CRI/ICEIT
NEWSLETTER

VOL. 21 NO. 2 – April 2011
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".

Detection of Dicofol and Related Pesticides in Human Breast Milk

Dicofol (trade name, Kelthane) is a pesticide that is used world-wide for agricultural applications. Since dicofol has a similar structure to DDT (dichlorodiphenyltrichloroethane), it is associated with similar concerns to DDT and its metabolites such as its persistence, bioaccumulation, long-range transport and adverse effects on humans, animals and the environment. Dicofol is manufactured from technical-grade DDT by chlorination to an intermediate, Cl-DDT, followed by hydrolysis to dicofol. Unreacted DDT and Cl-DDT are degraded to *p,p'*-DDE, which remains in the technical-grade dicofol as an impurity. In Japan, dicofol was used as a pesticide from 1956, and then banned in 2004. However, dicofol has been widely used in agricultural practices in China until the present time and is suspected of being one of the major sources of DDTs in cotton fields. Dicofol exerts acute toxicity toward humans and is thought to be a human carcinogen. Regarding its acute toxicity, neurological damage and cognitive and emotional difficulties have been reported. A case-control study revealed an association of exposure to DDT and dicofol with prostate cancer.

There have been several reports on the levels of DDTs in human breast milk in Asian countries. The levels of ΣDDTs in human breast milk were reported to be higher in Chinese mothers than in Japanese and Korean mothers. Based on the ratio of DDTs (*o,p'*-DDT/ *p,p'*-DDT) used as indicator for the contribution of dicofol to the ΣDDT levels, the researchers suspected that a large proportion of the ΣDDTs in Chinese mothers may be attributable to exposure to dicofol. Moreover, there have been other reports suggesting that dicofol is a source of DDT atmospheric pollution. Other researchers demonstrated that DDT pollution in the atmosphere of Chinese cities was attributable to usage of DDT itself, rather than usage of dicofol.

In a new study, researchers determined dichlorobenzophenone, a pyrolysis product of dicofol as a surrogate chemical for dicofol in breast milk, using gas chromatography-mass spectrometry (GC-MS). The results of the study were expected to provide direct evidence for whether dicofol can contaminate human breast milk. In addition, the researchers examined whether dicofol could be the major source of ΣDDTs. To achieve this, samples collected in various geographic sites in the three Asian countries (China, Japan and Korea) were analyzed with the aim of providing insights into the magnitude of pollution with dicofol and ΣDDTs in Asian countries as of 2010.

One of the major limitations of this study is the sample size. In this study, 14 pools from 210 human milk samples were analyzed in total. This size may be sufficiently large to confirm the presence or absence of dicofol in human breast milk and may allow comparisons of the levels of dicofol among the three countries. However, the high and low levels of each pooled sample were averaged out by the pooling, and this masks potential domestic differences in the countries and significant correlations between each of the chemicals and associated factors such as age, body mass index or parity.

(Continued on page 2)

Detection of Dicofol and Related Pesticides in Human Breast Milk

(Continued from page 1)

In terms of the analytical method, the researchers determined the concentrations of dichlorobenzophenone as a surrogate chemical for dicofol. It is a pyrolysis product of dicofol during GC analysis as well as a degraded product of dicofol in the environment. Therefore, it is impossible to distinguish dichlorobenzophenone from two sources in this study. Future studies need to develop an analytical method to solve this issue, such as GC-MS with an on-column injection technique or use of liquid chromatography-mass spectrometry.

In the study, dichlorobenzophenone in human breast milk samples was successfully detected. The very small proportions of dicofol in the ΣDDT levels in the breast milk samples exclude a major role in the exposure to ΣDDTs. This is the first report to identify dicofol in human samples. The level of ΣDDTs in Chinese breast milk samples has decreased from 7700 to 1300 ng/g lipid during the period from 1983 to 1998. Nevertheless, the large daily intake of ΣDDTs through breast milk needs further monitoring.

Source: Chemosphere, Vol. 82, Issue 1, Pages 25-31, January 2011.

