CRI/ICEIT
NEWSLETTER

VOL. 22 NO. 4 – October 2012
ISSN 0858-2793
BANGKOK, THAILAND

Chulabhorn Research Institute

INTERNATIONAL CENTRE FOR ENVIRONMENTAL AND INDUSTRIAL TOXICOLOGY (ICEIT)

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A STUDY OF THE EFFECTS OF LONG-TERM EXPOSURE TO TRAFFIC PARTICLES

Both short-term and long-term exposure to particulate air pollution has been associated with cardiovascular morbidity and mortality in numerous epidemiological studies. The effects of long-term exposure are substantially larger than those of short-term exposure, suggesting differences in the mechanisms at play or differences in how the mechanisms are impacted on longer-term exposures. A number of pathways have been proposed to explain these associations, including, at the molecular level, increased oxidative stress, systemic inflammation and thrombotic potential. At the functional level, potential pathways include changes in autonomic function, which may result in changes in blood pressure (BP).

Elevated BP is an established risk factor for coronary heart disease and stroke and an important intermediate marker of cardiovascular health. The relationship between air pollution exposure and BP is still not well understood. Studies of short-term particulate matter (PM) exposure and BP show mixed results, with some studies showing an inverse association or no association and other studies showing positive findings. A key to understanding the mixed results in the observed health effects of PM is that PM is a complex mixture and the concentrations of its individual components vary regionally and seasonally.

Growing evidence suggests that traffic-related components of PM pollution contribute significantly to particle-related cardiovascular effects. For example, a recent chamber study examining the mechanisms of short-term effects of $PM_{2.5}$ on BP found that effects were much stronger for the samples collected from a high-traffic area. A study of BP and short-term exposure to a number of air pollutants found the strongest association with organic carbon and its estimated fossil-fuel combustion fraction. More research is needed to examine the relationship between traffic-related components of PM and BP, which will also help us understand the overall relationship between BP and PM.

Less is known about the relationship between long-term exposures to air pollution and BP, although mortality studies have found strong associations with long-term air pollution exposures. In particular, only one recent study in Taiwan has investigated the relationship between long-term average air pollution exposures and BP, which found a strong association between BP and 1-year averages of $PM_{2.5}$. Since traffic components of PM have been implicated as a key component in relation to cardiovascular disease, research is needed to address long-term exposure to traffic-related air pollution and BP.

Researchers in the present study sought to address these research gaps by examining the relationship between BP and 1-year average exposures to traffic related air pollution in a cohort study within the greater Boston area during 1996-2008. An important tool for studying within-city variation in air pollution is the development of geographic-based exposure models. Black carbon (BC) is a traffic-related particle and a common surrogate for traffic particles in general, weighted towards diesel particles. They have developed and applied a land-use regression model for traffic particles based on BC in the greater Boston metropolitan area.

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A STUDY OF THE EFFECTS OF LONG-TERM EXPOSURE TO TRAFFIC PARTICLES

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Study participants were from the Veterans Administration Normative Aging Study (NAS), a longitudinal study established by the Veterans Administration in 1963. The NAS is a closed cohort of male volunteers from the Greater Boston area with a mean age of 70 (aged 21-80 years) at entry, who enrolled after an initial health screening determined that they were free of known chronic medical conditions. Participants were re-evaluated every 3-5 years using detailed on-site physical examinations and questionnaires. Air pollution data were collected from 1995 onward, so 1-year average BC concentrations were available starting in 1996. This analysis restricted the study population to subjects who were still participating in clinic visits after 1 January 1996, and subjects were followed through December 2008. The analysis included 853 participants with complete information regarding BC concentrations and all covariates. At each study visit, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured.

BC exposures were estimated from a spatiotemporal model. Daily concentrations at the Boston central-site monitor were used as a predictor to reflect average concentration levels for a given day, serving as a direct estimate of the daily time effect. Data from 82 other stationary air monitors were used to fit the model and estimate the effect of each covariate in the land-use regression model. Covariates in the BC prediction model included measures of land use for each address (cumulative traffic density within 100 m, population density, distance to nearest major roadway and per cent urbanisation), geographic information system, location (latitude and longitude), daily meteorological factors (apparent temperature, wind speed and height of the planetary boundary layer) and temporal factors (day of week and day of season).

