CRI/ICEIT
NEWSLETTER

VOL. 25 NO. 3 – July 2015
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".

Biomonitoring of Trace Metals in Urine and Hair of Children Living Near Industrial Areas

Low-dose exposure to environmental pollutants, including trace metals, in non-occupational settings is becoming a serious problem, especially for pregnant women and children as they are considered the most vulnerable population subgroups.

Environmental exposures can threaten children's health *in utero* through the mobilization of various toxic compounds from maternal tissues during pregnancy, and at later stages through breast feeding. Exposure continues during childhood through food and water intake, inhalation and/or dermal absorption of metal elements.

Children show immature detoxification mechanisms. Their vulnerability is related to physical features (high surface area), nutritional aspects (children drink more water and eat more food per unit of body weight than adults) and behavioral patterns (direct contact with the ground, tendency to put everything into their mouths, etc.).

Subtle cognitive and neurobehavioral changes have been reported in children exposed to low doses of trace metals, even below concentrations considered safe for most people.

Human biological monitoring has become an important tool in environmental and public health for the assessment of internal doses to harmful substances. Although blood and urine analyses are traditional approaches for biomonitoring, human hair is an interesting matrix because hair concentrations of metal compounds are up to 10-fold higher than the levels found in blood or urine samples.

A biomonitoring study was conducted to assess exposure to arsenic and some trace metals (cadmium, mercury, manganese and lead) in urine and scalp hair from 261 children aged 6-9 years living near an industrial/mining region on the Southwestern coast of Spain (Huelva).

The study areas represent one of the most polluted estuaries in the world as a consequence of the discharge of smelters' plumes and mining related pollutants to air and rivers, with industrial activity influencing the trace element composition of particulate matter.

This is the first study which simultaneously analyzes those five metal elements into two different matrices (urine and hair) from a population of children.

The potential contribution of gender, water consumption, residence area and body mass index on urinary and hair metal concentrations was also studied.

The results from the sample indicate that urine levels of cadmium and total mercury in a proportion (25–50%) of the children living in these industrial/mining areas, was likely due to environmental exposure to metal pollution and might have an impact on health.

The only significant correlation between urine and hair levels was found for mercury. However, while hair content is related to past exposures, urinary levels reflect recent exposure except for cadmium. This toxicokinetic difference may account for the lack of correlations found in this study.

The greatest urine arsenic concentrations were found in children

(Continued on page 2)

Biomonitoring of Trace Metals in Urine and Hair of Children Living Near Industrial Areas

(Continued from page 1)

drinking well/spring water. It was suggested that different arsenic concentrations in drinking water could influence arsenic levels in children.

Although trace metal levels have been related to area of residence, this study found that there were no significant differences in metal concentrations in the urine (except for mercury) of children living in urban, metropolitan or rural areas.

Human hair can be a useful tool for biomonitoring temporal changes in metal concentrations, but levels are not correlated with those found in urine, except for total mercury, thus providing additional information.

Children are a particularly vulnerable population with regard to developmental and neurotoxic effects of metals and deserve special attention in biomonitoring programs. Furthermore, reference limits for adults may not necessarily be protective for children. Therefore, recognizing children's special vulnerability and diminishing their exposure to environmental pollutants would be a step forward in preventing potential environmental diseases in children.

Source: Chemosphere, Vol. 124, Pages 83-91, April 2015.

Lead and/or Cadmium induced Oxidative Stress in Blood, Liver and Kidneys

Lead (Pb) and cadmium (Cd) are toxic metals of great occupational importance, but are nowadays even more significant as environmental pollutants. Both metals can induce serious adverse health effects in the organs and various systems of an organism.

Pb and Cd toxicity have been comprehensively explored in many *in vitro* and *in vivo* studies, and various molecular, cellular and intracellular mechanisms have been proposed to explain the toxicological profiles of these two toxic metals.

With regard to the fact that thousands of compounds are present in the environment, from natural or anthropogenic sources, human exposure to toxic agents cannot be characterized as exposure to a single agent, but more correctly as an exposure to mixtures of these toxic agents.

Concurrent exposure to these metals may produce additive effects or synergistic/antagonistic interactions, or even produce completely new effects which are not seen with exposure to only one of the metals. Evaluation of these interactions is essential for risk assessment of their co-exposure and subsequent mitigation of assessed health risk.

