CRI/ICEIT
NEWSLETTER

VOL. 18 NO. 1 – January 2008
ISSN 0858-2793
BANGKOK, THAILAND

Chulabhorn Research Institute

INTERNATIONAL CENTRE FOR ENVIRONMENTAL AND INDUSTRIAL TOXICOLOGY (ICEIT)

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

The Sixth Princess Chulabhorn International Science Congress
The Interface of Chemistry and Biology in the 'Omics' Era: Environment & Health and Drug Discovery
Shangri-La Hotel, Bangkok, Thailand
November 25 – 29, 2007

The congress was organized to commemorate the 80th birthday celebrations of His Majesty King Bhumibol Adulyadej of Thailand. Presiding at the opening of the congress, HRH Princess Maha Chakri Sirindhorn represented His Majesty the King.

The theme of the congress derives from His Majesty's life-long vision of the application of scientific knowledge and discovery to the improvement of the quality of life of the Thai people.

The congress thus provided an appropriate opportunity to honor His Majesty's unique contributions to the many areas of science and technology which he has studied with keen appreciation and understanding, and then applied in the Royally Initiated Projects that have benefited the people of Thailand, as well as those in many other countries.

In her report to HRH Princess Maha Chakri Sirindhorn at the opening ceremony of the congress, Professor Dr. HRH Princess Chulabhorn, President of the Chulabhorn Research Institute, and Chairperson of the Organizing Committee of the congress, stated that "In science, one of His Majesty's major interests has long been the developments that have taken place in the study of genetics. The scientific program of the congress reflects His Majesty's profound interest in this field in which recent breakthroughs in research have opened up opportunities for improving quality of life and for redressing environmental degradation caused by short-sighted and selfish human activity. Thus the congress focuses on environment and health, and drug discovery, areas in which the interface between biology and chemistry has

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The Sixth Princess Chulabhorn International Science Congress
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become increasingly important. These are also areas in which recent developments have been catalyzed by new technology, which is a sub theme that will be highlighted in many of the presentations in the congress".

The scientific program of the congress, as well as featuring Keynote and Plenary lectures, was organized around a number of symposia. These included Environment-Gene Interactions; Environmental Epigenomics; Air Pollution; Nanotechnology, Nanomaterial and Safety Science; Cellular Response to DNA Damage/ DNA Repair; Chemicals and Microbes in Environment and Health; Biological Responses to Chemical Agents: Biomarkers; Cancer, Aging, & Inflammation in Mouse Models; Technologies for Drug Discovery, Development and Delivery; Chemoprevention; Natural Products; and Organic Synthesis.

The congress program also featured three workshops: Workshop on The Use of 'Omics' in Human Health Risk Assessment; Workshop on Collaborative Research, co-sponsored by WHO-IPCS/NIEHS; and Workshop on Interdisciplinary Approaches to Research on Arsenic Exposure, Susceptibility and Human Health: Current Advances and Future Directions.

There was also a roundtable discussion on the topic of Emerging Environmental Issues in Public Health: Their Impacts and the Role of Technology in Identifying and Addressing These Issues.

This year the congress attracted over 768 participants from 37 countries. There were 96 invited speakers from 22 countries, and a total of 346 poster presentations.

As in previous Princess Chulabhorn Science Congresses, in addition to the main congress program, there was a satellite meeting. On this occasion the meeting was organized by the Collegium Ramazzini in collaboration with the Chulabhorn Research Institute as a workshop on "Occupational and

Environmental Health in the Asia/ Pacific Region". The program of this two day satellite meeting is featured below.

Highlights of the scientific program of the congress included keynote lectures given by two Nobel Laureates, Dr. Richard J. Roberts (U.S.A.) on "The Genomics of Restriction and Modification"; and Dr. Richard R. Schrock (U.S.A.) on "Abiological Catalytic Reduction of Dinitrogen under Ambient Conditions". Also a closing lecture in the closing ceremony of the congress was given by Dr. Janet Woodcock (U.S.A.) on "Transforming Global Drug Development through New Science".

The Collegium Ramazzini Satellite Workshop

As on previous occasions during Princess Chulabhorn International Science Congresses, a related event was organized as a satellite meeting. On the occasion of the Sixth Princess Chulabhorn International Science Congress it was a workshop on the topic of "Occupational and Environmental Health in the Asia/Pacific Region" jointly organized by the Collegium Ramazzini and the Chulabhorn Research Institute from November 30 to December 1, 2007, at the Chulabhorn Convention Center, Bangkok, Thailand.