The study showed that long-term exposure to BC is associated with increases in BP in this older population, a finding that could explain part of the association of particulate air pollution with cardiovascular mortality. More research is needed to address the relation between traffic-related air pollution exposures and BP among diverse study populations, including women, other races and younger populations. Further research is also needed to study the role of diabetes, obesity and antihypertensive medication use in modifying the effect and to clarify other mechanisms underlying the association between BC and BP.

Source: Occupational and Environmental Medicine, Vol. 69, Issue 6, Pages 422-427, June 2012.

Biomarkers of Air Pollution and Lung Cancer: A Systematic Review

The association between exposure to ambient air pollution and the risk of lung cancer has been evaluated in a number of prospective studies. The evidence linking exposure to urban air pollutants, mainly particulate matter ($PM_{2.5}$ or PM_{10}), with lung cancer is generally consistent, albeit formal statistical significance was not always reached. Cohorts from the USA as well as from Europe demonstrated increased risks of lung cancer with higher exposure to PM and other substances present in polluted air, with statistically significant risk ratios ranging from 1.14 to 5.21.

The main strength of these studies resides in their prospective nature, with exposure being assessed long before disease ascertainment. However, causality is still uncertain. In the present systematic review, researchers evaluate the contribution of biological markers of internal dose, biologically effective dose, and early effect in epidemiological studies on air pollution, to ascertain whether such contribution reinforces causal reasoning.

Measurement of biological markers of dose and effect can improve investigation of the health effects of various exposures, including air pollution, by facilitating improved exposure assessment and increased understanding of mechanisms, thereby providing biological plausibility, and investigation of individual susceptibility.

This review aims to identify biological markers of dose and effect for which there is consistent evidence in the literature, to support the results of epidemiological studies on the effects of ambient air pollution. Epidemiological evidence from the selected studies has been assessed using a set of criteria that have been developed elsewhere. These account for (1) the total number of subjects investigated, (2) the degree of replication of findings across studies, and (3) potential protection from bias and/or confounding. Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) guidelines were also used to structure the analyses and to report the results.

Online databases PUBMED and OvidSP were searched to identify papers that evaluated the effects of ambient air pollution using biological markers up to January 2012. This search encompassed studies on subjects who have been exposed to environmental air pollution at their place of residence or at work, including traffic related air pollution. Search terms included 'ambient' and 'traffic-related air pollution', 'particulate matter', 'polycyclic aromatic hydrocarbons', 'benzene', 'NOx', and 'SOx'. References within each paper found during the initial search were also investigated and relevant papers identified. The resulting papers evaluated exposure using a variety of methods: personal air sampling, ambient pollution data from monitoring sites close to the place of residence or workplace, or traffic density in the place of residence. Only papers published in English were reviewed. The final reference list was based on relevance to the broad scope of this review, with papers without relevant exposure or outcome, studies on animals or *in vitro* studies, and perspectives and opinion reviews all excluded.

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GENOTOXIC POTENTIAL OF ARSENIC AT ITS REFERENCE DOSE

Arsenic, a proven genotoxic carcinogen, is a ubiquitous metalloid released in the environment from a variety of natural and anthropogenic sources. The occurrence of high contents of arsenic (mean 'inorganic arsenic') in ground waters is reported from many parts of the world including India and Bangladesh. Consequently, drinking water with elevated level of arsenic is the most common and primary source of arsenic exposure in humans and hence its toxic effects have now been recognized as a serious health hazard of global concern, affecting more than 100 million people worldwide.