This paper reviews short and long term studies conducted on Pb or Cd-induced oxidative stress in blood, liver and kidneys as the most prominent target organs of the toxicity of these metals and proposes the possible molecular mechanisms of the observed effects.

Although distinctively different in their specific toxic effects, the toxicity of Pb and Cd is certainly driven by induction of oxidative stress as an important mechanism of their toxicity.

Up-to-date studies have shown that both Pb and Cd, regardless of their non-redox nature, can cause oxidative stress in various organs, including blood, liver and kidney, by generation of free radicals and by affecting antioxidant defense system.

The effects of these metals on free radical generation are indirect, but include different mechanisms.

Pb induces inhibition of δ-aminolevulinic acid dehydratase (ALAD) which in turn increases the levels of δ-aminolevulinic acid (ALA) followed by the production of free radicals, while the effects of Cd can be mainly explained by its interaction with a Fenton metal (Fe^{3+}).

Literature data also indicate the effects of Pb and Cd on antioxidant defense system: Pb directly affects various enzymes by binding to —SH groups whereas Cd can inhibit the enzymes' activity even indirectly, as a consequence of interactions with bioelements.

Cd is the more potent inducer of the synthesis of metallothionein and has greater effect on the gene expression of antioxidant enzymes in comparison to Pb.

However, the exact mechanisms of oxidative stress induction, especially in terms of action at molecular and submolecular levels, remain to be further explained and this may be the key to understanding the differences between the threats these metals pose to human health as well as to the environment.

Pb and Cd are still important occupational agents and are even more important as global pollutants. However, investigations on the co-exposure to Pb and Cd on oxidative status in various target organs of their toxicity, especially at low doses present in the environment, are rather sparse and inconclusive.

Regarding research on the mechanisms of joint toxicity of Pb and Cd, the available studies provide evidence of synergistic or antagonistic interactions depending on duration, dose of exposure and type of investigated organ.

Studies on the toxicity of mixtures, not only of these two metals but also of mixtures of other metals and mixtures of metals with other toxic agents, continue to be one of the greatest challenges of contemporary toxicology.

Source: Food and Chemical Toxicology, Vol. 78, Pages 130-140, April 2015.

Air Pollution and Newborn Blood Pressure

Air pollution has been associated with increased blood pressure in adults and children.

Earlier studies have found that greater prenatal exposure to air pollution is related to low birth weight, preterm birth, and higher maternal blood pressure (BP) in pregnancy.

There is evidence that infant BP is influenced by prenatal maternal conditions such as hypertension and drug use. It is also known that the infant's weight, gestational age, and postnatal age, are relevant. Up to now, however, the effects of prenatal air pollution on neonatal BP have not been explored.

This recent study examined the association between newborn systolic blood pressure (SBP) and antenatal exposure to ambient air pollution. The antenatal period is a time of gestation, which is an important period of cardiovascular growth and development.

The study considered the potential effects of several air pollutants, including fine particulate matter ($PM_{2.5}$), black carbon (BC), nitrogen oxides (NOx), nitrogen dioxide (NO_2), ozone (O_3), and carbon monoxide (CO).

Prior studies have generally used PM as a proxy for air pollution exposure. BC, a traffic-related component of PM, has also been associated with BP in adults, and was considered as well.

Average exposures were calculated by trimester and during the 2 to 90 days before birth for temporally resolved pollutants at stationary monitoring sites, and for spatiotemporally resolved estimates of $PM_{2.5}$ and BC at the residence level.

The results show that increased estimated exposures to outdoor $PM_{2.5}$ and BC in the third trimester, but not in the first and second trimesters, were associated with higher systolic blood pressure (SBP) in newborns.

It is noteworthy that increased exposure to O_3 in the third trimester was associated with lower SBP in newborns, whereas exposure in the second trimester was associated with higher BP.

In addition, increased estimated exposures to CO or NOx during the second trimester also were associated with lower newborn SBP.

These results indicate that gaseous pollutants such as O_3, NOx, and CO may affect BP through a different biological pathway than particulate pollutants.

Neonatal BP may have a different meaning to BP measured later in infancy, childhood, or adulthood. From infancy onward, children tend to maintain their BP ranking, meaning that infants with relatively high BP are more likely to have high BP in adulthood.

Follow-up studies are needed to assess the implications of these findings for health during later childhood and adulthood.

Source: Environmental Health Perspectives, Vol. 123, No. 4, Pages 353-359, April 2015.

