cure
Shangri-La Hotel, Bangkok, Thailand
November 29 – December 3, 2012

The congress was held to commemorate the seventh cycle (84 years) of the birth of His Majesty King Bhumibol Adulyadej and also the eightieth birthday of Her Majesty Queen Sirikit, an auspicious occasion and a national celebration in which scientists from countries throughout the world were invited to share. The Congress welcomed a total of 97 invited speakers from 19 countries and over 700 participants from 32 countries.

The theme of the seventh Princess Chulabhorn International Science Congress reflects the concern at the increasing incidence of deaths worldwide from cancer, which has become an urgent global issue affecting everyone, either directly or indirectly.

It has been predicted that over the next 10 years as many as 84 million

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The Seventh Princess Chulabhorn International Science Congress
Cancer: From Basic Research to Cure

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people will die of cancer and more than 70% of them in the developing world. There is therefore an urgent need for international collaboration in all areas of basic, translational and clinical research to combat this deadly disease. Professor Dr. Her Royal Highness Princess Chulabhorn Mahidol thus deemed it important to organize this congress as a forum for presenting the latest development in all areas of cancer research including cancer etiology and molecular mechanisms, strategies for cancer prevention, early detection and diagnosis as well as therapeutic interventions, all of which are crucial in our battle to overcome cancer.

In her keynote address in the opening ceremony of the congress, Her Royal Highness Princess Chulabhorn emphasized that the environment and human lifestyles are major risk factors for cancer, with more than 70% of all cancer cases caused by environmental and lifestyle factors that may be preventable.

This was one of the main themes running through many of the presentations in the scientific program of the congress. The program, which spanned 5 days, featured a Nobel Laureate Lecture entitled "Cancer: The Genomic Era Arrives", given by John Michael Bishop from the U.S.A., and Plenary Lectures included "Molecular Epidemiology: Cancer Etiology and Prevention" by Christopher P. Wild (IARC, France); "Environmental and Occupational Determinants of Cancer: Interventions for Primary Prevention" by Maria P. Neira (WHO, Geneva); "Recognition of 'Foreign' Antigens by the immune System" by Ian A. Wilson (U.S.A.); "Inflammation

and Cancer: Interweaving MicroRNA, Free Radicals, Cytokine and p53 Pathways" by Curtis C. Harris (U.S.A.); "Understanding Early Life Exposures in Childhood and Adult Cancers" by William A. Suk (U.S.A.); "New Medicines for Cancer Arising from Surprising New Biology" by Paul Schimmel (U.S.A.); "The Role Of Obesity, Physical Activity and Metabolic Factors in Cancer Aetiology" by Elio Riboli (U.K.); and "Molecular Targets for Cancer Chemoprevention" by Vernon E. Steele (U.S.A.). In addition, there were also 12 Symposia and a Closing Session on Challenges and Opportunities: Cancer Treatment from Bench to Bedside. In all there were 207 poster presentations displaying research conducted by congress participants.

The program of the closing ceremony of the congress, in addition to the closing lecture entitled "Future Practice of Medicine" delivered by Michael Rosenblatt from the U.S.A., featured the signing of a landmark collaboration agreement between CRI and the Center for Cancer Research, National Cancer Institute, U.S.A. The signing ceremony was followed by the presentation of the Princess Chulabhorn Gold Medal Award to 3 distinguished recipients: Dr. John H. Duffus from the U.K., Professor Minoru Isobe from Japan, and Professor Gerald N. Wogan from U.S.A.

In her closing speech, Her Royal Highness Princess Chulabhorn emphasized that in order to address a complex disease like cancer, there is a need to pool resources in order to optimize opportunities for developments in prevention, diagnosis and treatment, through cooperation among research scientists, physicians, public health personnel and policy makers. The presentations, discussions and meetings conducted during the congress indicated how breakthroughs in cancer therapy might be achieved. Their realization will bring immediate benefits to sufferers in countries throughout the world. Theme for the next Princess Chulabhorn International Science Congress to be held in 2016, was announced: "**Environmental Health: Interlinkages among the Environment, Chemicals and Infectious Agents**".