LOW-LEVEL MATERNAL METHYLMERCURY EXPOSURE AND POTENTIAL IMPLICATIONS FOR THE HEALTH OF OFFSPRING

Mercury (Hg) is a global pollutant and known neurotoxin. Methylmercury (MeHg) is one of the most toxic forms of Hg due to its ability to cross the blood brain and placental barriers. Intake of fish is considered the primary exposure pathway because Hg is highly concentrated in the aquatic food web and the Hg dose from seafood is greater than 95% MeHg in predatory fish. Historical MeHg poisonings in Japan and Iraq confirmed human health impacts from MeHg exposure were most severe in the developing fetus due to irreversible neural damage.

However, MeHg exposure also occurs through rice ingestion. Rice is grown in an aquatic environment and although documented MeHg concentrations in rice are lower compared to fish tissue, human exposures exceed international guidelines in some regions where rice is a staple food and rice MeHg levels are elevated. Studies concerning human health exposure to MeHg should also include populations where maternal MeHg exposure occurs through ingestion of rice. Rice does not contain long-chain polyunsaturated fatty acids, which are associated with confounding developmental outcomes in offspring.

Unlike fish, rice is a poor source of micronutrients and vitamins. When rice is harvested, the outer inedible husk is removed exposing brown rice, which is composed of pericarp (about 2%), seed coat and aleurone layers (about 5%), the germ (3-4%) and endosperm (89-92%). During the milling process, the germ, pericarp and aleurone are removed, leaving polished white rice. Brown rice contains higher concentrations of some micronutrients, including 35% more zinc (Zn) and iron (Fe), since these nutrients are concentrated in the pericarp, aleurone and germ. Rice also contains phytate, an anti-nutrient that binds cations and limits the absorption of some micronutrients. In the developing world, where a high percentage of caloric intake is from polished white rice, Fe and Zn deficiencies are endemic. Micronutrients in rice, including Fe, Zn and selenium (Se), may affect cognitive outcomes or interact with Hg. Unlike fish tissue, rice is not a source of long-chain polyunsaturated fatty acids or iodine (nutrients in fish tissue).

Most Fe in the body is present in the erythrocytes as hemoglobin, where its main function is to transport oxygen from the lungs to the tissues. Fe deficiency potentially affects developmental brain processes, which are dependent on Fe-containing proteins and Fe-sulfur compounds. The maternal daily requirement for Fe increases during the second half of pregnancy due to the expansion of red blood cell mass and transfer of Fe to the developing fetus and placenta. It is estimated that 50% of pregnant women, and infants and children 1-2 years old are anemic, mostly in developing nations, and many more are Fe deficient. Maternal Fe deficiency may cause premature delivery, resulting in decreased Fe delivery to the fetus. Fe deficiency in infants and children affects cognitive function and psychomotor development.

Zn is an essential component in a large number of enzymatic reactions, which may reflect its flexible coordination geometry and lack of redox sensitivity. Maternal Zn deficiency decreased fetal neurobehavioral development, which was assessed through fetal movement and heart monitoring, while maternal Zn supplements were associated with a 0.4 cm increase in head circumference, a possible indicator of increased neurodevelopment.

Rice and fish tissue contain trace levels of Se (for fish tissue nutrients), and Se concentrations are not decreased when rice is milled. Se is an essential micronutrient and forms selenoproteins, which function as antioxidants and catalysts for the production of active thyroid hormone. Se may reduce the toxicity of Hg by forming inert metal selenide complexes; also, antioxidant properties associated with selenoproteins help eliminate reactive oxygen species induced by Hg exposure. However, evidence for reduction in MeHg toxicity in humans is not consistent.

Half the world's population depends on rice as a staple food, and

(Continued on page 3)

Association of Prenatal Exposure to Polycyclic Aromatic Hydrocarbons (PAHs) with Chromosome-specific Aberrations in Cord Blood

Chromosomal aberrations in peripheral blood lymphocytes are recognized as biomarkers that are predictive of cancer risk in adults and have been associated with environmental exposures occurring in utero or in childhood. In a subset of neonates from the Columbia Center for Children's Environmental Health (CCCEH) cohort, researchers have previously shown that occurrence of stable aberrations was neither random nor proportional to the genomic content of any given chromosome, and that the frequency of stable chromosomal aberrations (predominantly deletions and translocations), detectable by fluorescent in situ hybridization (FISH) using whole chromosome probes (WCP) for chromosomes 1-6 in cord blood, was positively associated with increasing levels of PAHs measured in maternal prenatal air samples.