A potential hazard of arsenic exposure, in addition to carcinogenic effect, is its reported genotoxicity in humans and animals. Various arsenicals have been widely reported to cause injury to DNA as well as damage in chromosomes. Previous studies on arsenic genotoxicity have, therefore, registered positive results in various test systems. Subsequently, many of these genetic abnormalities become causes of cancer. However, it has proven difficult to provide experimental evidence of carcinogenicity of inorganic arsenic in laboratory animals except those shown by a few recent works where mice developed tumors after transplacental or whole-life exposure of arsenic.

The World Health Organization formulated guidelines to ensure the safety of drinking water, and a permissible level of arsenic in drinking water (10 µg/L) has been established as its provisional guideline value or its maximum contaminant limit (MCL), that has earlier been estimated to pose no measurable risk to cancer based on human cancer data and cost benefit balance. There are, however, estimated risks of lung cancer (14-67 incidence/10,000 people) and bladder cancer (12-50 incidence/10,000 people) in the United States even at the exposure level of 10 µg/L of arsenic in drinking water. Moreover, the United States Environmental Protection Agency has recommended an exposure level of arsenic (0.3 µg/kg/day) as its reference dose (RfD) for human to which one can be exposed on a daily basis with almost no likelihood of any adverse effect. This recommendation is based upon the 'no observed adverse effect level' (NOAEL) of arsenic that failed to induce skin lesions in a study population of Taiwan exposed through drinking water. This exposure level of arsenic (RfD) corresponds to an average daily intake (by a person of about 70 kg) of 2 L of water having arsenic contamination at its water quality guideline value (10 µg/L).

To date, no study has been done to evaluate the genotoxicity of arsenic at the exposure level of 0.3 µg/kg/day (equivalent to the human reference dose or index dose of arsenic) and hence, experiments are needed to be carried out at this exposure level to ascertain its potential in inducing any discernible genotoxic effect. The present work was therefore aimed to assess the genotoxic potential of arsenic in mice through chromosome abnormality test (CAT) upon exposure to doses equivalent to its human reference dose and its multiples.

The genotoxicity of arsenic species, however, does not involve direct covalent interaction with DNA. A vast array of experimental observations suggest that arsenic genotoxicity is primarily linked to the generation of reactive oxygen species (ROS) during its biotransformation, and the resulting oxidative stress seems to play a critical role in producing damage in DNA and chromosomes. Though the details of arsenic mediated generation of ROS remain to be elucidated, evidence suggests that oxidative methylation of arsenic during its biotransformation is one of the proposed mechanisms of ROS formation. Methylated arsenic species can release redoxactive iron from ferritin, which then promotes the conversion of superoxide radical and hydrogen peroxide in to highly reactive hydroxyl radicals through Haber-Wiess reaction. Arsenic methylation has been further found to be associated with oxidative damage to DNA, involving the formation of DNA adducts, DNA-protein cross links and even DNA base lesions.

Arsenic can also induce oxidative damage in proteins and enzymes due to its high affinity for their sulfydryl groups. Interaction of arsenic with SH-groups induces structural modification in proteins leading to the inactivation of many enzymes. Arsenic mediated oxidative damage in enzymes is also reported to interfere with the DNA repair mechanisms by either inhibiting ligation or down regulating the gene expression of DNA repair enzymes such as DNA polymerase β. Arsenic exposure has also been shown to deplete glutathione, a thiol based non-protein antioxidant, due to its involvement in arsenic metabolism or due to the thiol preference of arsenic for direct binding. Arsenic mediated inhibition of the enzymes of DNA repair and decrease in glutathione level drastically affect the cellular protective mechanisms against ROS, leading to increased level of oxidative damage in cells. Furthermore, arsenic binding to tubulin is also known to cause perturbation of spindle apparatus and induction of chromosome endoreduplication leading to aneuploidy, polyploidy and even mitotic arrest.

The human equivalent reference dose of arsenic, exhibiting marked genotoxic potential in mice, did not represent an exposure level of its 'no-effect limit dose'. Although both mouse and human have been shown to exhibit perceptible genetic damage upon exposure to arsenic, the response in them may vary due to different pharmacokinetics and pharmacodynamics between species. However, because almost all epidemiological studies have been done at higher endemic arsenic concentrations, further risk assessment in populations exposed to its low levels will be highly instrumental in establishing permissible limits of arsenic in drinking water.

