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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".

Ministerial Regional Forum on Environment and Health in South-East and East Asian Countries Bangkok, Thailand 9 August 2007

Professor Dr. Her Royal Highness Princess Chulabhorn Mahidol, President of the Chulabhorn Research Institute, presided over the opening of this inaugural Forum attended by Ministers of Health and of The Environment from 14 countries in the South-East and East Asian Region: Brunei Darussalam, Cambodia, China, Indonesia, Japan, Lao People's Democratic Republic, Malaysia, Mongolia, Myanmar, the Philippines, Republic of Korea, Singapore, Thailand and Vietnam.

The aim of the Forum was to explore the forms of collaboration needed to address the urgent environmental health issues confronting the countries in the region and adversely affecting the lives and well being of the population, with the main product being an endorsed Charter of the Regional Forum on Environment and Health in South-East and East Asian Countries – Framework for Cooperation. The composition and work plans for the Thematic Working Groups of the 6 priority areas, including Air Quality; Water Supply, Hygiene and Sanitation; Solid and Hazardous Waste; Toxic Chemicals and Hazardous Substances; Climate Change, Ozone Depletion and Ecosystem Change; and Contingency Planning, Preparedness and Response in Environmental Health Emergencies, were also discussed.

Local hosts of this landmark event were the Government of Thailand's Ministry of Natural Resources and Environment and Ministry of Public Health together with the Chulabhorn Research Institute.

The World Health Organization, through its Regional Offices for the South-East Asia and Western Pacific regions, and the United Nations Environment Programme, through its Regional Office for Asia and the Pacific, formed the Secretariat.

Preparation for this regional Ministerial Forum began in December 2005 when the Chulabhorn Research Institute hosted a Scientific Conference on Asia Pacific Environmental Health --- Significant, Emerging and Current Challenges, Research and Capacity Building Opportunities, Collaborative Response Needs. It was the informed discussion and deliberation of this Scientific Conference that provided the initiative and the rationale for the present Regional Ministerial Forum, setting the agenda of major concerns that are emerging regionally and globally with the

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Ministerial Regional Forum on Environment and Health in South-East and East Asian Countries Bangkok, Thailand 9 August 2007

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increasing impacts of environmental changes on human health.

These concerns and the measures needed to address them were the focus of the keynote lecture delivered by Professor Dr. Her Royal Highness Princess Chulabhorn, and also of the Scientific Segment of the Ministerial Forum, which was chaired by Her Royal Highness.

In her opening address, Her Royal Highness welcomed the Ministers of Health and Environment from 14 countries in the South-East and East Asia regions, and emphasized the urgency of the environmental health issues that confronted us all. The task to be undertaken at this meeting was to determine the strategies and actions that might bring a halt to the harm that is currently being inflicted on the environment, on human health and livelihood, and indeed on the very quality of life of the planet.

Her Royal Highness stated that scientists, policy makers and administrators must work closely together to find solutions to the current problems undermining environmental health in order to ensure sustainable growth and development in the region.

Every opportunity must be taken to ensure that this essential task is carried out as a matter of the utmost urgency. Her Royal Highness announced that to assist in this endeavor, and with the endorsement of Thai Ministers of Natural Resources and Environment and Public Health, the Chulabhorn Research Institute has established a special fund of 100 million Thai baht for education, training and research in environmental health for the region.

Further collaborations would be welcomed from countries that participated in this Forum.

In her Keynote Lecture, Professor Dr. Her Royal Highness Princess Chulabhorn outlined the human health problems that could be directly linked to the environment, and emphasized that a unified approach to these problems by environment and health sectors was needed to effectively target and solve environmental health problems.

Her Royal Highness stated that the problem of indoor air pollution was increasingly important in the Asia Pacific region. In addition to studies on short term effects, the long term effects of exposure to carcinogenic compounds in air pollution also required serious attention. Related issues such as atmospheric brown cloud also deserved urgent attention.