To confirm and expand upon these observations, in a new study, researchers examined whether the association with air PAHs is chromosome-specific and extends to smaller chromosomes.

Using whole chromosome paints for chromosomes 1-6, 11, 12, 14 and 19, and a 6q sub-telomere specific probe, researchers scored 48 cord bloods (1500 metaphases per sample) from newborns monitored prenatally for airborne PAH exposure in CCCEH. Frequencies of stable aberrations were calculated as incident aberrations per 100 cell equivalents scored, and examined for association with airborne PAHs. Aberrations in chromosome 6 occurred more frequently than predicted by genomic content. Levels of both prenatal airborne PAHs and stable aberration frequency in chromosomes 1-6 decreased to half the levels reported previously in the same cohort. The mean stable aberration frequency was 0.45 in chromosomes 11-19. After adjusting for gender, ethnicity, and household smokers, the mean stable aberration frequency increased with increasing PAH exposure: with a doubling of prenatal PAHs exposure, the mean stable aberration frequency for the chromosome 1-6 group increased by a factor of 1.49; for chromosomes 11-19 mean stable aberration frequency increased by 2.00; for chromosome 6 alone, it increased by 3.16; there was no increase for chromosomes 1-5. Aberrations in chromosomes 11, 12, 14, 19 and 6 were associated with prenatal exposure to PAHs in air, even at lower levels of PAHs in air. The observed chromosome-specific effects of prenatal airborne PAHs raise concern about potential cancer risk.

The data suggest that the effect of prenatal PAH exposure on incidence of chromosomal aberrations persists even at lower levels of PAH exposure and may be concentrated on specific chromosomes. Together these findings suggest that PAH exposure may have significant sub-clinical genetic effects at birth and suggest the need for a better understanding of potential pathways in the development of seemingly disparate effects of PAHs on the newborn. Further exploration to determine PAH-susceptible regions on chromosome 6 may provide insight into mechanisms of PAH related toxicity. This work suggests that decreasing airborne PAH levels through effective public policies may ultimately contribute to decreasing cancer risk.

Source: Mutation Research, Vol. 703, Issue 2, Pages 108-114, December 2010.

LOW-LEVEL MATERNAL METHYLMERCURY EXPOSURE AND POTENTIAL IMPLICATIONS FOR THE HEALTH OF OFFSPRING

(Continued from page 2)

despite the challenges, studies concerning maternal-offspring low-level MeHg exposure should also include populations where polished white rice is the primary exposure pathway. Unlike a cohort that consumes fish tissue regularly, populations depending on polished white rice as a staple food may be underexposed to micro-nutrients, which may confound results. However, the interaction between MeHg and micronutrients in rice is unknown and should be investigated to determine the risk of low-level maternal MeHg exposure to the developing fetus.

Source: Environmental Pollution, Vol. 159, Issue 4, Pages 1017-1022, April 2011.

Occurrence and Fate of a Commonly Used Pesticide in the Atmosphere – A Study of Air Particles and Rain in Agricultural Areas of the Midwestern United States

Although the use of pesticides in agriculture has significantly increased crop yields, concerns exist about the environmental occurrence and fate of pesticides. Approximately 400 million kilograms of pesticides were used in the United States in 2001.

The agricultural sector accounted for about 76% of this use. Within U.S. agriculture in 2001, herbicides, insecticides, fungicides, and other pesticides accounted for 64, 11, 6, and 19%, respectively.

Some fraction of applied pesticide can move away from the application area. A wide variety of pesticides has been observed in different environmental media, including natural water bodies, soil, and atmosphere. Some semivolatile persistent pesticides (dichlorodiphenyl-trichloroethane [DDT], hexachloro-cyclohexanes [HCHs], trifluralin, and metolachlor) have been observed to be transported regionally and globally in the atmosphere. The extent of the pesticide flux from the landscape to the atmosphere is affected by the amount applied, method of application, meteorological conditions, and physical-chemical characteristics of the pesticide. Pesticides can be introduced into the atmosphere though spray drift, volatilization, and wind erosion of soil particles to which they are attached. The removal of pesticides from the local atmosphere includes deposition (wet or dry), photochemical reaction, and advective transport. In the atmosphere, pesticides are distributed between particle and vapor phases based on the vapor pressure of the chemical, ambient temperature, and concentration of suspended particulate matter.