Source: Ecotoxicology and Environmental Safety, Vol. 80, Pages 126-131, June 2012.

CHLORPYRIFOS EFFECTS IN ESTROGEN-DEPENDENT OR -INDEPENDENT BREAST CANCER CELLS

Organophosphate pesticides (OPs) comprise a group of toxic substances that are used in agriculture for insect and plague control. The use of insecticides represents the main environmental risk due to the high mass of product annually applied affecting aquatic species and human health. Chlorpyrifos (CPF) is a broad spectrum OP. The primary target of CPF toxicity is the central and peripheral nervous system, due to its ability to inhibit the acetylcholinesterase activity.

Breast cancer is the most frequent malignant disease in women. Exposure to estrogens throughout a woman's life is a risk factor for the development of this malignancy. Estrogen receptor alpha (ERα) is the major regulator of breast cancer tumor behavior. In the mammary gland, 17β-estradiol (E2) promotes cell proliferation in both normal and transformed epithelial cells by modifying the expression of hormone responsive genes involved in the cell cycle and/or programmed cell death. ERα phosphorylation in tyrosine 537 (Y537) is required to stimulate the Src/Shc/Ras/Erk pathway in MCF-7 cells and the inhibition of this phosphorylation interferes in ER/Src association and prevents receptor-dependent Src/Erk signaling, the expression of cyclin D and the stimulation of G1-S progression of the cells. A recent analysis has revealed that high levels of phospho-tyrosine 537-ERα (p-Y537-ERα) are associated with poor overall survival in breast cancer patients.

CPF was recognized as an endocrine disruptor since it has been demonstrated to possess the ability to interfere with the ERβ mRNA steady state levels. Moreover, researchers have demonstrated that CPF has antiandrogenic activity and significantly decreases testosterone biosynthesis. A recent epidemiological study of pesticide applicators reported a significant correlation between CPF use and lung and rectal cancer. In addition, it has been reported that there is an interaction between CPF and E2 in the digestive gland of the marine mussel, indicating that the preexposure to sublethal concentrations of the pesticide affects the transcriptomic fingerprint that is induced in response to E2.

Furthermore, it is amply demonstrated that OPs are able to generate oxidative stress affecting the different antioxidant enzymatic systems. Particularly, CPF may induce damage by DNA, RNA, lipid and protein oxidation, which in turn, alters the cell physiology and provokes cell death. Reactive oxygen species (ROS) are described as potent mutagens, increasing genomic instability and, thereby, contributing to the initiation as well as the progression of cancer. In addition, a moderate increase of ROS has been found to stimulate cellular proliferation. Although estrogens have been postulated to induce antioxidant effects in several tissues, their action on estrogen-dependent tissues are still not clear. It has been reported that estrogens may increase mitochondrial ROS production through an ER-dependent way.

The aim of this present work was therefore to investigate the effect of CPF on cell proliferation and the ER -dependence of this action employing estrogen-dependent (MCF-7) and estrogen-independent (MDA-MB-231) breast cancer cell lines. Researchers also analyzed CPF action on the cell cycle distribution and the cyclins that are implicated in G1-S and intra-S checkpoints. Finally, the action on cell death and ROS production were studied. Researchers demonstrated the ability of CPF 0.05 μM to induce cell proliferation through ER in hormone-dependent breast cancer cells. In contrast, CPF 50 μM induces intra-S arrest modifying checkpoint proteins, through a mechanism that may involve changes in redox balance in MCF-7. In MDA-MB-231, they have found that CPF 50 μM produces an arrest in G2/M phase which could be related to the capacity of the pesticide for binding to tubulin sites altering microtubules polymerization.

Taken together, the results of the study provide new evidence on the action of the pesticide CPF as an environmental breast cancer risk factor due to its effects on the mechanisms that moderate breast cell proliferation.