Carbon Monoxide Pollution and Neurodevelopment

Although an association between air pollution and adverse systemic health effects has been known for years, the effect of pollutants on neurodevelopment has been underappreciated.

Infants and children appear to be uniquely vulnerable to the neurotoxicity of air pollution due to the susceptibility of the brain during critical periods in development and the potential for exposure to such neurotoxicants in both the fetal milieu and the postnatal environment.

Recent evidence suggests a possible link between air pollution and neurocognitive impairment and behavioral disorders in children. However, the exact nature of this relationship remains poorly understood.

Air pollution is a heterogeneous mixture of gases and particulate matter. The main gaseous components of air pollution are ozone, carbon monoxide (CO), nitrogen dioxide, and sulfur dioxide. As a by-product of incomplete combustion of hydrocarbons, CO is a major component of motor vehicle-related pollution, tobacco smoke, and gas stove pollution.

CO is of particular interest as a known neurotoxicant and a potential public health threat because it can cross the placenta to gain access to the fetal circulation and the developing brain.

This new study reviews overt CO toxicity and the policies regulating CO exposure, details the evidence suggesting a potential link between CO-associated ambient air pollution, tobacco smoke, and learning and behavioral abnormalities in children. It also describes the effects of subclinical CO exposure on the brain during development, and provides mechanistic insight into a potential connection between CO exposure and neurodevelopmental outcome.

Studies include how CO can disrupt a number of critical processes in the developing brain, and provide a better understanding of how this specific neurotoxicant may impair neurodevelopment. However, further investigation is needed to better define the effects of perinatal CO exposure on the immature brain.

Current policies regarding CO standards were established, based on evidence of cardiovascular risk in adults with pre-existing comorbidities.

As understanding about the risks of CO exposure during critical periods of human development increases, emerging data should guide and inform future revision of the standards and guidelines regulating CO exposure. This will be necessary in order to take into account the vulnerabilities and nuances of the fetus and developing child.

Ultimately, enhanced knowledge and consideration will beneficially impact the safety and well-being of infants and children around the world.

Source: Neurotoxicology and Teratology, Vol. 49, Pages 31-40, May-June 2015.

Association of Persistent Organic Pollutants and Non-persistent Pesticides with Diabetes in Asia

Rapid agricultural and industrial development in Asia over the past 50 years has led to high exposure levels of potentially toxic chemicals including persistent organic pollutants (POPs) and non-persistent pesticides (pyrethroids and organophosphates).

Concurrent with these increases in chemical exposure, diabetes in Asia has also become much more prevalent.

In 2013, 43% of the 382 million adults with diabetes in the world were found to live in two Asian countries: 98.4 million people in China and 65.1 million people in India.

Not surprisingly, emerging scientific evidence has associated diabetes with environmental pollutants.

The U.S. National Toxicology Program Workshop conducted in January 2011 concluded that evidence is sufficient to support an association of some organochlorine POPs, particularly trans-nonachlor, dichlorodiphenyldichloro-ethylene (DDE), polychlorinated biphenyl (PCB) congener 153, and dioxins, with type 2 diabetes.

A new investigation was conducted to systematically review the literature of studies published up to November 2014, concerning the association of POPs and non-persistent pesticides (pyrethroids and organophosphates) with diabetes and diabetes-related health outcomes in Asia.

However, the results showed that the evidence relating POPs and non-persistent pesticides with diabetes in Asian populations is equivocal.

Positive associations were reported between serum concentrations of polychlorinated dibenzodioxins and dibenzofurans (PCDD/Fs), PCBs, and several organochlorine pesticides (DDT, DDE, oxychlordane, trans-nonachlor, hexachlorobenzene, hexachlorocyclo-hexane) with diabetes. PCDD/Fs were also associated with blood glucose and insulin resistance, but not beta-cell function.

There were substantial limitations in the literature. Most of the studies reviewed were cross-sectional in design. Dose-response assessment was lacking and there was variability in exposure and outcome assessment. Few studies have evaluated the association between POP and organophosphate exposure and the pathogenic process that leads to diabetes, such as insulin resistance, and beta-cell function.

Gaps include differences by disease outcomes. It is still not clear how POP exposure varies by sex, race or ethnicity, especially when considering varying levels of adiposity, insulin resistance, and beta-cell function. Nor has it been ascertained which POPs may be most feasible or effective to intervene upon in Asia with the goal of reducing the prevalence of diabetes.