Her Royal Highness emphasized the need to apply sound scientific knowledge in the development of policy decisions to address environmental health problems. Thus the present Forum presented a unique and very important opportunity to initiate national and regional strategies to bring about safer, more sustainable economic and human development and to solve the human health problems that currently prevent us from attaining that goal.

After Her Royal Highness' Keynote Lecture, the Scientific Segment of the Ministerial Regional Forum continued with presentations by Professor Sir Gordon Conway, Professor of International Development from the Imperial College in London and Professor Margaret Liu, Foreign Adjunct Professor of the Karolinska Institute in Stockholm. The session was chaired by Professor Dr. Her Royal Highness Princess Chulabhorn with Professor Nay Htun of the International Research Institute for Climate Prediction from the Columbia University in New York acting as facilitator.

In his presentation, Professor Sir Gordon Conway provided data on the importance of climate change in relation to environment and health. The effects of climate change on biodiversity, rainfall, soil erosion, floods, emergence of zoonotic diseases and the emergence and re-emergence of infections and vector-borne diseases, e.g. malaria and dengue were highlighted.

Professor Margaret Liu, in her presentation, emphasized the inter-dependence of environment and health, suggesting that improvements to health and the environment can synergize. For example, ameliorations in the cleanliness of water supplies coupled with a first-generation cholera vaccine should provide greater protection than the simple additive effect of the two approaches.

Scientific knowledge and technology need to be advanced to deal with many current challenges and specialists need to have a broad perspective so that knowledge can be translated into policy and action.

In the dialogue that followed between the distinguished panelists and Ministers from many of the countries represented at the Forum, the eminent Minister respondent from Republic of Korea, the proposed host for the Second Regional Forum scheduled for 2010, recognized that environment and health represented a new challenge to the Asia region. He welcomed the opportunity to participate in the Ministerial Regional Forum and called for the continued cooperation among participating countries.

Ministers welcomed the ongoing role of the Chulabhorn Research Institute in capacity building in environmental health as an essential foundation for sustainable growth and development in this region.

The Bangkok Declaration on Environment and Health prepared by the Secretariat of the High-Level Officials' Meeting and Ministerial Forum was endorsed with amendments for submission to the Ministerial Meeting.

BANGKOK DECLARATION ON ENVIRONMENT AND HEALTH

Having met at the First Ministerial Regional Forum on Environment and Health in Southeast and East Asian countries jointly organized by the United Nations Environment Programme (UNEP) Regional Office for Asia and the Pacific and the World Health Organization (WHO), Regional Offices for the Western Pacific and South-East Asia, and hosted by the Government of Thailand and the Chulabhorn Research Institute (CRI) on 9 August, 2007 in Bangkok, Thailand,

Recognizing that the environment in which we live greatly affects our health,

Acknowledging the importance of ensuring the protection of human health and the environment,

Understanding that children, women, the elderly and the poor are among the most vulnerable to and suffer most from environmental deterioration,

Conscious that improving environmental quality and health and ensuring sustainable economic growth are key components of poverty reduction,

Realizing that the maintenance of health and well being depend on environmental quality and sustainable development;

Underlining the importance and cost effectiveness of giving priority to preventive action,

Conscious of the urgency to take immediate coordinated action involving all relevant government agencies, organizations from the private sector, civil society including Non Governmental Organizations (NGOs), academia and media,

Aware that solutions require inter-disciplinary and cross sectoral interventions with experts from physical and natural sciences, health and social sciences, development, finance and other fields,

Realizing the specific characteristics, cultural diversity and needs of the region, notably its unprecedented economic development, rapid urbanization and population growth and widespread poverty,

Mindful that many environmental and health issues are transboundary in nature and that globalization has highlighted the interdependence of nations, communities and individuals,

Keeping in mind existing international agreements on the protection of the ozone layer, climate change, biodiversity conservation, the management of chemicals and wastes and other initiatives related to environment and health,

Mindful of the precautionary approach and guided by the polluter pays principle and the norms of good governance including civic engagement and participation, efficiency, equity, transparency and accountability,