Glyphosate (N-[phosphono-methyl] glycine), a broad-spectrum, nonselective, and postemergence herbicide, is the most widely used pesticide in the United States. It has been used extensively in conjunction with genetically modified crops since 1996.

This is the first report on the ambient levels of glyphosate, and its major degradation product, amino-methylphosphonic acid (AMPA), in air and rain. Concurrent weekly integrated air particle and rain samples were collected during two growing seasons in agricultural areas in Mississippi and Iowa. Rain was also collected in Indiana in a preliminary phase of the study. The frequency of glyphosate detection ranged from 60 to 100% in both air and rain. The concentrations of glyphosate ranged from <0.01 to 9.1 ng/m^3 and from <0.1 to 2.5 µg/L in air and rain samples, respectively. The frequency of detection and median and maximum concentrations of glyphosate in air were similar or greater to those of the other high-use herbicides observed in the Mississippi River basin, whereas its concentration in rain was greater than the other herbicides.

Glyphosate and its degradate, AMPA, were frequently observed in air particles and rain at all three locations that were studied in the agricultural areas of the midwestern United States. Glyphosate occurred at concentrations equal to or greater than the concentrations of other high-use herbicides previously studied in the midwest. The presence of glyphosate in air is due either to spray drift or wind erosion, because it will have no tendency to be volatile because of its low vapor pressure and ionic character in moist soils. The presence of AMPA in air is due to wind erosion, because it is formed in the soil. The maximum concentrations of glyphosate in the air and rain correspond to the period of its application. It is not known what percentage of the applied glyphosate is introduced into the air, but it was estimated that up to 0.7% of application is removed from the air in rainfall. Glyphosate is efficiently removed from the air. It is estimated that an average of 97% of the glyphosate in the air is removed by a weekly rainfall ≥ 30 mm.

Source: Environmental Toxicology and Chemistry, Vol. 30, No. 3, Pages 548-555, March 2011.

RISK ASSESSMENT OF MIXED EXPOSURES TO PESTICIDES – THE POTENTIAL FOR TOXICOKINETIC INTERACTION

People are exposed daily to multiple pesticides, at low levels, via the diet. Intake of pesticides is regulated by using limits such as maximum residue levels (MRL) and acceptable daily intakes (ADI). However, these limit values are necessarily set by consideration of the toxicology of each individual compound. No recognized frame-work exists to evaluate exposure to multiple residues, so consequently the current risk assessments may not adequately reflect the reality of dietary intake in the general population.

When present as a mixture, compounds have the potential to interact to alter the toxicokinetic or toxicodynamic profile from that which would be observed during exposure to any of the individual components. *In vitro* data obtained using human liver fractions have shown that pesticide mixtures can interact to inhibit the rate of metabolism of some compounds. Specifically, low-levels of organo-phosphate were found to inhibit the hydrolytic metabolism of permethrin. If similar interactions occurred *in vivo* they could alter the bioavailability of some pesticides, which would have implications for the risk assessment of these compounds.

As part of a program of research into biomarkers of pesticide exposure, researchers previously conducted volunteer exposure studies for oral doses of deltamethrin, pirimicarb and chlorpyrifos-methyl at their respective ADIs. Exposure to chlorpyrifos, using a

(Continued on page 6)

HEALTH EFFECTS OF OCCUPATIONAL EXPOSURE TO PESTICIDES – A STUDY FROM INDIA

In India, the use of pesticides has increased exponentially in the last few decades, which is attributed mainly to increasing population and booming economy. Pesticides are used in a variety of combinations and researchers in different parts of the world are actively involved in carrying out studies in exposed populations to assess the risk involved due to occupational exposure. Very few studies from India however, have examined the occupational hazards due to pesticide-exposure. People in developing nations like India are at a higher risk of chronic exposure to these chemicals because of poor working conditions and unawareness of the potential hazards. Hence, the main objective of this study was to assess the genotoxic effects of pesticides, acetylcholinesterase (AChE) levels, and hepatic and renal toxicity in workers exposed to pesticides as well as in healthy control subjects.