Given that the burden of diabetes in this part of the world is already significant and expected to increase, well-conducted research is urgently needed on these pervasive exposures to inform policies which can help mitigate the diabetes epidemic in Asia.

Source: Environment International, Vol. 76, Pages 57–70, March 2015.

Vitamin E Ameliorates Memory Defects in Lead-Treated Rats

Human exposure to lead (Pb^{2+}) occurs via food, water, air and soil. The toxic effects of Pb^{2+} depend on both duration of exposure and dose. Pb^{2+} can damage various systems of the body, including the hematopoietic, renal, and skeletal systems, with the central nervous system being its primary target.

Pb^{2+} has been widely recognized as a potent central neurotoxicant that interferes with neuronal function and brain activity in animals and humans.

Although the effects of Pb^{2+} on learning and memory have been extensively reported, the molecular mechanisms by which Pb^{2+} produces these effects have not yet been completely defined.

Because oxidative stress can induce brain damage in animal models, it may also contribute to learning and memory deficits in humans. Vitamin E, which is well known for its established health benefits, including antioxidant, neuroprotective, and anti-inflammatory properties, has also been shown to prevent brain damage and cognitive deficits in rats due to oxidative stress.

This study attempted to determine whether vitamin E supplements can prevent Pb^{2+}-induced memory impair-ment. To test this possibility, researchers administered a long-term diet (for 30 days) containing Pb^{2+} and vitamin E in Wistar rats.

After the 30-day period, the rats were tested using a passive avoidance task (acquisition test). In a retrieval test conducted 48 h after the training, step through latency (STL) and time in the dark compartment (TDC) were recorded.

The results of the study showed that chronic exposure to high doses of Pb^{2+} significantly increased both the number of trails required for learning and the TDC. However, it decreased the STL in the passive avoidance test.

These results indicate that impairments of learning and memory in Pb^{2+}-exposed rats are dose dependent and can be inhibited by antioxidants such as vitamin E.

The study emphasized the importance of the treatment period and dosage for both Pb^{2+} and vitamin E, and concluded that vitamin E can ameliorate memory defects in Pb2+-treated rats.

Proper diet and vitamin supplements appear to be a simple and inexpensive way to counter the effects of toxic agents that cannot be completely eradicated from our environment

Source: Physiology & Behavior, Vol. 144, Pages 90-94, May 2015.

Methylmercury Exposure in Asian Populations at Risk

Environmental pollution in global waterways has resulted in the contamination of fish with methylmercury (MeHg). Ingestion of fish contaminated with MeHg can lead to adverse health outcomes, particularly when exposure occurs *in utero*.

Exposure to MeHg via fish consumption during pregnancy results in blood levels that cross the placenta and concentrate in the fetal brain, leading to risk of behavioral and cognitive abnormalities in offspring.

At the same time, consumption of fish during pregnancy also confers health benefits such as improved vision and cognitive development in offspring, and in adults, lower risk of sudden cardiac death at least in part due to the omega-3 fatty acids in fish.

Therefore, optimal health requires a balance of the risks and benefits of fish consumption.

The National Health and Nutrition Examination Survey (NHANES) 2011–2012 included measurements of total blood mercury (TBHg) and MeHg as well as a unique race/ethnicity category for Asians, allowing for improved analysis of determinants of risk.

Measuring TBHg and monitoring fish consumption to detect elevated MeHg are first steps toward establishing recommendations for clinical screening for mercury exposure.

This study was conducted to characterize the current burden of MeHg exposure in the US among subgroups (Asians) who are at risk of health effects due to frequent fish consumption or due to their physiologic vulnerability to MeHg's effects, specifically women of child bearing age (WCBA) and adults ≥50 years of age (the aging cardiovascular system).

The validity of screening procedures, using TBHg testing and questions pertaining to fish consumption, was calculated to predict elevated MeHg.

The results are a matter of concern due to the percentage of Asian WCBA and Asian adults ≥50 years of age who are at risk of health effects due to MeHg exposure. Asian WCBA continue to have increased MeHg exposure from fish consumption, putting their offspring at risk of adverse neurodevelopmental outcomes.

Currently no guidelines exist for mercury screening in clinical care.

The results show that monitoring TBHg is a valid screening test for elevated MeHg among high risk groups. Adding a fish consumption question to a sequential screening procedure among WCBA and adults ≥50 years of age has similar validity to the TBHg used alone but requires drawing blood from only 50–80% of those who would receive blood testing in universal blood screening.