Taking note of the various efforts being undertaken by various countries at the national and regional levels, and

Noting that the capacity building through education and training should be our major focus,

We, the Ministers of Health and Environment and government representatives from Brunei Darussalam, Cambodia, China, Indonesia, Japan, Lao People's Democratic Republic, Malaysia, Mongolia, Myanmar, Philippines, Republic of Korea, Singapore, Thailand and Vietnam adopt the Charter of the Regional Forum on Environment and Health,

Establish the Regional Forum on Environment and Health as described by the Charter,

Agree to cooperate to improve inter-agency, multi-sectoral, regional and international cooperation, coordination and planning, to facilitate capacity building, the exchange of information, technology, and resources and the tackling of transboundary and common issues.

Urge government departments, private sector, civil society including NGOs, academia, labour, and media to be actively involved in this process, building ownership and commitment,

Approve the composition and work plans of the Thematic Working Groups on health impacts and implications of (1) air quality, (2) water supply, hygiene and sanitation, (3) solid and hazardous waste, (4) toxic chemicals and hazardous substances, (5) climate change, ozone depletion and ecosystem change, and (6) contingency planning, preparedness and response in environmental health emergencies,

Request the regional Thematic Working Groups on the 6 priorities to implement their work plans as agreed, taking into account the availability of resources,

Request research and training institutions such as CRI and others to play a key role in providing human resource development for the region,

Request UNEP and WHO to serve as the joint Secretariat to support the operations of the Regional Forum and its subsidiary bodies,

Call upon international partners to support the implementation of the Charter of the Regional Forum on Environment and Health,

Continue to develop and implement National Environment and Health Action Plans (NEHAPs) or equivalent plans to address specific priority environmental health risks prevailing in our countries, and

Agree to meet again 3 years from now in the Republic of Korea to review the progress made in the implementation of NEHAPs or equivalent plans and the work plans of the Thematic Working Groups, and discuss and agree on new directions and priorities of our collaboration.

BRAIN TUMORS AND EXPOSURE TO PESTICIDES

A study has been conducted in southwestern France to examine the relationship between exposure to pesticides and brain tumors in adults

This population-based case-control study is one of the largest specifically exploring the role of occupational and environmental pesticides. The participation rate in the study was high, but non-participating cases were older and more frequently presented gliomas or lymphomas than the participating cases. Elderly people might have been more frequently exposed to pesticides as the part played by agriculture was greater in previous decades in France. Their underparticipation would decrease the risk estimates.

The study design enabled accurate data on pesticide use to be obtained but did not provide information about the specific pesticides responsible. Unfortunately, because of trade interests, information on the use of specific pesticides in a given area is not available in France. The reliability of farmers' pesticide use reporting is debatable as the number of pesticides used in vineyards is large, approaching 20 in a single treatment period, and an even larger number during a farmer's whole life. Moreover, the brain injury and memory impairment of some of the subjects precluded asking for accurate details of pesticide names. This is why pesticide assessment relied on expertise. However, because interviewers were not blinded to the disease status, it might be argued that they probed more deeply into the exposure of cases than of controls. This bias was minimised by using well-trained interviewers, a standardised questionnaire and by the fact that the distribution of subjects among interviewers was not dependent on the case-control status.

However the index exposure used has some limitations: it is a generic index, not taking into account differences between classes of pesticides (formulation, volatility, dermal penetration, etc) specificities of use like the type of equipment, the duration of the treatment days, the use of protective equipment, etc. This approach only enables researchers to differentiate between users and non-users, and to rank users according to their frequency and duration of use to different gradients of pesticide exposure.

More than 70% of exposed cases in the highest quartile were exposed in the years 1965 to 1985 and half of them or fewer were exposed before 1950 or after 1985. Therefore, if the association observed is genuine, it might be suggested that the exposure leading to the occurrence of brain tumor may be the pesticides used in the 1965-85 period. In vineyards, pests controlled by the majority of pesticide applications are fungi such as mildew, black-rot and oidium. In this time period, inorganic substances (copper, sulphur), dithiocarbamates (mancozeb, mancopper, maneb, propineb, zineb) and phthalimides (captafol, folpet, captan) were recommended for use on these fungi.