The two day workshop attracted over 161 participants and the sessions were given by 23 speakers from 10 countries.

This workshop was a major collaboration between the Collegium Ramazzini and the Chulabhorn Research Institute. It was opened by Professor Philip Landrigan, Chairman of Department of Community & Preventive Medicine, Professor of Pediatrics, Mount

Sinai School of Medicine, New York, and President of the Collegium Ramazzini, and by Dr. Mathuros Ruchirawat, Vice President of the Chulabhorn Research Institute.

The main themes of the workshop were Children and the Environment; Toxic Chemicals and the Environment; and Toxic Chemicals in the Workplace.

In the workshop program, the three main themes were elaborated in eight sessions comprising the following:

- Overview of Children's Health and the Environment
- Arsenic and the Health of Children
- New Developments in the Study of Air Pollution and Effects on Human Health
- Health Impacts of Gasolines and Oxygenated Fuel Additives
- Pesticides, Food Additives and Other Contaminants
- Overview of Occupational Health
- Asbestos
- Benzene

The Roundtable Discussion, which brought the workshop program to a close, provided the opportunity for discussion on the ways in which the Collegium Ramazzini might collaborate with regional partners in future studies in occupational and environmental health to maintain and carry forward the momentum of the present workshop.

THE PRINCESS CHULABHORN GOLD MEDAL AWARD

Professor Dr. Her Royal Highness Princess Chulabhorn has instituted the "Princess Chulabhorn Gold Medal Award" to honor and acclaim persons or organizations that are world renowned and whose work has received international acclaim. Importantly, recipients will have provided important and sustained support to the advancement of science in developing countries.

The fourth award presentation was made in November 29, 2007 at a special ceremony during the Sixth Princess Chulabhorn International Science Congress.

The awardees were:

- Professor Herman Autrup
- Professor Ram Sasisekharan
- Mr. Sivavong Changkasiri
- Mr. Kittipan Kanjanapipatkul

INTERNATIONAL RECIPIENTS

Professor Herman Autrup, Professor of Environmental Medicine at the University of Aarhus, Denmark who has earned the very highest international reputation for his work on the interface between environment and health.

Professor Ram Sasisekharan, currently Underwood-Prescott Professor of Biological Engineering and Health Science and Technology at Massachusetts Institute of Technology is a pioneer in the field of glycomics as well as nanobiotechnology. The application of his innovative work to the treatment of cancer has had a major impact both scientifically and clinically.

THAI RECIPIENTS

Mr. Sivavong Changkasiri, a former Permanent Secretary of the Ministry of Industry who played a pivotal role in the development of the educational program at the Chulabhorn Research Institute and to initiating links with industrial partners.

Mr. Kittipan Kanjanapipatkul, a former director of the Department of Technical and Economic Cooperation, a former Secretary-General of the Colombo Plan who has helped to promote international cooperation and educational exchange among developing nations.

ASSESSING THE RISK OF PARKINSON'S DISEASE BASED ON INTRANASAL DELIVERY OF AGROCHEMICALS

The pathogenesis of Parkinson's Disease (PD) is still poorly understood, but epidemiological data suggest that environmental toxins might constitute a risk factor.

Although specific pesticides have not been clearly implicated, a group of these agrochemicals, that are complex I inhibitors, such as paraquat, or rotenone, produce PD symptoms in laboratory animals when they reach the basal ganglia through non-natural ways of penetration such as direct nigrostriatal infusion, or systemic intraperitoneal or intravenous administration.

The current methods of administration of these neurotoxins have provided valuable information about the pathophysiology of PD, but they provide little information on risk for environmental exposure because these methods bypass the physical and metabolic defenses of the organism. It is not known if the same compounds could induce Parkinsonian symptoms when they enter the body through more natural routes such as ingestion, skin contact or inhalation. Other pathways of penetration have been rarely documented in humans. Therefore, a formal proof that Parkinsonian toxins might lead to development of PD when they contact the body at natural sites of exposure is still lacking.