The Princess Chulabhorn Gold Medal Award

Professor Dr. Her Royal Highness Princess Chulabhorn established the **"Princess Chulabhorn Gold Medal Award"** to honor world-renowned individuals or organizations whose work has received international acclaim. Importantly, recipients shall have provided important and sustained support to the advancement of science in developing countries. In 2012, the award presentation was held at the closing ceremony of the Seventh Princess Chulabhorn International Science Congress.

Gold Medal Awardees (in alphabetical order):

Dr. John H. Duffus, Director of the Edinburgh Centre for Toxicology, U.K.

Dr. Duffus has had a long and distinguished career in environmental toxicology, both in academics and research, as well as in the role of advisor or consultant to national and international organizations, e.g. the publication of his pioneering textbook on "Environmental Toxicology" led to an invitation from the WHO Regional Office for Europe to become their main consultant on Manpower Development for Chemical Safety under the International Programme on Chemical Safety. During that time, he prepared a strategy for developing courses and curricula in toxicology, and organized short international courses in toxicology and risk assessment in various different countries, including Thailand. Dr. Duffus has authored or contributed significantly to more than 200 major publications, and has elected a Titular Member of the Commission on Toxicology of the International Union of Pure and Applied Chemistry; a subsequent Chair of the Commission; a Chair of the IUPAC Working Party that prepared the IUPAC Glossary for Chemists of Terms Used in Toxicology; a member of the U.K. Royal Society of Chemistry Environment, Health and Safety Committee; a founding member of the Royal Society of Chemistry Toxicology Group; and worked with the U.S. Society of Toxicology in the production of the Internet-based toxicology course, ToxLearn.

Dr. Duffus' significant contributions to training programs organized by CRI has had an extensive and lasting impact on human resources development and sustainable development in environmental toxicology in Thailand and South East Asia.

Professor Minoru Isobe, Emeritus Professor of Nagoya University and Chair Professor, National TsingHua University, Taiwan

Professor Isobe is recognized worldwide as a leading authority in Organic Chemistry, in particular Organic Synthesis, as well as Natural Products Chemistry and Bioorganic Chemistry. He is most notable in the fields of total synthesis with stereo chemical control of very complex natural products and bioorganic chemistry of bioluminescence, marine toxins, insect hormones, ion selective ionophore, and chemical biology of molecular interaction between natural products and target proteins. Professor Isobe is the author of over 300 original research articles and more than 80 review articles and books, and has long been involved with the International Union of Pure and Applied Chemistry, including as IUPAC Division President of Organic and Biomolecular Chemistry, and IUPAC Task Group Chair of a project entitled, "Strategic Planning for a new East Asian Network for Organic Chemistry". He has received many awards in recognition of his work, including the Medal with Purple Ribbon from the Emperor of Japan.

Professor Isobe has made many outstanding contributions to human resource development in the field of chemistry in Thailand, including as initiator and founding member of the very successful Asian Core Program: Cutting Edge Organic Chemistry in Asia, as well as visiting professor at the Chulabhorn Graduate Institute.

Professor Gerald N. Wogan, Emeritus Professor of Toxicology and Emeritus Professor, Department of Chemistry, Massachusetts Institute of Technology, U.S.A.

Professor Wogan's seminal contribution to science and human health is the development of a new paradigm for demonstrating the impact of an environmental contaminant on human health, the ultimate target being the prevention of the toxic effect in a human population. With his longtime collaborator, Dr. George Buchi, he was able to isolate, purify and determine the structure of aflatoxin, and subsequent studies on metabolism and carcinogenicity allowed the characterization of the structure of DNA adducts, which could be used as biomarkers of exposure. These studies led to the discovery that aflatoxin was a major cause of liver cancer in Asia and Africa, and this paradigm for aflatoxin became widely adopted as the model for conducting human epidemiology studies on environmental toxins. Professor Wogan was elected to the U.S. National Academy of Sciences, and is the author of over 200 key scientific research papers. He has received the General Motors Cancer Research Foundation Mott Prize, the Society of Toxicology Lifetime Achievement Award, the Chemical Industry of Toxicology Founders Award, the Princess Takamatsu Cancer Research Fund Award of Merit, as well as the Society of Toxicology Distinguished Lifetime Toxicology Scholar Award.