The study evaluated serum levels of aspartate amino transferase (AST), alanine amino transferase (ALT) and alkaline phosphatase (ALP) as hepatic function test and urea, uric acid, creatinine, protein and albumin as renal function test in occupational workers and control subjects. All these biochemical parameters were found significantly different in occupational workers as compared to control subjects. The results are supported by previous studies where similar results were observed due to pesticides exposure. A significant decrease in the serum albumin level in occupational workers as compared to control subjects was observed. The reduction in serum protein, particularly albumin, could be attributed to change in protein, free amino acid metabolism and their synthesis in the liver. This decrease may be due to the loss of protein either by reduction in protein synthesis or increased proteolytic activity or degradation. Urea and creatinine are waste products of protein metabolism and need to be excreted by the kidney. Therefore, a marked increase in serum urea and creatinine confirms an indication of functional damage to the kidney. Since kidney damage is the only significant factor that increases serum creatinine level, the present study indicates that the kidney was adversely affected by the use different organophosphates (OPs) in the occupational workers.

AChE activity is known as biomarker of chronic toxicity in human following pesticide exposure. The present study reports decreased AChE activity in the occupational workers as compared to control subjects. This decrease in activity is in agreement with previous reported studies. The decrease in AChE activity might be related to the neuroimmunoregulatory role of this enzyme. Since AChE and gamma glutamyl transpeptidase (GGT) are both membrane-bound enzymes, GGT could interact with the neurotransmitter (acetylcholine) that may be removed from the binding with AChE and may result in decreased activity of AChE. Several studies have demonstrated that AChE level can vary widely with alcohol consumption or individual difference in enzyme value. In this context, no significant difference was observed in AChE activity and consumption of alcohol in workers as well as in control subjects. No correlation between AChE activity and comet assay parameters was observed, which is supported by other studies. However, a possible correlation was observed between AChE activity and duration of exposure to different OPs in occupational workers, concluding that with the increase in the duration of exposure to mixture of some OPs, there is a decrease in AChE activity.

Pesticide exposed subjects were investigated for genotoxic effects in the current study using the comet assay. The results indicate that occupational exposure to some OPs induces highly significant increase in the level of DNA damage in occupational workers than control subjects, which is consistent with other reports. An earlier study examined that *in vitro* and *in vivo* administration of chlorpyrifos resulted in two fold increases in DNA single strand breaks. The researchers demonstrated that several OPs may induce the production of reactive oxygen species and oxidative tissue damage which may contribute to toxic manifestation of pesticides.

Occupational exposure to xeno-biotics may result in their covalent binding to DNA, which may lead to chromosome alterations and could be an initial event in the process of chemical carcinogenesis. In general, the induction of genotoxicity such as chromosomal and DNA lesions may lead to further problems of mutagenic and carcinogenic activity. DNA damage is the underlying cause of mutations leading to cancer. This is in line with previous epidemiological studies that demonstrated a relationship between pesticides exposure and the occurrence of cancer.

Previous reports show that smoking and age are associated with DNA damage, whereas in the present study, no positive association between age, smoking and comet assay variables was found.

The genotoxicity observed in the present investigation may be partially attributed to insufficient protective measures used by the occupational workers. This is supported by the fact that proper safety equipment/procedures may significantly reduce the risk of developing genetic disorders in the population exposed to pesticides. Similarly, positive genotoxicity was reported in studies where the workers exposed to pesticides had used insufficient protective measures. It has also been reported that individuals working for at least 6 months under low levels of contamination of pesticides and with appropriate protective measures could substantially reduce genotoxicity.

In conclusion, this is the first study to evaluate concurrently the DNA damage along with AChE activity and several other biochemical parameters related to hepatic and renal toxicity in occupational workers exposed to several OPs and normal healthy subjects from an Indian population. The results indicate that occupational exposure to mixture of pirimiphos methyl, chlorpyrifos, temephos and malathion may cause (i) DNA damage, (ii) decrease in AChE activity, and (iii) hepatic and renal toxicity. Further, AChE activity decreases with the increase in duration of exposure to these OPs. Therefore, there is an urgent need to educate all those who are involved directly or indirectly with the profession of handling pesticides (including contractors and government officials) about the importance of using protective equipment and potential hazards of occupational exposure to these carcinogenic agents. It is also recommended that occupational workers are required to train regularly and are always given appropriate personal protective equipment, and there is a need for strong pesticide safety regulations that should be vigorously enforced.

Source: Environmental Toxicology and Pharmacology, Vol. 31, Issue 2, Pages 278-285, March 2011.