Source: Toxicology Letters, Vol. 213, Issue 2, Pages 184-193, September 2012.

ORGANOPHOSPHATE PESTICIDE EXPOSURE AND NEURODEVELOPMENT: A STUDY IN YOUNG SHANGHAI CHILDREN

More than 300,000 tons of pesticides are used in agriculture each year throughout China, with organophosphate pesticides (OPs) accounting for more than one-third of these pesticides. OPs are popular because of their broad spectrum of applications, potent toxicity to insects, relatively low costs, and decreased likelihood of pest resistance.

Recent studies indicate that pesticide exposures are widespread in some susceptible populations, including pregnant women and children. Young children are more susceptible to pesticide exposure due to their unique activity patterns and physiological characteristics. Pound for pound of body weight, young children drink more water, eat more food, and breathe more air than adults. Furthermore, they spend more time playing and crawling on the floor where pesticides may settle and have increased nondietary ingestion through frequent hand-to-mouth and object-to-mouth contacts. Young children may also be more susceptible to the potentially neurotoxic effects of pesticides, not only because their organ systems, specifically the brain and central nervous system, are developing rapidly but also because they have lower levels of detoxifying enzymes (paraoxonase or chlorpyrifos-oxonase) that deactivate OPs than adults. All these factors indicate that children may be more vulnerable to exposure.

The hazard of pesticides to children's health has been the subject of great concern globally since the publication of the report "Pesticides in the Diets of Infants and Children" by the National Academy of Sciences (U.S. NAS) in 1993. In developing countries like China, in which OPs are heavily used for agriculture, concerns regarding the adverse health effects of exposure to OPs among child are increasing. This subject area is particularly important because of the OP exposure problems associated with rapid development and a large population. Until now, little information on OP exposure and children's health has been available in China.

The present study evaluated the relationship of OP urinary metabolite levels with neurodevelopment as measured by the Gesell Developmental Schedules (GDS) and investigated the current status of OP exposure in young Shanghai children, China. It tested the hypothesis that after adjusting for potential confounders, exposure to OPs in young children would be associated with lower developmental quotients (DQs) in motor, adaptive, language, and social areas.

A few previous studies have examined low-level chronic exposure to OPs and children's neurodevelopment, and also they have reported inconsistent results. Therefore, it is challenging to conduct studies to evaluate the effects of OP exposure on neurodevelopmental outcome. For example, a recently published, large longitudinal study from the agricultural Salinas Valley of California, examined the relationship between prenatal and child OP urinary metabolite levels and the children's performance at 6, 12, and 24 months of age according to the Bayley Scales of Infant Development (Mental Development (MDI) and Psychomotor Development (PDI) Indices). The study found adverse associations between prenatal dialkyl phosphate (DAP) exposure and MDI at 24 months of age, but children's concurrent DAP levels were unexpectedly positively associated with MDI scores. No associations were observed between prenatal or child DAP exposure and MDI at 6 or 12 months of age or with PDI at any of the three time points. This study also did not observe significant associations between metabolite levels and any of the DQ scores in the motor, adaptive, language, and social areas.

The present study is the first in China to examine possible adverse effects of OP exposure on children's neurodevelopment. However, this study also has several limitations. First, although measurement of DAP metabolites is the most current method to characterize and integrate exposure to multiple OPs that originate from different sources, urinary metabolite levels may reflect exposure not only to OP parent compounds, but also to the potentially nontoxic preformed metabolites in the environment. Second, as in most studies on the effects of pesticide exposure, researchers measured OP urinary metabolites at a single time point only.

In summary, OP metabolite levels were not found to be associated with DQ scores in young children. However, these results should be interpreted with caution given the relatively high levels of child OP urinary metabolites in Shanghai. A large longitudinal study with repeated measurement of exposure levels in urine samples is needed to examine the relationship between OP exposure and child neurodevelopment.

Source: Environmental Science & Technology, Vol. 46, Issue 5, Pages 2911-2917, March 2012.