Consumption of aspartame was associated with a decrease in risk. The role of aspartame in brain tumor was suggested from equivocal experimental studies dealing with its carcinogen effects on rodent brain and from the observation that aspartame might be metabolised in nitrosurea-like molecule. From an epidemiological perspective, only one ecological study examined the question, but could not reach definitive conclusions. Treatment of house plants was also associated with an increase in risk of brain tumor. The question about such exposure was rather limited in the present study and recall bias cannot be ruled out. This is why this subject warrants further research, because exposure to pesticides for such purposes is acknowledged to be far lower than in agricultural settings, and because similar results have never been reported in previous studies. None of the other measures collected in the study appeared to be related to this variable or could signify a confounding effect. It is not completely clear what types of pesticide are being, and have been, sold in the past for use on house plants, but as the general population does not easily identify specific pests, "total treatment" (insecticides and fungicides) are commonly purchased. It is a matter of concern that they are sprayed in closed dwellings and that they are recommended for use every week.

Living in a rural area tended to be associated with a decrease in risk. Even if not significant, this result could appear inconsistent with the close relationship between "agriculture" and "rural setting". However, 60.7% of subjects in rural settings were not classified as being occupationally exposed to pesticides in the present study. The lower risk in rural areas, together with the slight decrease for subjects living in a district planted with vineyards, does not favour a role of environmental exposure to pesticides near treated areas in the occurrence of brain tumors.

This study supports the role of pesticides in brain tumors but only for high levels of occupational exposure, in treatment tasks and also in re-entry conditions, in an agricultural setting where fungicides are predominantly used. Further studies on larger samples are needed to determine if the risk is more specifically associated with gliomas, and to investigate a possible association with specific families of pesticides. A higher risk for gliomas, the histological subtype consistently more common in men than in women, would suggest that differences in occupational exposure between men and women could contribute to the differences in rates between them. In addition, the treatment of house plants seemed to be associated with the risk of brain tumors. However, the authors said further work was needed to investigate whether specific chemicals in the pesticides were linked to gliomas, and whether women were more susceptible as in the study they were more likely to spray houseplants.

Source: Occupational and Environmental Medicine, Vol. 64, August 2007.

Air Pollution as an Important Risk Factor for Atherosclerosis

Atherosclerotic cardiovascular disease is the leading cause of death in the western world. In addition to the classical risk factors such as serum lipids, smoking, hypertension, aging, gender, family history, physical inactivity, and diet, recent data have implicated air pollution as an important additional risk factor for atherosclerosis. The strongest and most consistent association between air pollution and cardiovascular morbidity and mortality has been ascribed to ambient particulate matter (PM). Large-scale prospective epidemiological studies have shown that residence in areas with high ambient PM levels is associated with an increased risk of premature cardiopulmonary death. A study by the American Cancer Society reported a 6% increase in cardiopulmonary deaths for every elevation of 10 μg/m^3 in PM concentration. Although the mechanism of cardiovascular injury by PM is poorly understood, it has been shown that the particles are coated by a number of chemical compounds, including organic hydrocarbons (for example, polycyclic aromatic hydrocarbons and quinones), transition metals, sulfates and nitrates. In studies looking at the effects of diesel exhaust particles (DEP) on the lung, researchers have shown that the redox cycling organic hydrocarbons and transition metals are capable of generating airway inflammation through their ability to generate reactive oxygen species (ROS) and oxidative stress. Supporting proteome analyses confirmed that organic PM extracts induce a hierarchical oxidative stress response in macrophages and epithelial cells, in which the induction of electrophile-response element (EpRE)-regulated genes (for example, heme oxygenase 1, catalase, and superoxide dismutase) at lower levels of oxidative stress prevented the more damaging pro-inflammatory and pro-apoptotic effects seen at higher levels of oxidative stress. It is now widely recognized that oxidant injury is one of the principal mechanisms of PM-induced pulmonary inflammation and that this mechanism could also be applicable to the atherogenic effects of PM.