RISK ASSESSMENT OF MIXED EXPOSURES TO PESTICIDES – THE POTENTIAL FOR TOXICOKINETIC INTERACTION

(Continued from page 4)

similar protocol but with different volunteers, has also been studied. Now, a new study describes investigations of the potential for interaction between these compounds when administered as mixtures. Deltamethrin and pirimicarb represent a pyrethroid and a carbamate pesticide, respectively, that are commonly found in food purchased by consumers in the UK. They have been administered orally, to the same pool of volunteers used in previous studies, together with chlorpyrifos-methyl, a commonly occurring organophosphate residue, as a mixed dose at their respective ADIs in order to investigate whether any changes to their toxicokinetic profile could be detected at dietary-relevant levels.

The metabolite excretion profiles for each of the pesticides investigated were remarkably similar, whether administered as an individual compound or as part of a mixed dose. In common with other pesticides, metabolite excretion was almost complete within 24h of exposure, with peak levels being detected around 4h post-dose. Statistical analysis of 24h cumulative metabolite excretion and elimination half-lives showed no significant difference between the single and the mixed-exposure scenarios. Any metabolic interactions, that have been previously reported *in vitro,* would be expected to significantly alter these toxicokinetic parameters in the mixed-dose exposures.

The seemingly conflicting results between the *in vitro* and *in vivo* studies may be explained by a dose-dependent interaction. It is difficult to scale up from the concentration of compounds used for *in vitro* incubations to the available dose following oral administration to human volunteers and computational modeling approaches are beyond the scope of this study. However, while *in vitro* studies have clearly demonstrated the potential for metabolic interactions to occur, the human *in vivo* data indicate that the administered doses of pesticides were below the threshold where any significant effects could be observed.

The data presented in the study indicate that no significant interactions have occurred during the two mixed-exposures. These findings indicate that toxicokinetic interactions between pesticide residues found on food are unlikely to be significant at dietary-relevant levels, so long as exposures are controlled below the ADI.

Source: Toxicology Letters, Vol. 200, Issue 1-2, Pages 41-45, January 2011.

Changes in Human Brain Metabolism Resulting from Childhood Lead Exposure

Despite public health efforts toward reducing body lead burden, exposure to lead hazards remains an international environmental health problem. Lead hazards, including paint in toys and consumer products, contaminants in foods and herbal medicines, and residential contamination from dust, water lines, and soil continue to threaten children's health. In the United States, contaminated older housing stock (built before 1950) continues to expose significant numbers of children to elevated lead environments (dust and soil). Thus, improving our understanding of how the brain manages lead exposure throughout life and at all exposure levels continues to be an important area for research.

Cognitive and executive dysfunction, learning disabilities, and antisocial behaviors are among the impairments attributed to lead exposure in children that persist into adulthood. Lead exposure, even at levels <10 µg/dL, has been associated with these adverse effects in children. Although much is known regarding the neurotoxicity of lead, how lead produces these clinical deficits remains poorly understood. The influence of lead exposure on the developing central nervous system and the mechanisms by which lead disrupts brain metabolism in children are complex.

Now a new study has examined the association between mean childhood blood lead levels and *in vivo* brain metabolite concentrations as adults, determined by proton magnetic resonance spectroscopy (MRS) in a birth cohort with documented low-to-moderate lead exposure.

Adult participants from the Cincinnati Lead Study (mean age, 20.8 years) completed a quantitative, short-echo proton MRS protocol evaluating seven regions to determine brain concentrations of *N*-acetyl aspartate (NAA), creatine and phosphocreatine (Cr), cholines (Cho), myo-inositol, and a composite of glutamate and glutamine (GLX). Correlation and multiple linear regression analyses were conducted.

Mean childhood blood lead levels were associated with regionally specific brain metabolite concentrations adjusted for age at imaging and Full-Scale intelligence quotient. Adjusted analyses estimated for a unit (micrograms per deciliter) increase in mean childhood blood lead concentrations, a decrease of NAA and Cr concentration levels in the basal ganglia, a decrease of NAA and a decrease of Cho concentration levels in the cerebellar hemisphere, a decrease of GLX concentration levels in vermis, a decrease of Cho and a decrease of GLX concentration levels in parietal white matter, and a decrease of Cho concentration levels in frontal white matter.