Professor Wogan is a greatly revered advisor to CRI, with his first contribution to the development of research in Thailand being the MIT-Thai program, which was founded to address the health problem of liver cancer that affected much of the developing world. He has also been instrumental in making it possible for Thai graduate students to receive research training at MIT, Johns Hopkins or Harvard University laboratories as part of their post-graduate education.

Collaboration on Liver Cancer Research between the Chulabhorn Research Institute and the Center for Cancer Research, US National Cancer Institute

Shangri-La Hotel, Bangkok, Thailand, December 3, 2012

Professor Dr. Her Royal Highness Princess Chulabhorn Mahidol, President of CRI, signed a landmark agreement for collaboration on liver cancer research with the Center for Cancer Research of the US National Cancer Institute (CCR/NCI) at the closing ceremony of the 7th Princess Chulabhorn International Science Congress. The project entitled, "Thailand's Initiative in Genomics and Expression Research for Liver Cancer (TIGER-LC)" is a major research collaboration involving CRI, the Chulabhorn Hospital, Khon Kaen University's Faculty of Medicine, Chiang Mai University's Faculty of Medicine, Thailand's National Cancer Institute, and the US National Cancer Institute.

This is a timely and highly important endeavor, as liver cancer is the third most deadly and fifth most common cancer worldwide. In Thailand, liver cancer represents the primary cause of cancer-related deaths. While hepatocellular carcinoma is the most frequent primary cancer of the liver in the world, with rising incidence in western countries, the incidence of cholangiocarcinoma, a bile-duct-related cancer, is prevalent in the northeast of Thailand.

Research laboratories at the CCR and CRI are interested in identifying biomarkers that may be useful towards the elucidation of the molecular mechanism(s) underlying liver cancer development. Under the agreement, CCR/NCI and CRI will test the primary hypothesis that certain genomic factors modify liver cancer susceptibility.

The proposed study, which is designed to be exploratory and hypothesis-generating, will have the added benefit of creating a large collection of tissues and biological samples obtained from persons afflicted with liver cancer. The collection, which will include serum and urine samples, as well as frozen tumor specimens from pre-therapy resection when applicable, is required for biomarker discovery and gene expression analysis. Additionally, if certain genes are found to be associated with cancer risk, this tissue resource will be used to further validate biomarker discovery.

From left to right: Prof. Dr. HRH Princess Chulabhorn (CRI), Dr. Robert H. Wiltrout (CCR/NCI)

The agreement is a prime example of the kind of national and international collaboration that is of great importance in cancer research.

Association of High Levels of Urban Vehicle Emissions and Allergic Respiratory Diseases

High levels of urban vehicle emissions are associated with increasing incidence of allergic respiratory diseases. Diesel exhaust particles (DEPs), the major pollutants derived from vehicular traffic, induce a variety of cardiovascular and respiratory diseases, which lead to significant morbidity and mortality in susceptible populations. DEP exposure is associated with asthma, and might exacerbate allergic lung inflammation and induce functional lung changes. DEP exposure induces cytotoxic and pro-inflammatory responses, and significantly alters cytokine production.

Airway epithelial cells represent the first contact point for inhaled substances. Airway epithelial cells form a physical barrier and protect the lung against pathogens and particulates inhaled from the environment. Secretory and ciliated cells create a moving mucus layer that traps and efficiently removes most inhaled particulates that settle out of each inhaled breath, and epithelial cells can trigger additional innate host defense processes.