Atherosclerosis is a chronic vascular inflammatory process where lipid deposition and oxidation in the artery wall constitute a hallmark of the disease. Infiltrating lipids come from low density lipoprotein (LDL) particles that travel into the arterial wall and get trapped in a three-dimensional cagework of extracellular fibers and fibrils in the subendothelial space, where they are subject to oxidative modifications leading to the generation of “minimally modified” LDL (mm-LDL). Such oxidized LDL is capable of activating the overlying endothelial cells to produce pro-inflammatory molecules such as adhesion molecules, macrophage colony-stimulating factor (M-CSF) and monocyte chemotactic protein-1 (MCP-1) that contribute to atherogenesis by recruiting additional monocytes and inducing macrophage differentiation. In a new study, researchers have hypothesized that PM-induced oxidative stress synergizes with oxidized lipid components to enhance vascular inflammation, leading to an increase in atherosclerotic lesions.

The researchers used human microvascular endothelial cells to study the combined effects of a model air pollutant, DEP, and oxidized 1-palmitoyl-2-arachidonyl-sn-glycero-3-phosphorylcholine (ox-PAPC) on genome-wide gene expression. The cells were treated in triplicate wells with an organic DEP extract, ox-PAPC at various concentrations, or combinations of both for 4 hours. Gene-expression profiling showed that both the DEP extract and ox-PAPC co-regulated a large number of genes. Using network analysis to identify coexpressed gene modules, the researchers found three modules that were most highly enriched in genes that were differentially regulated by the stimuli. These modules were also enriched in synergistically co-regulated genes and pathways relevant to vascular inflammation. This synergy was validated *in vivo* by demonstrating that hypercholesterolemic mice exposed to ambient ultrafine particles exhibited significant upregulation of the module genes in the liver.

The study found that DEP and oxidized phospholipids synergistically affect the expression profile of several gene modules that correspond to pathways relevant to vascular inflammatory processes such as atherosclerosis.

Source: Genome Biology, Vol. 8, July 2007.

ELEVATED OXIDATIVE DAMAGE IN LEAD TOXICITY

Lead (Pb^{2+}) is one of the major widespread toxic metals found in the environment with potential danger to human health due to its multifaceted action with a broad range of physiological and biochemical dysfunctions. It is known that Pb^{2+} has detrimental effects on the central and peripheral nervous systems, and the hemopoietic, cardiovascular and reproductive systems, kidneys and liver. Pb^{2+} intoxication causes anemia, which is partially due to a decreased life span of circulating red blood cells (RBC).

Evidence over the last three decades using *in vivo* and *in vitro* models has pointed to elevated oxidative damage in Pb^{2+} toxicity with the involvement of reactive oxygen species (ROS). Several studies have demonstrated that *in vivo* lead toxicity involves the hematological system by inhibiting γ-aminolevulinic acid dehydratase (ALAD) leading to aminolevulinic acid (ALA) accumulation. Moreover, studies have reported that accumulated ALA induces ROS generation. Reduction in RBC antioxidant enzyme activities in lead-

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Use of Animal Models to Study Potential Adverse Health Effects from Welding Fume Inhalation

It has been estimated that more than 5 million workers worldwide are exposed to welding aerosols on a daily basis. Welding is a common industrial process used to join metals. Complex mixtures of aerosol and gaseous by-products are formed during welding. The generated fumes are composed of an array of metals, such as iron, manganese, chromium, and nickel, volatilized from the welding electrode. Welders also are exposed to gases, such as ozone and carbon monoxide, that may affect their health. Over the past 40 years, numerous studies have evaluated the health effects of welding. Most studies have focused on the pulmonary effects associated with welding fume exposure. Bronchitis, metal fume fever, lung function changes, siderosis, immunosuppression, and a possible increase in the incidence of lung cancer have all been reported in welders. Even less is known about the nonpulmonary effects associated with welding, specifically the potential neurological effects.