EFFECTS OF PRENATAL EXPOSURE TO CHLORPYRIFOS – A COMMON ORGANOPHOSPHATE PESTICIDE

Prenatal exposure to chlorpyrifos (CPF), an organophosphate insecticide, is associated with neurobehavioral deficits in humans and animal models. Chlorpyrifos (CPF) is a widely used, broad-spectrum organophosphate insecticide first registered in 1965 for agricultural uses and pest control before regulatory action by the Environmental Protection Agency that phased out residential use in 2001.

In a new study, researchers investigated associations between CPF exposure and brain morphology using magnetic resonance imaging in 40 children, 5.9-11.2 y, selected from a nonclinical, representative community-based cohort. Twenty high-exposure children (upper tertile of CPF concentrations in umbilical cord blood) were compared with 20 low-exposure children on cortical surface features; all participants had minimal prenatal exposure to environmental tobacco smoke and polycyclic aromatic hydrocarbons. High CPF exposure was associated with enlargement of superior temporal, posterior middle temporal, and inferior postcentral gyri bilaterally, and enlarged superior frontal gyrus, gyrus rectus, cuneus, and precuneus along the mesial wall of the right hemisphere. Group differences were derived from exposure effects on underlying white matter. A significant exposure x IQ interaction was derived from CPF disruption of normal IQ associations with surface measures in low-exposure children. In preliminary analyses, high-exposure children did not show expected sex differences in the right inferior parietal lobule and superior marginal gyrus, and displayed reversal of sex differences in the right mesial superior frontal gyrus, consistent with disruption by CPF of normal behavioral sexual dimorphisms reported in animal models. High-exposure children also showed frontal and parietal cortical thinning, and an inverse dose-response relationship between CPF and cortical thickness.

The current study is part of a larger ongoing cohort study of minority women and their children conducted by the Columbia Center for Children's Environmental Health (CCCEH) at Columbia University. The project started in 1997 before residential use of CPF was phased out. CPF measured in the children's umbilical cords indicated the degree to which they had been exposed to the pesticide *in utero*, largely through their mothers' exposures to pesticides sprayed in apartment buildings.

Previous reports from CCCEH investigators found an association between higher CPF exposures and lower birth weights. By age 3 years, children with higher *in utero* CPF exposure were more likely than lower-exposure children to score lower on tests of cognitive and psychomotor development, and by age 7 they were more likely to have lower IQ and working memory scores. The current study assessed magnetic resonance imaging (MRI) data for 40 children at age 6-11 years, half of whom had umbilical plasma CPF levels of 4.39 pg/g or greater and half of whom had levels below 4.39 pg/g. Exposure to lead, another environmental toxicant linked to cognitive problems, was low in all the children.

Children in the higher-exposed group were more likely to have significant enlargement of the regions of the brain that control attention, language, social cognition (e.g., ability to recognize faces), emotion and inhibition, and executive functions (e.g., planning and reasoning), compared with the lower-exposed group. These differences are consistent with findings from animal studies of CPF exposure. In the lower-exposed group, children with greater brain enlargement tended to have lower IQ scores, but this relationship was not seen in the higher-exposed group.

The scans revealed that much of the brain enlargement consisted of glia, or white matter. CPF damages neurons and glia and generates scar tissue in animal models, and it is speculated that similar damage could account for the enlargement seen in the children. Higher CPF exposure also was associated with reduction or reversal of normal sex-related differences in brain development. For instance, the right parietal lobe is generally larger in girls than boys, but this was reversed in higher-exposed children. The behavioral consequences of these alterations, if any, are unknown.

Brain differences between the two groups were found at CPF exposure levels well below current EPA dietary reference doses (0.005 mg/kg/day for the general public and 0.0005 mg/kg/day for women and children).

The combination of epidemiologic and brain imaging data in this study provides some of the strongest evidence to date that prenatal exposure to CPF causes neurodevelopmental problems in children.