Small airway epithelial cells (SAECs) reside in the lower respiratory tract where the earliest pathophysiologic pro-inflammatory changes associated with asthma, chronic obstructive pulmonary disease and cystic fibrosis occur. DEP exposure leads to an inflammatory response via upregulation of the receptor for advanced glycation end-products (RAGE) in both primary cells and immortalized alveolar carcinoma cell lines. Upregulation of RAGE induces a pro-inflammatory cascade, but other mechanisms are implicated, and the biophysical effects of DEP on epithelial cells, even those associated with RAGE expression remain largely unexplored.

In this study, confocal Raman spectroscopy, atomic force microscope (AFM) and multiplex ELISA were applied to analyze the biophysical responses (biomechanics and biospectroscopy) of normal human primary small airway epithelial cells (SAECs) and human lung carcinoma epithelial A549 cells to *in vitro* short term DEP exposure (up to 2 h). Raman spectroscopy allows the study of living cells under physiological conditions, without labels and fixation. Atomic force microscopy (AFM) has demonstrated intrinsic links between clinical human diseases and cellular biomechanics.

The study successfully measured quantitative effects of short term DEP exposure on normal human lung SAEC and human lung cancer-derived A549 cells using confocal Raman spectroscopy and AFM and found correlations with several key inflammatory markers. Raman spectroscopy and principal components analysis of spectra produced clustered data that easily distinguished between cell types and treatments. Tentative assignments

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TRACE ELEMENTS IN SELECTED FOODS AND DIETARY INTAKE BY YOUNG CHILDREN IN THAILAND

Currently, increasing demand for food safety has stimulated research regarding the risk associated with consumption of food contaminated with toxic elements and pesticides. Intensive food production to supply a rapidly increasing population also requires additional nutrients applied to plants and animals. Some elements can be widely spread in the environment and be taken up and accumulated in agricultural products through the application of fertilizers or supplements. Some are necessary nutrients for growth and function of plants. These elements include iron (Fe), zinc (Zn), copper (Cu), chromium (Cr), manganese (Mn) and selenium (Se). On the other hand, some elements such as cadmium (Cd), arsenic (As), lead (Pb) and mercury (Hg) are toxic and can contaminate the human food chain. Application of commercial fertilizers, manures and sewage sludge containing toxic elements, pollution from mining and industry can also contaminate foodstuffs. These toxic elements are not biodegradable, some having long biological half-life and they can accumulate in organs and may lead to undesirable side effects in the future.

Food and drinking water are the major sources of exposure to toxic chemicals. Therefore, exposure and risk of element(s) toxicity are modulated by the diet and nutritional status. Special concern should be given to infants and young children. When growing, breast milk alone is not sufficient to meet the child's nutritional needs. Therefore, complementary foods such as rice, meat, vegetable and infant formula are needed to fill the gap between nutritional requirement and milk supply. Some elements in complementary food such as Cu, Fe and Zn are essential micronutrients for biological functions in the human body, whereas some elements (e.g. Cd, As, Pb) can be toxic when taken in excess.

Aluminum (Al) concentration in milk was found to be higher in soy-based and casein hydrolysate formulae than breast milk and whey-based formulae. Infants may be at risk from Al toxicity when consuming infant formula containing more than 300 µg Al/L. Al toxicity causes encephalopathy, metabolic bone disease and microcytic anaemia. Cd exposure and accumulation also start at a young age. Its accumulation in kidney is responsible for nephrotoxicity and osteoporosis, which are observed at the adult age. In school-age children, high urinary Cd levels were associated with immune suppressive effects. For 4-9-year-old children, cereals like bread, pasta and rice showed the highest contribution to Cd, Hg and Pb intake. Exposure to As from drinking water was associated with reduced intellectual function in 6-year-old children in Bangladesh. In addition, children exposed to either high As or fluoride in drinking water also had increased risk of reduced Intelligence Quotient scores. Recently, children in India aged 13-18 years were found to have a relative higher potential risk of skin lesions caused by As-contaminated cooked rice than 1-6-year-old children. In Bangladesh, 10-year-old children consuming tube-well water with an average concentration of 793 µg Mn/L may be at risk from Mn-induced neurotoxicity. Researchers found a dose-response association between Mn concentrations in water and test scores of performance and verbal ability in children. Soy or rice beverages containing higher levels of Mn than milk-based infant formulas should not be used to feed infants because they may increase the risk of adverse neurological effects.