These preliminary findings should be used to pursue additional research evaluating ways to incorporate screening and prevention education into routine clinical care. Studies already show that warning patients about contaminants in fish can result in decreased fish consumption to below recommended frequencies (two servings per week).

More work is needed using larger datasets before screening guidelines can be tailored for specific ethnic groups or according to fish consumption frequency.

It will be important to identify and resolve unintended negative outcomes of screening such as a decrease in the consumption of healthy fish and a resulting loss of the health benefits of omega-3 fatty acids in fish.

Source: Environmental Research, Vol. 140, Pages 56-64, July 2015.

New *In Vivo* Assay for Estrogenic Disruption Research

Endocrine disruption describes a property of exogenous chemicals, either natural or manmade, that leads to perturbation of biological function via endogenous endocrine systems.

However, endocrine disruption encompasses broad classes of chemicals that individually affect diverse biological signaling pathways. Thus, there is a need to focus on identifying which substances are endocrine-disrupting chemicals.

High-throughput *in vitro* assays help with preliminary screening, but they can't identify how a compound may affect the body. Some *in vitro* screens can assess whether a chemical binds to the ligand-binding domain of the estrogen receptor, but the ability to bind to the receptor says nothing about the consequences of that binding.

In vivo methods will be needed to explore how the same estrogen receptor that binds to so many different kinds of ligands induces so many different effects.

In this recent study, researchers designed a multi-pronged approach that combines transcriptional and phenotypic end points in order to evaluate chemicals suspected to affect estrogen signaling and classified as short- or long-acting estrogen.

The study used biological end points in uterine tissue and a signature pattern-recognizing tool that identified coexpressed transcripts. Using an *in vivo* system, the objective was to develop and test a panel of transcripts for use as biomarkers and phenotypic uterine responses in order to classify potentially estrogenic compounds.

The end points used are relevant to uterine tissue, but the resulting classification of the compounds is important for other sensitive tissues and species.

(Continued on page 6)

Glyphosate Causes Behavioral Changes and Alterations in Dopaminergic Markers in Male Rat

In recent years, reports of glyphosate exposure in humans and animal models suggest that both the commercial mixture containing glyphosate and the active ingredient glyphosate could have neurotoxic effects, which may affect the dopaminergic system, probably by oxidative stress.

In human studies, the herbicide glyphosate has been detected in brain and cerebrospinal fluid after exposure to commercial mixtures, revealing that the active ingredient can cross the blood brain barrier. Also, abnormal electro-encephalogram (EEG) activity and a Parkinsonian syndrome characterized by limb tremor at rest, global akinesia and rigidity have been observed after occupational exposure and accidental ingestion of the commercial mixture of glyphosate.

In animal models, oral exposure to the commercial mixture of glyphosate during pregnancy was associated with increased enzymatic activity of isocitrate dehydrogenase in the brain of pregnant dams, while the activities of isocitrate dehydrogenase, glucose-6-phosphate dehydrogenase and malate dehydro-genase were found to be increased in the fetal brain.

The dopaminergic nigrostriatal and mesolimbic systems are involved in the control of movement and motivated behaviors, and have been shown to be vulnerable to herbicides such as paraquat and atrazine.

However, there have been no systematic studies evaluating the effects of the repeated and acute exposure to glyphosate on the dopaminergic systems in an *in vivo* model.

This new study evaluated the integrity of the nigrostriatal and mesolimbic dopaminergic systems by assessing biochemical (monoamine content, tyrosine hydroxylase (TH) levels and specific binding to D1 and D2-dopamine (DA) receptors) and histological (mesencephalic TH+ cells) dopaminergic markers and their relationship with spontaneous locomotor activity in male Sprague-Dawley rats that were repeatedly or acutely exposed to glyphosate.

Repeated glyphosate exposure results in hypoactivity accompanied by decreases in specific binding to D1-DA receptors in the nucleus accumbens (NAcc). Such acute exposure to glyphosate has evident effects on striatal DA levels. These results suggest that glyphosate affects the dopaminergic system.

It is important to note that D1-DA receptor binding was reduced in the NAcc, and showed a positive correlation with the decrease observed in ambulatory activity recorded immediately after glyphosate administration. These findings are consistent with studies that have shown that both the NAcc and D1-DA receptors are involved in motor control.