A relatively unexplored way of penetration of xenobiotics is the nasal cavity. The nasal mucosa exhibits a large surface area, porous endothelial membrane, high total blood flow, avoidance of first-pass metabolism, and a weak blood-brain barrier. Drugs are cleared rapidly from the nasal cavity after intranasal administration, resulting in rapid systemic drug absorption but there is also a tight communication between extra and intracranial vessels that may favor delivery to the brain. In addition, several compounds may gain access to the brain via the olfactory nerve track or through the olfactory epithelium by mechanisms that are not well understood.

In a recent study, a new model based on daily inoculation of neurotoxins in the nasal cavity of C57BL/6 mice for 30 days was used to evaluate risk of three complex I inhibitors, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone and paraquat. These compounds displayed very different effects on motor activity, striatal dopamine and dihydroxyphenylacetic acid (DOPAC) levels and loss of dopaminergic neurons. MPTP-treated mice developed motor deficits that correlated with a severe depletion of striatal dopamine levels, and loss of tyrosine hydroxylase staining in substantia nigra and striatum. By contrast, rotenone-treated mice or rats were asymptomatic. Paraquat induced severe hypokinesia and vestibular damage but did not alter the nigro-striatal system.

Determining if industrial compounds could induce PD is of great relevance for public health and agriculture and for this reason the studies conducted with rotenone and other pesticides have been polemic in recent years. It is important to determine if the intranasal method of delivery provides a good prediction of chemical hazard by comparing these results in rodents with the available data in humans. Interestingly, in agreement with the mice data, there is one case report of a drug addict that acquired PD after inhalation of MPTP-contaminated heroin. Regarding paraquat, abundant literature describes systemic poisoning by ingestion and inhalation, but there is little evidence of neuronal damage and no development of Parkinsonism by survivors. Moreover, there are very few reports of rotenone poisoning in humans and none through the nasal route. This compound is used frequently in fish factories where it is taken by fish through the gills. As the nasal mucosa, gills exhibit a large surface area, high total blood flow and avoidance of first-pass metabolism. Interestingly, there is no evidence of Parkinsonism in fish treated with rotenone or paraquat.

This study suggests that, besides their common target at the mitochondria, specific physicochemical properties such as solubility, metabolic assimilation and clearance, selectivity of the blood-brain barrier, and uptake by midbrain dopaminergic neurons may limit the noxious effect of these toxins. Moreover, this study sets up the basis for development of a new test to assess the risk of PD based on intranasal delivery of agrochemicals.

Source: Environmental Neurology, Vol. 208, November 2007.

Health Effects of Exposure to Carbofuran in Industrial Workers

Carbofuran (2,3-dihydro-2,2-diethylbenzofuran-7-yl-methylcarbamate) belongs to *N*-methylcarbamate insecticides. It was introduced to the market in the year 1967 by FMC Corporation and Bayer AG. It is used for the control of soil-dwelling and foliar-feeding insects and nematodes in vegetables, beet, maize, oilseed rape, potatoes, soy beans, rice, coffee, cucurbits, vines, bananas, mushrooms and other crop. On the global plane, in the year 2002 about 400 tonnes of carbofuran has been consumed. Although carbofuran is one of the most popular granular insecticides, since 1993 in economically developed countries a trend in the reduction of the use of carbamates could be observed. The main reason could be their high toxicity to humans and animals.

Literature data on carbofuran genotoxicity *in vitro* and *in vivo* are very scarce. There are few papers indicating that occupational exposure to this AChE inhibiting insecticide might be connected to increased risk of developing non-Hodgkin's lymphoma and lung cancer. Other authors showed its genotoxicity *in vitro*. Now a new study has used comet and cytokinesis-block micronucleus (CBMN) assay combined with centromere probes to evaluate genome damage in lymphocytes of workers employed in carbofuran production. Also, the level of AChE activity in blood and plasma was measured. Only few workers exhibited AChE activity below 85%. Comet assay parameters were slightly but significantly elevated compared to control subjects, especially the long-tailed nuclei ratio. The correlation between AChE activity and comet assay parameters was found to be poor, but there was significant effect of smoking and alcohol intake on the latter. In binucleated lymphocytes of workers significantly increased number of micronuclei, nuclear buds, and nucleoplasmic bridges was detected. Proportion of micronuclei with centromere, DAPI signal positive micronuclei was also elevated. Micronucleus assay parameters also appeared to be significantly influenced by duration of

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The Effects of Air Pollution and Smoking on Placental Cadmium, Zinc Concentration and Metallothionein Expression

Placenta provides a connection between maternal and fetal circulations, and all the necessary nutrients for fetus. It permits the passage of trace elements and minerals such as calcium (Ca), copper (Cu), zinc (Zn) and iron (Fe) that are necessary for growth and development. On the other hand, prevention of transport of toxic materials such as cadmium (Cd) can be achieved by the binding of these metals by mediator molecules, like metallothionein (MT).