Intake of a wide variety of foods will help children to meet their nutrient requirements for growth. World Health Organization suggests different kinds of foods such as egg, meat (or liver), poultry, fish, rice, wheat, potato, spinach, pumpkin and guava for feeding non-breastfed children of 6-24 months of age in South Asia. Several studies in different countries have evaluated both macro elements (Ca, Mg, Na, K, P) and trace elements (Fe, Zn, Cu, Se) including some toxic elements (Pb and Cd) in various foods such as cereals, vegetables, fruit, milk and dairy products, meat and meat products and fish. It has also been reported that significant concentrations of As, Cd, Hg and Pb were present in common foods (e.g. vegetables, cereals, fruits, fish and shellfish, meat, eggs) from seven cities of Catalonia, Spain. Results showed that cereal was the group showing the highest contribution to daily intake of Cd, Hg and Pb while fish and shellfish were the main foods responsible for high As intake in children aged 4-9 years. Therefore, it is very important to study the contents of trace elements including some toxic elements (Cd, As, Pb) in various foodstuffs normally eaten by infant and young school children. The objective of this present study was to determine the elemental concentrations (Mg, Ca, Mn, Fe, Cu, Zn, V, Cr, Co, Ni, Se, Mo, Al, As, Cd and Pb) in selected complementary foods usually consumed by children in Thailand. The estimation of daily intake of some toxic elements was also calculated for children aged 6-24 months. Related regulatory agencies and parents should be concerned to minimize the intake of food and drinking water contaminated with these toxic elements in young children.

The study found that some foods such as pig kidney and liver contained high levels of toxic elements, especially As and Cd. Therefore, these should not be used to feed infants or children frequently because these elements can be accumulated in the human body, leading to health effects in the future. For most other foods, the presence of toxic elements was below the Maximum Limits as set by CODEX and the European Commission. In addition, the current study also provided an assessment on children's exposure to the toxic elements As and Cd. Poultry, pig liver and rice contributed to high daily intakes of As and Cd in children. Soybean milk contained higher Mn concentrations than cow-based infant formula. Therefore, regular consumption of soybean milk may contribute to additional intake of Mn in children. The information from this study can assist parents and relevant regulatory agencies to minimize intake of food and drinking water, contaminated with these toxic elements, for human consumption and in particular for young children.

Source: Food Additives & Contaminants: Part B, Vol. 6, No. 1, Pages 55-67, January 2013.

ASSOCIATION OF HIGH LEVELS OF URBAN VEHICLE EMISSIONS AND ALLERGIC RESPIRATORY DISEASES

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of specific Raman bands suggest that short term DEP exposure (2 h) causes specific biomolecular changes in DNA/RNA, protein, lipid and carbohydrate components of the target cells. These results demonstrated that DEP treatments can decrease cell elasticity and alter membrane surface adhesion force, findings that may help provide sub-cellular scale mechanisms for airway remodeling as in asthma and tumor metastasis in lung cancer. Analyses of cytokine and chemokine responses showed a corresponding biochemical response to DEP exposure. Exposure to this component of air pollution may initiate inflammation to accompany biomechanical responses for both SAEC cells and A549 cells. The results from Raman spectral analysis, AFM biomechanics analysis, and cytokine and chemokine analyses clearly showed that SAEC cells were more sensitive to DEP exposure than A549 cells. These findings suggest that DEP exposure triggers important biochemical and biophysical changes that are closely related to early pathological changes at the scale of previously normal individual human lung cells.