Also, the results show that the striatum and NAcc were differentially vulnerable to glyphosate exposure. This may be due to the peculiar anatomic and physiological properties of the nigrostriatal and mesolimbic pathways. In this study, ambulation and rearing behavior correlated with D1-DA binding in the NAcc but not in the striatum; on the other hand, stereotypical behavior, which is considered to be controlled by the striatum, was not as affected and did not correlate with DA binding. This suggests a differential sensitivity to glyphosate in these nuclei.

Additional experiments are necessary in order to unveil the specific targets of glyphosate on dopaminergic system, and to discover whether glyphosate could be affecting other neurotransmitter systems involved in motor control.

Source: NeuroToxicology, Vol. 46, Pages 79-91, January 2015.

New In Vivo Assay for Estrogenic Disruption Research

(Continued from page 5)

These biomarkers and responses are measured at 2 and 24 hours after administration of the test chemical to determine whether the substance is long- or short-acting.

The researchers tested the assay on a compound known as diarylheptanoid (D3), which comes from *Curcuma comosa* Roxb., a member of the ginger family. D3 is believed to have estrogenic properties and is used by Thai women to relieve symptoms of menopause.

The results show that both the uterine effects and the gene transcription activity of D3 at 2 and 24 hours were consistent with a short-acting estrogen.

This new assay enables researchers to determine whether a chemical has estrogenic effects, and also gives them the ability to classify the substance as a short- or long-acting estrogen.

This is important in predicting potential responses in various populations. For instance, girls and postmenopausal women may be more sensitive to effects of short-acting estrogens because their bodies do not produce long-acting estrogens.

The next big hurdle for endocrine disruptor research is figuring out how to translate the results of these and other assays into risk assessments, and also figuring out similarities and differences between different environmental estrogens.

Source: Environmental Health Perspectives, Vol. 123, No. 4, Pages 344-352, April 2015.

IARC Announced the Carcinogenicity of Tetrachlorvinphos, Parathion, Malathion, Diazinon, and Glyphosate

On March 20th, 2015, after convening a meeting of 17 cancer experts from 11 countries, the International Agency for Research on Cancer (IARC; Lyon, France) announced its assessment of the carcinogenicity of 5 organophosphate pesticides including tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate.

The results of the IARC evaluations are as follows:

The herbicide **glyphosate** and the insecticides **malathion** and **diazinon** were classified as *probably carcinogenic to humans (Group 2A).* The evidence in humans is from studies of agricultural exposures in the USA, Canada, and Sweden published since 2001.

The insecticides **tetrachlorvinphos** and **parathion** were classified as *possibly carcinogenic to humans (Group 2B)* based on convincing evidence that these agents cause cancer in laboratory animals.

The **Group 2A** category of *"**probably** carcinogenic to humans"* is used when there is limited evidence of carcinogenicity in humans but sufficient evidence of carcinogenicity in experimental animals.

Limited evidence means that a positive association has been observed between exposure to the agent and cancer but that other explanations for the observations (chance, bias, or confounding) could not be ruled out.

This category is also used when there is limited evidence of carcinogenicity in humans but strong data on how the agent causes cancer.

The **Group 2B** categorization of *"**possibly** carcinogenic to humans"* often means that there is convincing evidence that the agent causes cancer in experimental animals but little or no information about whether it causes cancer in humans.

For the herbicide **glyphosate**, there is limited evidence of carcinogenicity in humans for non-Hodgkin lymphoma. In addition, there is convincing evidence that glyphosate also can cause cancer in laboratory animals. Glyphosate increased pancreatic Islet-cell adenoma in male rats. In male CD-1 mice, glyphosate induced a positive trend in the incidence of a rare tumour, renal tubule carcinoma.

A study reported a positive trend for haemangiosarcoma in male mice. Glyphosate and glyphosate formulations induced DNA and chromosomal damage in mammals, and in human and animal cells *in vitro.*

Glyphosate is a broad-spectrum herbicide and currently has the highest production volumes of all herbicides. Its use has increased sharply with the development of genetically modified glyphosate-resistant crop varieties.

For the insecticide **malathion**, there is limited evidence of carcinogenicity in humans for non-Hodgkin lymphoma and prostate cancer. In mice, malathion increased hepatocellular adenoma or carcinoma (combined). In rats, it increased thyroid carcinoma in males; hepatocellular adenoma or carcinoma (combined) in females; and mammary gland adenocarcinoma after sub-cutaneous injection in females.