The potential adverse health effects associated with welding fume inhalation can be challenging to study. Welders are not homogeneous group. Their exposure can vary due to differences in industrial setting, work area ventilation, the types of welding processes and material used, and exposures to other occupational hazards, such as solvents and asbestos. Little information is available about the causes and potential mechanisms by which welding fume inhalation may adversely affect health. The use of animal models and the ability to control the welding fume exposure may be helpful in the elucidation of these mechanisms.

In the United States, the Health Effects Laboratory Division of the National Institute for Occupational Safety and Health (NIOSH) has recently developed a welding program. This welding fume generation and inhalation exposure system can simulate real workplace exposures and allow for continuous welding for extended periods of time without interruption. The system is completely automated and uses computer-controlled robotic welder, which welds and replaces materials as they are consumed during the operation.

The goal of the program is to use animal models to assess the effects of welding fume inhalation on possible increases in lung tumorigenicity, susceptibility to lung infection, and the development of neurotoxicity. A series of short-term animal inhalation studies have been carried out that evaluate dose and time effects of stainless steel (SS) welding fume exposure on lung injury, inflammation, and defense response to infection. In summary, short-term exposure of rats to SS welding fume caused significant lung damage and suppressed lung defense responses to bacterial infection, but had a delayed effect on pulmonary inflammation. The observations and results generated from these acute studies will be the basis for designing a long-term animal inhalation study that will evaluate the potential toxic effects associated with welding fumes.

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

ELEVATED OXIDATIVE DAMAGE IN LEAD TOXICITY

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exposed workers and animals has been recently reported. Incubation of human whole blood for 24 h in the presence of Pb^{2+} caused a decrease in reduced glutathione (GSH), glutathione reductase and glutathione peroxidase in RBC. The implication of hydroxyl radicals (•OH) was suggested using a cell-free system containing oxyhemoglobin and ALA. Other studies have demonstrated that Pb^{2+} alone or in presence of hydrogen peroxide (H_2O_2) induce DNA strand breaks probably due to singlet oxygen generation.

Despite the many sources of evidence pointing to ROS involvement in RBC oxidative damage, few studies *in vitro* showing a correlation between Pb^{2+} toxicity and oxidative stress in RBC have been performed.

Moreover, the mechanisms by which Pb^{2+} induces hemolysis are not completely understood. For this reason, the involvement of oxidative stress in the mechanism of Pb^{2+}-induced pre-hemolytic lesion was investigated in a recent study by exposing RBC to Pb^{2+} *in vitro* and then separating the intact non-hemolysed RBC. Oxidative stress was investigated on human RBCs by *tert*-butyl hydroperoxide-initiated chemiluminescence method (CL). The results revealed that lead-induced time and concentration-dependent hemolysis and CL time curves showed a very narrow correlation with each other. GSH oxidation to oxidized glutathione (GSSG) and the stress index also increased significantly. Treatment of lead-exposed RBC with desferrioxamine, an iron-chelating agent or the chain-breaking antioxidant, Trolox, quenched light emission and inhibited hemolysis dramatically. Mannitol and sodium formate, •OH scavengers, on the contrary, did not inhibit CL or hemolysis, significantly. These data indicate that lead-induced lipid peroxide formation is mediated by a metal-driven Fenton reaction but do not support the direct involvement of •OH radicals in this process. By contrast, results in the present study revealed a decrease in light emission and decreased hemolysis in the presence of histidine, a singlet oxygen scavenger.

These results suggest that membrane damage and hemolysis of RBC are mediated by Pb^{2+} through free radical reactions and that singlet oxygen plays a significant role in this process.