Source: Toxicology Letters, Vol. 215, Issue 3, Pages 181-192, December 2012.

Near-roadway Pollution and Childhood Asthma

The emerging consensus that exposure to near-roadway traffic-related pollution causes asthma has implications for compact urban development policies designed to reduce driving and greenhouse gases.

Compact urban development would reduce urban sprawl, leading to shorter driving distances and ultimately less regional air pollution. But it would also mean greater housing density in a given area, potentially increasing the number of residences near major roadways. Given that exposure to traffic emissions near roadways is strongly associated with asthma and related symptoms in children, a new study focuses on how air pollution reduction paired with changes in the proportion of children living near major roadways might affect overall rates of asthma-related outcomes within an urban population.

Traditionally, studies of air pollution and asthma have focused on acute effects – that is, exacerbation of asthma symptoms caused by traffic-related exposure. This work distinguishes between direct effects of regional pollution on asthma symptoms and longer-term effects of living near a roadway on the development of asthma.

Previously collected data were used to estimate the prevalence of asthma and the occurrence of asthma-related outcomes (e.g., bronchitis episodes) in Los Angeles County in 2007. Los Angeles County roadway locations were paired with census and community data to determine the proportion of children living within 75 m of a major roadway. Monitoring stations provided annual average daily concentrations of sample regional traffic-related and secondary pollutants.

Nearly 18% of Los Angeles County children lived within 75 m of a major roadway. The authors estimated that approximately 27,100 asthma cases (8% of the total reported) could be at least partly attributed to living near a major roadway, whereas the combined effects of traffic proximity and regional nitrogen dioxide explained an estimated 70,200 episodes of bronchitis among children with asthma. If regional pollution were reduced by 20% but 3.6% more children (based on total county population) lived near a major roadway, an estimated 5,900 more cases of asthma would occur; if 3.6% fewer children lived by a major roadway with the same reduction in pollution, the estimated number of cases would drop by 5,900.

Reducing regional pollution by 20% would result in 19,900 fewer episodes of bronchitis, assuming 3.6% fewer children lived close to a major roadway. There would be 15,580 fewer episodes if the 20% decrease in regional pollution was accompanied by a 3.6% increase in proportion of children living near major roadways.

The implications of near-roadway exposures for the burden of disease due to air pollution have not been fully appreciated. The results of this study indicate that risk assessment focusing exclusively on regional pollutant effects substantially under-estimates the impact of air pollution on childhood asthma because it does not account for exacerbations caused by exposures other than air pollution among the approximately 8% of children with asthma in Los Angeles County whose asthma can be attributed to pollution from near-roadway pollution exposure based on proximity. Moreover, the burden of asthma exacerbation among children whose asthma was caused by living near roadways, and the potential benefits of reducing near-roadway exposures, are disproportionately larger for more severe and more expensive outcomes, such as hospital admissions and emergency department visits.

Although this study focused on the impact of near-roadway exposure on asthma, there is emerging evidence that these exposures also contribute to atherosclerotic heart disease, chronic obstructive pulmonary disease, lung cancer, and childhood neuro-developmental outcomes. Therefore, the implications of near-roadway exposure for the total burden of disease associated with air pollution are potentially quite large. However, the potential increase in physical activity associated with more compact urban design and walkable neighborhoods should also be considered. Although there is little evidence that exercise improves asthma, physical activity has known cardiovascular health benefits that could outweigh potential detrimental effects of near-roadway exposure. A more comprehensive assessment of all health-relevant benefits of planned greenhouse gas (GHG) policies would be useful for policy makers. Nonetheless, it is clear that by using available health information to develop "win-win" policies to prevent childhood respiratory disease as cities are redeveloped to reduce GHG emissions, a much larger burden of disease could be prevented.

Source: Environmental Health Perspectives, Vol. 120, No. 11, Pages 1619-1626, November 2012.