Studies conducted in various parts of the world have regarded human placenta as an indicator organ when exposed to metals. Smoking is the major source of cadmium. Each cigarette contains 1-2 □g Cd. Daily Cd intake of smokers can be twice as much as non-smokers. Depending on the number of cigarettes smoked a day, birth weight of the babies and the weight of the placenta are lower in smokers than in non-smokers.

Exposure of humans to Cd in industrial work environments is mainly due to inhalation of this metal at small doses (50 □g/m^3). Exposure to Cd results in fetotoxic and embryotoxic effects. Cd accumulates in the placenta of mothers exposed to Cd during pregnancy. Binding of Cd is related to MT synthesis and partially protects the fetus from the detrimental effects of the metal. At the cellular level, one of the most important bivalent metal (Zn, Cd and Cu) binding proteins is MT. This low-molecular weight (6000-7000 Da) cysteine-rich protein is important for the regulation of Zn homeostasis and metabolism. It has been proposed that MT maintains Zn homeostasis at the cellular level by increasing Zn and regulating the distribution, excretion and short-term storage of Zn. Presence of Cd and Zn are potent factors for the MT synthesis. MT binds to Cd with greater affinity than Zn. Therefore Zn is easily released from MT and transported while Cd strongly binds MT. Presence of MT has been shown in human placenta and fetal membranes. Zn is a trace element necessary for the growth of the fetus. Insufficient transport of Zn from the placenta to the fetus may be held responsible for low birth weight in babies of smoker women. Increase in placental Cd concentration as well as increase in Zn has been reported in smokers. Placenta plays an important role in the production of sex steroid hormones necessary to maintain pregnancy. It is the primary source of progesterone during pregnancy. Researchers have argued that smoking may cause spontaneous abortions by decreasing progesterone concentration.

Now a new study has been designed to determine the placental Zn and Cd levels in mothers who were smokers, mothers who were thought to be exposed to air pollution, and mothers who were non-smokers and to investigate the relationship between the expression of placental MT binding these metals and blood progesterone level. Placental Zn and Cd levels were measured by atomic absorption spectrometry. Presence of placental MT was determined immunohistochemically. Placental changes were examined by light microscope after Haematoxylin & Eosin and Periodic Acid Schiff (PAS) staining. Immunohistochemical MT staining of syncytiotrophoblastic and villous interstitial cells were scored as positive or negative.

Among the 92 mothers included in the study, 33 were smokers (Group I), 29 had been exposed to air pollution (Group II) and 30 were non-smoker rural residents who had never been exposed to air pollution (Group III). Mean off-spring birth weight and mean placenta weight of Group II were lower when compared with those of the other two groups. In Group I, mean placental Cd and Zn were higher than in other groups. In Group II, mean placental Cd and Zn levels were higher than those of Group III. Blood progesterone levels of subjects in Group I were the lowest of all groups. While the mean count of villi was the highest in Group III; the highest mean count of syncytial knots was in Group II. Thickening of vasculo-syncytial membrane was most prominent in Group I. Similarly, MT staining was positive and very dense in 72.7% of cases in Group I. MT staining was positive in 69.0% and denser in Group II cases compared to 36% (11/30) in Group III.

This study showed that smoking increased Cd levels in placenta and accompanied an increase in placental MT expression immunohistochemically. The effects of exposure to air pollution are equally harmful as smoking related effects.

Source: Toxicology, Vol. 238, August 2007.

Health Effects of Exposure to Carbofuran in Industrial Workers

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exposure to carbofuran. Together with published data on carbofuran's effect on health these results might indicate the need for further evaluations of its genotoxicity using a range of different cytogenetic techniques.