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

RISK OF UROTHELIAL CARCINOMA FROM URINARY ARSENIC

Urothelial carcinoma (UC) arises exclusively from the urothelium including the renal pelvis, ureter, bladder and urethra, with bladder cancer being the most common form. In most developed countries, it is among the top 10 leading cancers. The most well known risk factor for UC is cigarette smoking. Current cigarette smokers have approximately a two- to three-fold risk compared to non-smokers. The mechanism by which cigarette smoking causes bladder cancer has yet to be determined. It seems likely that the risk is related to a large number of carcinogenic chemicals in cigarette smoke.

It has previously been shown that chronic arsenic intoxication due to contamination of artesian well water with inorganic arsenic compounds is responsible for elevated mortality rates from cancers of the bladder, renal pelvis and/or ureter, lung and other organs in Taiwan. More specifically, it has been demonstrated that bladder cancer mortality rates for patients who consumed well water with arsenic levels of 600 µg/L or higher had a mortality rate of over 30 to 60 times greater than the unexposed population. Evidence from elsewhere in the world also suggests that ingested inorganic arsenic very likely causes internal cancers. It has also been shown that combined cancer mortality rates are as high as 1 out of 100 people from drinking water containing 50 µg/L of arsenic. Two reports from the National Research Council (USA) have also affirmed that cancer risks might be of the order of 1 in 100 at an arsenic level of 50 µg/L. This estimated cancer risk is more than 100 times greater than that for any other contaminant in drinking water at the maximal contaminant level. Thus, within the United States, the maximum contaminant level for arsenic in public water supplies will be lowered from 50 µg/L, a level that was established in 1942, to 10 µg/L in 2006. The arsenic concentration allowance in public water supplies in Taiwan was 50 µg/L; in 2000, a new standard of 10 µg/L was then announced. According to the Taipei Water Department of Taipei City Government, the average arsenic concentration of tap water in Taipei is 0.7 µg/L ranging from non-detectable to 4.0 µg/L. Whether cancer risks are higher at 50 µg/L than at 10 µg/L is still debatable. Even without confounding factors, reduction of cancer risks with the new standard of 10 µg/L will not be seen for decades. However, should it be shown that arsenic metabolic capability affects cancer risks in subjects exposed 50 µg/L of arsenic, it might still be carcinogenic for some genetically predisposed subjects.

To explore the association between individual risk and urinary arsenic profile in subjects without evident exposure, 177 UC cases and 313 age-matched controls were recruited between September 2002 and May 2004 for a case-control study. Urinary arsenic species including the following three categories, inorganic arsenic (As^{III} + As^{V}), monomethylarsonic acid (MMA^{V}) and dimethylarsinic acid (DMA^{V}), were determined with high-performance liquid chromatography-linked hydride generator and atomic absorption spectrometry. Arsenic methylation profile was assessed by percentages of various arsenic species in the sum of the three categories measured. The primary methylation index (PMI) was defined as the ratio between MMA^{V} and inorganic arsenic. Secondary methylation index (SMI) was determined as the ratio between DMA^{V} and MMA^{V}. Smoking is associated with a significant risk of UC in a dose-dependent manner. After multivariate adjustment, UC cases had a significantly higher sum of all the urinary species measured, higher percent MMA^{V}, lower percent DMA^{V}, higher PMI and lower SMI values compared with controls. Smoking interacts with the urinary arsenic profile in modifying the UC risk. Differential carcinogenic effects of the urinary arsenic profile, however, were seen more prominently in non-smokers than in smokers, suggesting that smoking is not the only major environmental source of arsenic contamination since the UC risk differs in non-smokers. Subjects who have an unfavorable urinary arsenic profile have an increased UC risk even at low exposure levels.

Source: Toxicology and Applied Pharmacology, Vol. 218, January 2007.

ENVIRONMENTAL RISK FACTORS FOR PARKINSON'S DISEASE AND PARKINSONISM

Parkinson's disease is a neurodegenerative disease characterized by progressive degeneration of the dopaminergic neurons of the substantia nigra. It is the second commonest neurodegenerative disease after Alzheimer's disease, and in the UK has a lifetime prevalence of between 0.1 and 0.3% of the population. There is evidence that both genetic and environmental factors are important determinants, and a family history of the disease has been shown to be a risk factor. It seems likely that Parkinson's disease is not a single disease but a number of phenotypically similar illnesses. A variable range of genetic and environmental interactions may produce these conditions and it may be that any individual risk factor will only affect susceptible subjects.