ENVIRONMENTAL NITROGEN DIOXIDE EXPOSURE AND THE PROGRESSION OF ISCHEMIC STROKE

Nitrogen dioxide (NO_2) is one of the components of nitrogen oxides (NO_x), which represents an important urban pollutant in most developed cities of the world because of its massive discharge from motor vehicle exhaust and stationary sources such as electric utilities and industrial boilers. In atmospheric chemistry and air pollution and related fields, NO_x refers specifically to NO and NO_2. Because NO_2 can also be formed from NO oxidation after emission, add to its stronger oxidization, it has been a strong indicator in atmospheric environment monitoring and a potential risk factor in adverse effects exploration.

Ischemic stroke is the second leading cause of death and the most frequent disease leading to disability in the world, with a high incidence affecting up to 0.2% of the population every year. In China, the rate of ischemic stroke increased by almost 9% every year. In USA, stroke rates in five to 44-year olds rose by about a third within 10 years. Worryingly, the risk factors for ischemic stroke have not been fully clarified, and the effective means to control its morbidity and mortality have not been found.

In the last decade, an increasing body of epidemiologic literature has provided compelling evidence to link outdoor air pollution to stroke mortality, with positive associations being observed for NO_2, sulfur dioxide (SO_2), ozone (O_3), carbon monoxide (CO) and particulate matter (PM). Findings from a 9-city US study found that an increase in the Inter Quartile Range value of air CO, NO_2, PM_{10} and SO_2 pollution was associated with 2.83, 2.94, 2.33, and 1.35% increases respectively, in hospital admissions for ischemic stroke. Data from studies in the urban area of Como, Italy and Hangzhou, China showed that NO_2, SO_2 and PM_{10} were significantly associated with admission and mortality of local ischemic stroke. NO_2 seems also to influence the outcome of stroke patients according to an investigation in Tokyo, Japan showing that a 10 mg/m^3 increase in NO_2 was associated with a 28% increase in risk of death from ischemic stroke. A cohort study carried out in Danish also addressed that long-term exposure to outdoor air pollution from NO_2 may contribute to the development of ischemic stroke, especially severe ischemic strokes leading to death within 30 days. These effects, however, are not conclusive given the limited number of studies, their small size and their methodological constraints, which also lead to some contrary results. Moreover, relative molecular mechanisms cannot be elucidated by epidemiologic studies.

In ischemia-reperfusion injury, the role of endothelial dysfunction and inflammation is well established. Endothelin-1 and endothelial nitric oxide synthase (eNOS) derived NO are two important endothelial regulators with antistatic function on each other in cerebrovascular system. Their balance plays a critical role in regulation of normal vascular homeostasis. Once impaired, it will cause blood flow reduction, energy metabolism interruption, and following injuries associated with ischemia in the brain. Many studies emphasize that focal cerebral ischemia is associated with a marked inflammatory reaction that contributes to the evolution of the tissue injury. One typical characteristic is the accumulation of inflammatory elements including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2) and intercellular adhesion molecule 1 (ICAM-1), etc. Overproduction of these enzymes, cytokines, and adhesion molecules could increase blood coagulation and promote thrombus formation, and then lead to disturbance in the blood supply to the brain, eventually contribute to both necrotic and apoptotic neuronal death. Clarification of endothelial and inflammatory responses after NO_2 inhalation should help us to understand the mechanisms of NO_2 induced ischemic stroke.

The present study was designed to confirm the role of NO2 pollution in the etiology of stroke reported by epidemiological studies under experimental conditions, and to elucidate relative mechanisms. The lowest concentration (0.25 mg/m^3) used in this study is closely approximate to the Chinese national air quality standards of 3rd class; 5 mg/m^3 is the peak level encountered outdoor and indoor, which is similar with the lowest effect value in humans; whereas the intermediate and highest concentrations (10 and 20 mg/m^3) corresponded to the effect levels reported in experimental studies.