Human biomonitoring using AChE assay and two cytogenetic techniques may be very useful to assess and control the risk of long-term outcomes associated with exposure to carbonates. From a practical point of view in the clinical laboratory, it is necessary to monitor basic physiological functions, cholines-terase activity and other parameters not only for diagnostic purposes but also preferably for the regulation of medical treatment, and for accounting for the differences in toxicity among the compounds with the same mechanism of action.

Source: Food and Chemical Toxicology, Vol. 45, December 2007.

EFFECTS OF LEAD EXPOSURE ON SKELETAL DEVELOPMENT

In spite of efforts to reduce human exposure, lead toxicity continues to be a major environmental health concern in the United States and in other industrial countries. Although recent research has focused on understanding its toxic effects in the developing peripheral and central nervous system, lead (Pb) also impacts other developmental processes, including those that occur in the hematologic and skeletal systems. In fact, the skeleton has long been recognized as a major reservoir for ingested Pb and a number of reports demonstrate an inverse correlation between blood Pb concentrations and growth in terms of height, weight, and chest circumference.

Given the strong epidemiologic data, as well as the findings of a recent study that fracture healing and chondrocyte differentiation are affected by Pb, researchers have performed a series of *in vitro* experiments to elucidate the underlying mechanism of toxicity during chondrogenesis and chondrocyte differentiation. They employed micromass cultures of mesenchymal stem cells, a culturing technique that has been used previously as a model to study the early events of embryonic limb development. Cell lines with chondrogenic potential, such as C3H10T1/2 cells, and primary limb bud mesenchymal cells plated at high density undergo differentiation to form distinct cartilage nodules. Thus, besides being used to study limb development, these models have been used to define factors and signaling events involved in chondrogenesis. Transforming growth factor-β (TGF-β) and bone morphogenetic protein (BMP) both induce chondrogenesis in mesenchymal stem cell populations. Prostaglandin E_2, through protein kinase A signaling also induces chondrogenesis, whereas retinoic acid is considered an inhibitor of chondrogenic commitment possibly via down-regulation of TGF-β/Smad signaling. Thus various signaling pathways are associated with chondrogenesis, but BMP signaling is particularly important because recombinant BMP proteins are currently approved for clinical use to enhance bone healing in tibia nonunions and spine fusion.

Regarding the signaling pathways, TGF-β and BMP signals are mediated by Smad transcription factors that bind to type I TGF-β receptors and are phosphorylated following ligand binding to type II receptors. Both the BMP receptor-associated Smads (1, 5, and 8) and the TGF-β receptor-associated Smads (2 and 3) are released into the cytoplasm upon phosphorylation, complex with Smad4, and translocate into the nucleus where they regulate gene expression. Because TGF-β receptor and BMP receptor-associated Smads compete for Smad4 and other downstream signaling molecules. these pathways antagonize one another such that when one pathway increases, the other decreases. They also have opposing effects in chondrocytes in which TGF-β inhibits and BMP promotes chondrocyte differentiation. However, in mesenchymal stem cells, both TGF-β and BMP have been shown to enhance chondrogenesis, with the most robust effect in response to BMP signaling. Assessing the impact of Pb on the propagation of these specific signaling events would provide mechanistic insight into how Pb may affect chondrogenesis and chondrocyte differentiation.

In the present study, researchers found that BMP signaling is also regulated by Pb. BMP receptor signaling occurs in a manner analogous to the TGF-β pathway, with Smad1/5/8 binding to the type I BMP receptor, followed by phosphorylation of these factors upon ligand activation. Using a polyclonal antibody that recognizes all three BMP receptor-associated Smads, they found that the basal phosphorylation state was not altered by Pb alone, but the induction of phosphorylation of Smad1/5/8 was markedly inhibited by Pb. Similarly, although Pb did not alter basal activation of the BMP-Smad responsive reporter 12 x SBE, Pb significantly reduced activation of this reporter by BMP-2. Thus, similar to TGF-β signaling, Pb regulates BMP signaling only during activation of the pathway by ligand. Interestingly, the effects are opposite, with Pb inhibiting BMP-Smad phosphorylation and stimulating TGF-β-Smad phosphorylation. Overall, the potent inhibition of BMP-2-induced Smad1/5/8 signaling by Pb represents the most robust signaling effect identified to date in a skeletal cell type with regard to a candidate mechanism of Pb toxicity.