A Danish cohort study found an increased risk of first hospital admission with Parkinson's disease in agricultural workers. A prospective cohort study in Hawaii (the Honolulu Heart Program) found that plantation work for more than 10 years was associated with an increased relative risk of Parkinson's disease. A cohort study of workers exposed to pesticides in Washington State, using detailed exposure information, found a marginally non-significant increased prevalence ratio of Parkinson's disease among those with the longest exposures. A prospective cohort study in southwestern France (the PAQUID study) has reported an increased relative risk of Parkinson's disease among men with occupational pesticide exposure. Although most studies show a positive association between pesticide exposure and Parkinson's disease, no specific agent has been implicated consistently. Agriculture employs a range of pesticides and so identifying the causative agent is extremely difficult. Similarly, the degree of pesticide exposure that may lead to Parkinson's disease is unknown. Necropsy studies have found increased levels of organochlorine pesticides in the brains of patients with Parkinson's disease. Acute reversible parkinsonism has been described after organophosphate pesticide poisoning. One German case-control study found an association between the use of organochlorine compounds and alkylated phosphates/carbamates and Parkinson's disease. Cases of parkinsonism have been reported after occupational exposure to maneb: a manganese-containing carbamate pesticide (manganese ethylene-bis-dithiocarbamate). Paraquat, a widely used bipyridyl herbicide, is structurally similar to 1-methyl-4-phenylpyridinium and has been linked to parkinsonism in both epidemiological surveys and laboratory work, while rotenone, another insecticide, is used to induce parkinsonism in a rat model of the disease.

Now a five-centre case control study of 959 prevalent cases of parkinsonism (767 with Parkinson's disease) and 1989 controls has been carried out in Scotland, Sweden, Italy, Romania and Malta.

Cases were defined using the United Kingdom Parkinson's Disease Society Brain Bank criteria, and those with drug-induced or vascular parkinsonism or dementia were excluded. Subjects completed an interviewer-administered questionnaire about lifetime occupational and hobby exposure to solvents, pesticides, iron, copper and manganese. Lifetime and average annual exposures were estimated blind to disease status using a job-exposure matrix modified by subjective exposure modeling. Results were analyzed using multiple logistic regression, adjusting for age, sex, country, tobacco use, ever knocked unconscious and family history of Parkinson's disease.

Adjusted logistic regression analyses showed significantly increased odds ratios for Parkinson's disease/parkinsonism with an exposure-response relationship for pesticides (low vs no exposure, odds ratio (OR) = 1.13, 95% CI 0.82 to 1.57, high vs no exposure, OR = 1.41, 95% CI 1.06 to 1.88) and ever knocked unconscious (once vs never, OR = 1.35, 95% CI 1.09 to 1.68, more than once vs never, OR = 2.53, 95% CI 1.78 to 3.59). Hypnotic, anxiolytic or antidepressant drug use for more than 1 year and a family history of Parkinson's disease showed significantly increased odds ratios. Tobacco use was protective (OR = 0.50, 95% CI 0.42 to 0.60). Analyses confined to subjects with Parkinson's disease gave similar results.

The association of pesticide exposure with Parkinson's disease suggests a causative role. Repeated traumatic loss of consciousness is associated with increased risk.

This large study thus confirms the previously described negative association between tobacco smoking and Parkinson's disease, which is probably owing to a true neuroprotective effect of tobacco smoke constituents. In agreement with previous studies, no evidence was found that alcohol consumption was associated with disease. In conclusion, this study has provided important evidence of the increased risk of Parkinson's disease in relation to exposure to pesticides. The exposure-response relationship suggests that pesticide exposure may be a causative and potentially modifiable risk factor.

Source: Occupational and Environmental Medicine, Vol. 64, October 2007.

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