Source: Proceedings of the National Academy of Sciences, Vol. 109, No. 20, Pages 7871-7876, May 2012.

Environmental Lead Exposure and Brain Cancer: A Taiwanese Study

Over the past several decades, epidemiologic studies of brain cancer have examined the many risk factors associated with the disease, however there have been few consistent findings. Investigations of brain tumor clusters can be time-consuming and are often inconclusive because of disease heterogeneity and unknown or inadequately characterized exposures, latency periods, and/or base populations. Additionally, the prognosis of brain cancer patients is still poor. Less than 3% of brain cancer patients are still alive at 5 years after diagnosis. Hence, investigation of the etiology of brain cancer remains extremely important.

Lead has been added to petrol (gasoline) as an anti-knocking agent since the 1920s in order to improve fuel performance and reduce wear on vehicle engines. Since this time, leaded petrol has been reported to cause more lead exposures than any other source worldwide. During the 1970s, health impacts associated with lead emissions from vehicles became a widely discussed issue. Many studies have reported that environmental lead emissions have resulted in significant health effects to the central nervous system, haem-synthesis, reproductive system, as well as psychological and neurobehavioral functions, and may even increase the risk of cancer. Many large population based studies have recently been conducted to explore the relationship between environmental lead emissions and diseases. Strong associations have been found between blood lead levels (BLLs) and increased risk of all-cause, all cancer, stroke and cardiovascular mortality. Even when BLLs were between 5 and 9 μg/dl a significant association with the disease risk could still be found. However, the epidemiological literature for an association between lead exposure and brain cancer is inconclusive.

In principle, petrol lead emissions are considered to be more representative of environmental lead exposure than BLLs. It has been observed throughout the world that the lead content of various environmental components have decreased after the replacement of leaded petrol. In Taiwan, environmental lead exposure has generally declined since the mid-1990s largely because of the implementation of the Petrol-Lead Phase-Out Program (PLPOP) in 1981. The implemented scenarios provided a unique opportunity to study the long-term effects of the reduction of environmental lead exposure on the development of brain cancer.

In the present study, in order to adjust for possible confounding effects, both potential factors and medical resource data were included in the data analysis. The results obtained from this study allowed the examination of brain cancer to be associated with the environmental lead emissions within any given country.

In this study, the age-standardized incidence rates of brain cancer were shown to be highly significantly correlated with the high and median Petrol-Lead Emission Areas (PLEA) compared to small PLEA. The authors believe that this is the first evidence ever being shown in the lead literature based on the long-term observation of petrol lead emissions and brain cancer incidence.

Globally, the annual age-standardized incidence rates of brain cancer are 3.7 per 100,000 for men and 2.6 per 100,000 for women. Rates appear to be higher in more developed countries (men: 5.8 and women: 4.1) than in less developed countries (men: 3.0 and women: 2.1). The results indicated that the varieties of age-standardized incidence rates of brain cancer were from 3.3 to 2.5 per 100,000 for men and 2.5 to 1.8 per 100,000 for women during 1999-2007. The lower incidences in the study may be partly due to ethnic differences in susceptibility to development of brain cancer. Some reports indicated that Caucasians are more frequently affected than people of African or Asian descent.

The present study found an association between environmental lead exposure and risk of brain cancer: the populations living in higher PLEA experienced an increase in cancer incidence. Historical organic lead exposure was largely confined to tetra-ethyl lead used as an additive in gasoline; tetra-ethyl lead was broken down into inorganic lead when gasoline was burned. Cancer researchers have classified lead as possible human carcinogen and its inorganic compounds as probable human carcinogens. Although the etiology of brain cancer remains largely unknown, there are several known mechanisms that show lead exposure impacting the risk of brain cancer. Lead has been shown to pass the blood-brain barrier which may result in elevated lead levels in brain tissue. Lead is thought to play a facilitative role in carcinogenesis, involving inhibition of DNA synthesis and repair, oxidative damage, and interaction with DNA-binding proteins and tumor suppressor proteins. Besides, brain tissues are reported to be relatively susceptible to oxidative stress and lipid peroxidation, suggesting that the brain may be sensitive to the lead toxicity effects.