The complex regulation of the Smad signaling molecules makes it unlikely that the induction of chondrogenesis by Pb is caused by direct alteration of these pathways. Although BMP and TGF-β signaling pathways have antagonistic effects on some cells, including growth plate chondrocytes where TGF-β inhibits and BMP-2 stimulates maturation, both signals enhance chondrogenesis in mesenchymal stem cell populations. An earlier study has shown that BMP-4 stimulates chondrogenesis in C3H10T1/2 and MC615 chondroprogenitor cells through activation of the BMP-receptor-associated Smads. TGF-β signaling through Smad2 and Smad3 is associated with enhanced chondrogenesis in murine mesenchymal stem cells. Additionally, the action of these factors is dependent

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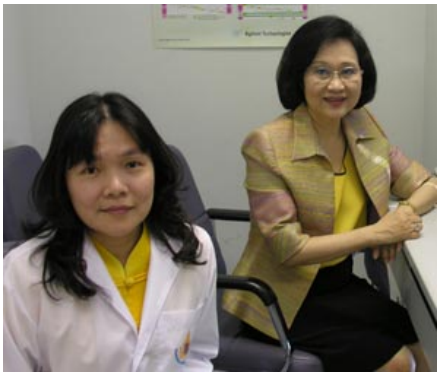
NEW STUDY LINKS CHANGES IN GENE EXPRESSION IN INFANTS TO ARSENIC EXPOSURE

Professor Dr. HRH Princess Chulabhorn Mahidol, President of CRI

In a collaborative study, researchers at the Chulabhorn Research Institute (CRI) in Thailand and of the Massachusetts Institute of Technology (MIT) in the United States have found that the children of mothers exposed to water supplies contaminated with arsenic during their pregnancies showed gene expression changes that could lead to cancer and other diseases later in life, even if the children themselves were never directly exposed to arsenic.

The new study, in establishing the potential harmful effects of prenatal exposures, provides a possible method of screening populations to detect signs of arsenic contamination. Moreover, it is the first study to provide evidence of genome-wide changes resulting from prenatal exposure from any environmental contaminant.

Arsenic contamination is a health concern worldwide with millions exposed to levels that exceed the World Health Organization (WHO) safety standard of 10 parts per billion (ppb). The element was classified as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC) and has been implicated in such diseases as vascular disorders and diabetes.



Mathuros Ruchirawat, Ph.D., CRI (right) and Panida Navasumrit, Ph.D., CRI (left)

The CRI research team included HRH Princess Chulabhorn Mahidol, President of CRI, and Mathuros Ruchirawat, Vice President for Research (CRI), in Bangkok, working with Leona Samson, director of the MIT Center for Environmental Health Sciences and Rebecca Fry, a research scientist at the Center.

Leona Samson Ph.D., MIT

Rebecca Fry Ph.D., MIT

The investigators recruited 32 healthy, pregnant women between the ages of 20 and 40 for the study. Twenty three of the women lived in the Ron Pibul District of southern Thailand in villages that had been classified as high-level arsenic contaminated areas as a result of extensive tin mining from the 1960s to 1980s. Levels of arsenic in groundwater in the area are as much as 50 times the WHO standard. Women with toenail arsenic levels representing exposure below the WHO limit of 10 ppb served as a control group.

During the subjects' pregnancies, the CRI investigators collected toenail samples, which were analyzed for total arsenic concentrations that reflect past exposures. After delivery of the women's children, a sample of newborn cord blood was collected for microarray analysis of gene expression. The researchers then performed data analysis to identify genes that showed modulated expression as a result of prenatal exposure and also to determine transcription factor binding sites and molecular interactions.

Microarray analysis identified approximately 450 genes that were differentially expressed between the two populations, 90 percent of them showing an increase in expression level. The investigators were able to isolate three arsenic-associated gene expression signatures and found that even the smallest set, which included eleven genes, showed 83 percent accuracy in predicting prenatal arsenic exposure. The eleven genes fall into gene ontology categories related to cell growth and death, stress and immune response, and inflammation.