Gray-matter NAA reductions associated with increasing childhood blood lead levels suggest that sustained childhood lead exposure produces an irreversible pattern of neuronal dysfunction, whereas associated white-matter choline declines indicate a permanent alteration to myelin architecture.

Source: Environmental Health Perspectives, Vol. 119, No. 3, Pages 403-408, March 2011.

EFFECT OF AGE-DEPENDENT EXPOSURE TO LEAD IN MALE RATS

Lead (Pb) is known to induce a broad range of physiological, biochemical, and behavioral dysfunctions in laboratory animals and humans. This includes age specific variations in absorption, retention, and tissue distribution.

Both occupational and environmental exposures remain a serious problem in many developing and industrializing countries. However, for adults, acute occupational Pb poisoning is becoming a less important issue due to better working conditions and significant improvements in protective standards. Children are more vulnerable to Pb exposure for mainly three reasons: young children are more at risk of ingesting environmental Pb through normal mouthing behaviors, the average fractional gastrointestinal absorption of Pb is much greater in infants and young children than in adults, and the developing nervous system is thought to be far more vulnerable to the toxic effects of Pb than the mature brain. Chronic low-level Pb exposure during this period reduces the IQ levels significantly, and unfortunately, most of the neuro-behavioral impacts are irreversible.

Pb toxicity is closely related to its accumulation in certain tissues, and its interference with the bioelements whose role is critical for several physiological processes. Pb has been found to produce a wide range of biochemical and physiological dysfunctions in humans and laboratory animals. Many studies have explored the mechanisms and symptoms of this toxicity through the years, but recent studies have reported Pb as a potential agent for inducing oxidative stress by the production of reactive oxygen species (ROS) and disturbance of prooxidant and antioxidant balance that is found in cells. ROS are produced during normal cellular function. They include hydroxyl radicals ($^{\bullet}OH$), super oxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and nitric acid (NO). These free radicals may oxidize nucleic acids, proteins, lipids, or DNA and can initiate degenerative diseases. ROS produce tissue damage through multiple mechanisms including excito-toxicity, metabolic dysfunction, and disturbance of intracellular homeostasis of calcium. The role of oxygen-derived species in causing cell injury or death is increasingly recognized: superoxide and hydroxyl radicals are involved in a large number of degenerative changes, often associated with an increase in peroxidative process, and linked to low antioxidant concentration.

Antioxidants are substances that either directly or indirectly protect cells against adverse effects of xenobiotics, drugs, carcinogens, and toxic radical reactions. Several biologically important compounds have been reported to have antioxidant functions. These include vitamin C (ascorbic acid), vitamin E (a-tocopherol), vitamin A, b-carotene, metallothionin, poly-amines, melatonin, nicotinamide adenine dinucleotide phosphate (NADPH), adenosine, coenzyme Q-10, urate, ubiquinol, polyphenols, flavo-noids, resveratrol, nitroxides, gluta-thione (GSH), glutathione peroxi-dase (GPx), superoxide dismutase (SOD), catalase (CAT), thioredoxin reductase, nitric oxide synthase, heme oxygenase, and eosinophil peroxi-dase. In fact, oxidative stress occurs when generation of free radicals (i.e., molecules with one or more unpaired electrons) exceed the capacity of antioxidant defense mechanisms (i.e., pathways that provide protection against harmful effects of the radicals). SOD is an important antioxidative enzyme used extensively as a biochemical indicator of pathological states associated with oxidative stress because of the protective role it plays against deleterious effects triggered by superoxide radical anions. SOD destroys the free radical superoxide by converting it to molecular oxygen (O_2) and H_2O_2 that can in turn be destroyed by CAT or GPx reactions. Another function of SOD is to protect dehydratases (dihydroxyacid dehydra-tase, aconitase, 6-phosphogluconate dehydratase) and fumarases A and B against activation by the free radical superoxide.

The liver and the kidney, being organs playing a vital part in the metabolism of Pb, are at especial risk of damage due to the oxidative action of this heavy metal. Pb is known to produce oxidative damage in liver and kidney tissues by enhancing per-oxidation of membrane lipids, a deleterious process solely carried out by free radicals. Also, Pb possesses a strong affinity to thiol groups (SH) of aminoacids. It has been revealed that Pb may affect the antioxidant barrier via inhibiting the functional SH groups of antioxidant enzymes such as SOD and CAT.