In the present study, researchers set up stroke rat model and exposed them to NO_2 at the same concentration for one week, and found that NO_2 exposure time-dependently delayed neurological structure and function recovery of middle cerebral artery occlusion (MCAO) rat, and worsened pathological injuries and apoptosis induced by MCAO operation. Endothelial and inflammatory responses, two common cellular pathomechanisms involved in ischemic brain damage, were induced in cortex by MCAO treatment and exacerbated by followed NO_2 inhalation. Expression of the endothelial and inflammatory biomarkers in stroke displayed the same tendency in healthy rats after sub-acute and sub-chronic NO_2 exposure as in MCAO model in a concentration-dependent manner. The data provide evidence that environmental NO_2 is an important inducer, and also a promoter of ischemic stroke, with eNOS, COX-2 and ICAM-1 being potential indicators of this effect.

Source: Toxicology Letters, Vol. 214, Issue 2, Pages 120-130, October 2012.

CALENDAR OF EVENTS

Short-term International Training Courses at Chulabhorn Research Institute, scheduled for 2013

	Training Course	Date	Final Date for Application
1.	Environmental Toxicology	April 18-26, 2013	February 28, 2013
2.	Occupational and Environmental Medicine	July 24-31, 2013	April 30, 2013
3.	Environmental and Health Risk Assessment and Management of Toxic Chemicals	December 1-17, 2013	September 27, 2013

Course Coordinator: *Khunying* Mathuros Ruchirawat, Ph.D.

Course Description:

1. **Environmental Toxicology (April 18-26, 2013)**

This course provides students and participants with a background of the major groups of toxic substances encountered by man and animals through food and the environment, and also through exposures at the workplace. These toxicants include mycotoxins, naturally occurring plant and animal toxins, toxic substances in air, water and soil, N-nitroso compounds, solvents, plastics, pesticides, pollutants and radiation (UV, electromagnetic, ionizing). The course focuses on the chemistry, fate and distribution in the environment, mechanisms of their action, toxic manifestation in living organisms, as well as toxic syndrome in human beings.

Requirement: Participants should have some basic knowledge in chemistry, biological sciences and medicine.

2. **Occupational and Environmental Medicine (July 24-31, 2013)**

The course is intended to be a basic introductory course in occupational and environmental medicine and is designed for medical students, physicians, nurses and other healthcare workers. It will review the major occupational and environmental hazards and the associated diseases. It will emphasize the importance of the occupational/environmental exposure history as a critical tool for proper diagnosis of occupational and environmental disease, and will discuss the multidisciplinary nature of occupational and environmental medicine and underscore that treatment, prevention and control of occupational and environmental diseases requires a team approach that includes physicians, nurses, industrial hygienists, environmental scientists, engineers and policy makers.

Requirement: Participants should have some background in the health sciences and will become part of a network of professionals involving physicians, nurses and other healthcare workers.

3. **Environmental and Health Risk Assessment and Management of Toxic Chemicals (December 1-17, 2013)**

The course is an integration of science and policy, covering the fundamental basis of environmental and health risk assessment and management from exposure assessment and risk characterization; mode of action and human relevance framework; the relationship between risk assessment and risk management; and the need for open, transparent and participatory acceptance procedures and credible communication methods. Emphasis will be placed on human health risk assessment, although the principles of ecological risk assessment will also be covered. Importantly, the course teaches the practical application of risk assessment methods to various problems, e.g. hazardous waste site release, through the use of case studies relevant to problems faced in developing countries, and describes the policy context in which decisions to manage environmental health risks are made. Teaching and learning aids such as electronic distance learning tools and IPCS risk assessment toolkit will be introduced

Requirement: Participants should have jobs/responsibilities related to assessment of risk from the use of chemicals.

Fellowships:

A limited number of fellowships are available that will cover roundtrip airfare, accommodation (on site) and meals, training material, and health insurance.

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More Information and Application:
please visit - http://www.cri.or.th/en/ac_actcalendar.php

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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