This study underscores that there is a robust prenatal response that correlates with arsenic-exposure levels that could modulate numerous biological pathways including apoptosis, cell signaling, the inflammatory response, and other stress responses, and ultimately affect health status. Arsenic contamination of the drinking water in the Ron Pibul area of Thailand is representative of that seen in many other areas of South East Asia, most notably Bangladesh, suggesting that prenatal exposures are likely to be endemic in these areas. Moreover, arsenic contamination of the Ron Pibul drinking water is roughly the same as that known to be present in many of the western United States, suggesting that prenatal arsenic exposure may also be a problem in the United States. These data contribute to our understanding of biological responses upon arsenic exposure, and show that prenatal exposure in human results in measurable phenotypic responses in the newborn.

This research study was chosen to be among the fifteen top papers to come out of NIEHS in 2007.

Source: PLoS Genetics, Vol. 3, November 2007 and Environmental Factor, NIEHS, January 2008.

EFFECTS OF LEAD EXPOSURE ON SKELETAL DEVELOPMENT

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on complex signaling, because it is clear that TGF-β and BMP signals act in combination with other signaling pathways. In ATDC5 cells, stimulation of chondrogenesis by TGF-β is mediated by activation of Smad pathways and the p38 and Erk1/2 MAP kinase pathways simultaneously. Furthermore, whereas Wnt/β-catenin signaling *in vivo* appears to stimulate osteogenesis over chondrogenesis, in human mesenchymal stem cell cultures TGF-β acts synergistically with Wnt/β-catenin signaling to induce chondrogenesis. Similarly, BMPs have been shown to act synergistically with Wnt/β-catenin signaling to induce chondrogenesis in C3H10T1/2 cells. Overall, it is clear that BMP and TGF-β Smad signaling is critical for induction of chondrogenesis; however, these pathways are only a part of multiple signaling events that contribute to the regulation of chondrogenic commitment.

To extend these signaling results, the study also examined the effect of Pb on other signaling pathways. Although no effects were observed on CRE and TOPFIASH activation using the respective luciferase-based reporters, the experiments showed that Pb inhibited basal AP-1-Luc reporter activity. AP-1 activation has been shown to inhibit chondrogenesis, so it is possible that the inhibition of AP-1 could be involved in the induction of chondrogenesis by Pb. The inhibition of AP-1 signaling in mesenchymal stem cells is in contrast to the findings in other cells where Pb induces AP-1 signaling activity. A previous study showed that Pb increased AP-1 and NF-κB signaling in chick embryonic chondrocytes in culture. Furthermore, *in vitro* Pb exposure in rats results in activation of AP-1 and NF-κB levels in multiple regions of the brain and in astrocytes in culture. *In vivo* Pb exposure results in increased NF-κB signaling in renal tubular cells and results in nephritis in rats. Similarly researchers found that Pb induces NF-κB signaling in MSCs as measured by induction of NF-κB-Luc reporter. However, because signaling on the NF-κB pathway has been shown to destabilize Sox9 mRNA and inhibit chondrogenesis, it is unlikely that Pb-induction of NF-κB signaling seen in MSCs is directly causing an enhanced chondrogenic response.

The induction of chondrogenesis by Pb in the current study is consistent with findings observed in an *in vivo* murine model of fracture healing. Mice with Pb levels similar to those found in humans with Pb intoxication had delayed healing of stabilized femur fractures. The effect was dose dependent, and cartilage was observed to be a major target. Pb-exposed mice had increased cartilage volumes, delayed chondrocyte maturation, persistence of cartilage, and reduced bone formation. Overall, the findings in the present study further support the hypothesis that Pb is an inducer of chondrogenesis.

The present study establishes that in addition to affecting chondrocyte maturation, Pb accelerates the differentiation of mesenchymal precursors into chondrocytes. Although Pb alters BMP and TGF-β signaling, the mechanism through which Pb regulates mesenchymal cell fate determination is complex and likely involves modulation and integration of multiple signaling pathways. Increased understanding of the mechanisms through which Pb regulates stem cell fate and subsequently affects tissue repair is critical, given the sensitivity of these tissues and the ubiquitous presence of Pb in our society and in other industrialized and developing nations.

Source: Environmental Health Perspectives, Vol. 115, September 2007.

CRI TRAINING ACTIVITIES FOR 2008

	Activity	Date
1	Detection of Environmental Pollution and Monitoring of Health Effects	March 3 – 14
2	Environmental Toxicology	April 16 – May 2

For more information, please contact Thailand International Development Cooperation Agency (TICA):

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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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