Based on these considerations, this study was carried out to investigate the effects of chronic exposure to Pb (50 mg/L) on liver and kidneys of two different age groups of male rats treated with Pb from delivery until puberty period (40 days) and postpuberty period (65 days). For this purpose, the concentrations of thiobarbituric acid reactive substance (TBARS), total SH, and SOD activity were measured in the liver and kidney of rats. Renal function was analyzed by determining creatinine, uric acid, and urea. Plasma activities of alanine aminotransferase, aspartate amino-transferase, alkaline phosphatase, and albumin were determined spectrophotometrically to evaluate hepatic function. These markers of damage were determined to assess the level of toxicity in these animals. The results clearly show that the administration of Pb produces oxidative damage in liver and kidney, as strongly suggested by the significant increase in TBARS, decrease in total SH, and the alteration of SOD activity. In young Pb-exposed animals, Pb-induced perturbations on the synthetic function of the liver and the kidney were more pronounced. However, nephropathy is evident for adult Pb-exposed animals. It is concluded that Pb induces severe hepatic and renal toxicity, which depends on the age of the animals and the target organ.

Source: Environmental Toxicology, Vol. 26, Issue 1, Pages 68-78, February 2011.

CONGRESS ANNOUNCEMENT

The 7th Princess Chulabhorn International Science Congress (PC VII)
CANCER: FROM BASIC RESEARCH TO CURE

November 13-17, 2011, Shangri-La Hotel, Bangkok, THAILAND

Chairperson of the Organizing Committee: **Professor Dr. HRH Princess Chulabhorn**

Keynote Speaker: ***J. Michael Bishop (Nobel Laureate, U.S.A.)***

ANNOUNCEMENT AND CALL FOR ABSTRACTS

The Congress will be held to commemorate the seventh cycle (84 years) of the birth of His Majesty King Bhumibol Adulyadej. The program will feature a Keynote Lecture, Plenary Lectures, Symposia, Roundtable Discussion and Poster Presentations. Concurrent worksho ps on issues relating to the focus of the Congress are also organized.

THEMES AND TOPICS:

Track 1: Cancer Etiology and Mechanisms

- Genetic alterations (DNA damage/repair)
- Cancer pathways – epigenetic changes
- Carcinogenesis: environment and emerging exposures
- Inflammation and cancer
- Cancer stem cells

Track 2: Early Detection, Diagnosis and Prognosis

- Molecular diagnostics
- Molecular approaches to early detection
- Circulating tumor cells as novel tumor biomarker
- Proteomic markers of prognosis and therapeutic outcomes

Track 3: Cancer Prevention

- Molecular approaches and targets for cancer prevention
- Diet and nutritional factors

Track 4: Towards the Cure

- Molecular targets for therapeutic intervention
  - Histone modifications
  - Non-coding RNAs (RNAi , siRNAs, miRNA)
  - Modulation of DNA repai r and cell death pat hways
- Targeting of cancer stem cells
- Drug design, disco very and development
- Biomarkers in anticancer drug discovery
- Adaptive biomarker driven therapy
- Recent advances in basic research and therapy of specific type of cancers

CALL FOR ABSTRACTS:

All congress participants are invited to submit abstracts for **poster presentations**. The final selection will be made by the Scientific Committee based on significance and quality of the work.

Deadline for abstract submission is on AUGUST 31, 2011.

For all further information, please visit the Congress Website:

http://pc.cri.or.th/pc7

The ICEIT NEWSLETTER is published quarterly by the International Centre for Environmental and Industrial Toxicology of the Chulabhorn Research Institute. It is int ended to be a source of information to create awareness of the problems caused by chemicals. However, the contents and views expressed in t his newsletter do not necessarily represent the policies of ICEIT.

Correspondence should be addressed to:

ICEIT NEWSLETTER
Chulabhorn Research Institute
Office of Academic Affairs
Vibhavadee-Rangsit Highway
Bangkok 10210, Thailand
Tel: +66 2 574 0615
Fax: +66 2 574 0616
CRI Homepage: <http://www.cri.or.th>

For back issues of our new sletter, please visit:

http://www.cri.or.th/en/envtox/et_newsletter.htm