Malathion caused DNA and chromosomal damage and also disrupted hormone pathways. Hormonal effects probably mediate rodent thyroid and mammary gland proliferation.

Malathion is currently used in agriculture, public health, and residential insect control. It continues to be produced in substantial volumes throughout the world.

For the insecticide **diazinon**, there is limited evidence of carcinogenicity in humans for non-Hodgkin lymphoma and lung cancer. However, in rodents, diazinon increased hepatocellular carcinoma in mice and leukaemia or lymphoma (combined) in rats, but only in males receiving the low dose in each study.

Diazinon induced DNA or chromosomal damage in rodents and in human and mammalian cells *in vitro.*

Diazinon has been applied in agriculture and for control of home and garden insects. Production volumes have been relatively low and decreased further after 2006, due to restrictions in the USA and the European Union.

The insecticide **tetrachlorvinphos** induced hepatocellular tumours in mice, renal tubule tumours in male mice, and spleen haemangioma in male rats.

Although bacterial mutagenesis tests were negative, tetrachlorvinphos induced genotoxicity in some assays (chromosomal damage in rats and *in vitro*) and increased cell proliferation (hyperplasia in rodents).

Tetrachlorvinphos is banned in the European Union. In the USA, it continues to be used on animals, including in pet flea collars.

The insecticide **parathion** increased bronchioloalveolar adenoma and/or carcinoma in male mice, and lymphoma in female mice. In rats, parathion induced adrenal cortical adenoma or carcinoma (combined), malignant pancreatic tumours; thyroid follicular cell adenoma in males; and mammary gland adenocarcinoma.

Although bacterial mutagenesis tests were negative, parathion induced DNA and chromosomal damage in human cells *in vitro.*

Parathion use has been severely restricted since the 1980s.

Detailed assessments will be published in *Volume 112 of the IARC Monographs: Some Organophosphate Insecticides and Herbicides* (in Press).

Source: The Lancet Oncology, Volume 16, No. 5, Pages 490-491, May 2015.

CALENDAR OF EVENTS

International Training Courses at Chulabhorn Research Institute
Schedule for 2015 - 2016

	Training Course	Date	Duration	Closing Date
1.	Environmental and Health Risk Assessment and Management of Toxic Chemicals	December 5-18, 2015	2 weeks	October 15, 2015
2.	Detection of Environmental Pollutants, Testing and Screening of Toxicity	February - March, 2016	2 weeks	November 25, 2015
3	Environmental Toxicology	May, 2016	2 weeks	February 25, 2016

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

Course Description:

1. Environmental and Health Risk Assessment and Management of Toxic Chemicals (December 5-18, 2015)

The course is an integration of science and policy, covering the fundamental basis of environmental and health risk assessment and management, from identification of hazard, assessment methods, the mode of action and human relevance framework, the inherent uncertainties in each step, the relationship between risk assessment and risk management, and the need for open, transparent and participatory acceptance procedures and credible communication methods. Emphasis is placed on human health risk assessment, although the principles of ecological risk assessment will also be covered. 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.

2. Detection of Environmental Pollutants, Testing and Screening of Toxicity (February - March, 2016)

This course covers both theoretical and practical aspects in toxicology relating to the detection of different types of toxicants and their associated toxicity. It presents the different analytical methods in environmental toxicology; toxic compounds in the environment, mechanisms of actions and their effects on man; how to monitor human exposure through the use of biomarkers; and modern techniques instrument analysis. Participants will have an opportunity to conduct hands on experiments and testing.

Requirement: Participants should have jobs/responsibilities related to the detection of toxicity from toxic compounds in the environment and their effects in humans.

Fellowships:

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

Contact: Chulabhorn Research Institute (CRI)
54 Kamphaeng Phet 6 Rd.,
Lak Si, Bangkok 10210, Thailand
Tel: +66 2 553 8535
Fax: +66 2 553 8536
E-mail: envtox@cri.or.th

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.

Correspondence should be addressed to:

ICEIT NEWSLETTER
Chulabhorn Research Institute
Office of Academic Affairs
54 Kamphaeng Phet 6 Road
Lak Si, Bangkok 10210, Thailand
Tel: +66 2 553 8535
Fax: +66 2 553 8536
CRI Homepage: <http://www.cri.or.th>

For back issues of our newsletter, please visit:

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