Brain cancer is a rare outcome, and thus, the sample size of individuals in this study is important. The present study obviously took the advantage for having a large number of populations with size greater than 23 million, since all cancer patients were required by law to register by their physicians in Taiwan, and therefore the population-based data are complete and accurate. Additionally, the petrol lead emissions reported in the governmental documents of Taiwan were not only representative of the environmental lead amounts, but also reflected the actual changes in environmental lead exposure in the Taiwanese population. In studying the effect of the PLPOP, this measurement is in general more suitable than that based on the blood lead level.

Progress in understanding primary brain cancer might result from studies of well-defined histological and molecular tumor types incorporating assessments of potentially relevant information on subject susceptibility and environmental and non-inherited endogenous factors. The present study is the first one which provides the evidence that the age-standardized incidence rates of brain cancer could be highly correlated with petrol lead emissions. The above finding can serve as a basis in the future for conducting more well-defined studies to investigate the relationship between the primary brain cancer and environmental lead exposures.

Source: Environment International, Vol. 40, Pages 97-101, April 2012.

CONGRESS ANNOUNCEMENT

The 7th Princess Chulabhorn International Science Congress (PC VII)
CANCER: FROM BASIC RESEARCH TO CURE
November 29 – December 3, 2012, Shangri-La Hotel, Bangkok, Thailand

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

Keynote Speaker: ***J. Michael Bishop (Nobel Laureate, U.S.A.), Cancer: The Genomic Era Arrives***

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

Deadline for abstract submission is on **September 1, 2012.**

For all further information, please visit: **http://pc.cri.or.th/pc7**

Biomarkers of Air Pollution and Lung Cancer: A Systematic Review

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Papers were categorised according to the type of biological marker under investigation. Biomarkers can reflect each step in a causal pathway from exposure to disease. They are usually grouped as biomarkers of: (1) internal dose; (2) biologically effective dose, indicating how much the exposure has damaged the molecules in the body and has possibly been removed by metabolic or repair mechanisms; (3) biological effects indicating changes in function or permanent alterations; (4) disease; and (5) susceptibility, which can modify transition rates at each step. Based on the figure, the biomarkers in this review were defined as biological markers of: (1) internal dose, which included 1-hydroxypyrene (1-OHP); (2) effective dose, which included DNA adducts and oxidized nucleobases; and (3) early effect, which included chromosomal aberrations (CAs), sister chromatid exchanges (SCEs) and micronuclei (MN), as well as mutations in the *Hypoxanthine phosphoribosyl transferase* (HPRT) gene and changes in methylation patterns.

Although information obtained from biomarkers adds to the knowledge obtained from prospective epidemiological studies on the effects of air pollution, the evidence overall is still incomplete and fragmented. Not only is the evidence for several markers still equivocal, but researchers are far from being able to reconstruct the full pathogenetic pathway that leads from external exposure to the outcome of lung cancer. Few studies have been conducted on epigenetic and non-genotoxic changes, so that the evidence is skewed in favour of genotoxicity biomarkers. Future efforts should be directed not only towards reducing uncertainty concerning the role of specific biomarkers, but also towards filling the gaps in the supposed pathogenetic pathways.

The present review evaluated the data available on some of the most relevant biomarkers of air pollution exposure, and used well accepted criteria to grade the cumulative evidence on each biomarker with respect to the amount of evidence, replication and protection from bias. Several biological markers of dose and effect related to carcinogenic mechanisms, and especially oxidised nucleobases, have been found to be associated with exposure to ambient air pollution, and some of these markers have also been associated with risk for lung cancer. These biological markers, which mark the continuum of progression from external exposure to cancer outcome, have the potential to shed light on the pathways of carcinogenesis, thus defining the association more clearly for public health interventions.

Source: Occupational and Environmental Medicine, Vol. 69, Issue 9, Pages 619-627, September 2012.

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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