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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".

Seminar on Atmospheric Pollution and Health Effects

March 18th - 20th, 2019

Chulabhorn Research Institute, Bangkok, Thailand

The Chulabhorn Research Institute (CRI) and the University of Bristol (UoB, UK) co-organized a **seminar on Atmospheric Pollution and Health Effects** between March 18th - 20th, 2019 at the Chulabhorn Research Institute, Bangkok, Thailand.

The seminar was attended by 48 participants, with 10 speakers from the UoB, US National Institute of Environmental Health Sciences, Public Health England, the Thai Pollution Control Department (PCD), Thammasat University and CRI, and 38 participants from Thailand, Vietnam and Lao PDR, including representatives from the United Nations Environment Programme (UNEP).

The seminar was organized into 3 main topics, including "Atmospheric Chemistry, Measurement and Modelling Techniques", "Atmospheric Pollution Measurements", and "Health Effects of Air Pollution".

In terms of atmospheric chemistry, measurement and modelling techniques, topics covered introductions to atmospheric chemistry and aerosol science, gas and aerosol measurement techniques, chemistry and dispersion modeling techniques, and urban dispersion experiments.

For atmospheric pollution measurements, topics covered air quality campaigns in the UK, ambient air monitoring in Thailand, Weather Research and Forecasting (WRF) -Chem modeling of air pollutants and particulate size distribution and metal content in Bangkok, and the current situation of ambient particulate matter in Thailand in terms of management and policy.

For the health effects of air pollution, topics covered the global health burden of air pollution, deposition of aerosols in the respiratory tract, biomonitoring of air

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Seminar on Atmospheric Pollution and Health Effects March 18th -20th, 2019 at the Chulabhorn Research Institute, Bangkok, Thailand

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pollutants and health effects, mechanisms of air pollutant-induced diseases and cancer, and the health risk assessment of air pollution.

The main objectives of the seminar was to share the latest information on air pollution research and to foster collaboration among the participating institutions and participants, who were mainly researchers and government officials working in the area of air pollution.

CRI's WHO COLLABORATING CENTRE ON CAPACITY BUILDING & RESEARCH IN ENVIRONMENTAL HEALTH SCIENCE & TOXICOLOGY

Official Visit of Technical Team to the World Health Organization's Regional Office for South-East Asia

On March 7th, 2019, a team of senior researchers from the Chulabhorn Research Institute (CRI), led by Professor Mathuros Ruchirawat, CRI Vice President for Research and Academic Affairs, paid an official visit to the World Health Organization's Regional Office for South-East Asia (WHO SEARO) in New Delhi, India, to review progress and next steps for the work carried out under the collaborative workplan between CRI and WHO; 2019 will be the second year of the new workplan (4th term), which was agreed in January 2018.

CRI's International Centre for Environmental Health and Toxicology (ICEHT) has been a WHO Collaborating Centre for Capacity Building and Research in Environmental Health Science and Toxicology since 2005.

The technical discussions covered the following areas: (1) the workplan for the 4th term and brief highlights of progress in the various activities over the previous year, (2) recent initiatives on Children's Environmental Health (CEH), including presentations by the Public Health Foundation of India, UNICEF, the US NIEHS, WHO and CRI, and conclusions on the planned activity on CEH according to the workplan, (3) training activities, including a planned in-country training course for Vietnam in 2019, and (4) on-going collaborations with WHO HQ, including the Risk Assessment Network and the Risk Assessment Training Course Database (RiskTrainDB).

In terms of the capacity building/ training programmes in Chemical Safety and Occupational and Environmental Health/Medicine, CRI organized 4 international training courses in 2018, attended by a total of 39 participants from 18 countries.

These courses are open to participants, primarily from the Asia Pacific region, and are taught by international experts from world-renowned academic and research institutions with a wealth of teaching experience in the region.

The organized courses in 2018 include:

	Training Course	Time
1	Detection of Environmental Pollutants and Monitoring of Health Effects	February 5 - 16, 2018
2	Environmental Toxicology	April 19 - 27, 2018
3	Environmental Immunotoxicology and Reproductive Toxicology	October 1 - 12, 2018
4	Environmental and Health Risk Assessment and Management of Toxic Chemicals	December 3 - 15, 2018

Those who are interested in applying for a fellowship to attend such training courses can check the calendar of events on CRI's website at http://www.cri.or.th/en/ac_actcalendar.php.

Fine Particulate Matter and Respiratory Hospitalizations among Childhood Cancers Survivors

Fine particulate ($PM_{2.5}$) pollution is linked to respiratory infections and is capable of exacerbating preexisting respiratory conditions among vulnerable children and adults.

Like children with preexisting respiratory conditions, survivors of childhood cancers may experience increased vulnerability to $PM_{2.5}$ due to lung damage and potential immunosuppression resulting from cancer and treatment with chemotherapy.

Respiratory conditions resulting from the chemotherapy used to treat cancer can begin within the first few months after treatment ceases. Such conditions include respiratory infection, difficulty in breathing, chronic coughing, and asthma.

Respiratory infections, like pneumonia and bronchitis are a particular concern in this population because survivors of childhood cancers face a significantly higher risk of infection than their siblings who have no cancer history.

Across the United States, respiratory infections and conditions are also linked to $PM_{2.5}$ pollution exposure, especially in the state of Utah.

Utah's $PM_{2.5}$ originates largely from traffic emissions, but winter inversions further expose Utah's population to 24-h $PM_{2.5}$ concentrations as high as 70 $\mu g/m^3$, roughly six times the 24-h national health standard (12 $\mu g/m^3$). As a result Utah has some of the worst short-term $PM_{2.5}$ pollution in the nation.

$PM_{2.5}$ in Utah has specifically been linked to acute lower respiratory tract infection among children, adolescents, and young adults, and to pneumonia in adults aged ≥65 years.

No studies have examined the short-term effects of $PM_{2.5}$ pollution on the respiratory health outcomes of childhood cancer survivors despite their propensity for respiratory problems.

This case-crossover study was conducted to identify the $PM_{2.5}$-associated odds for primary-respiratory hospitalizations and emergency department (ED) visits among childhood cancer survivors in Utah.

Current regulatory guidelines for air pollution may not be sufficient to protect vulnerable groups such as cancer survivors. To understand whether cancer survivors are affected by $PM_{2.5}$ pollution at sub-regulatory levels, the study examined the risk for respiratory hospitalizations and emergency department visits by the 24-h $PM_{2.5}$ National Ambient Air Quality Standard (NAAQS) of 35.4 $\mu g/m^3$ and by 25.0 $\mu g/m^3$, which was identified as a threshold for respiratory effects among an elderly population.

This study found that $PM_{2.5}$ was associated with a two-fold increase in the odds for hospitalizations caused by respiratory infection. Chemotherapy-treated survivors had a significantly higher risk of respiratory hospitalization attributed to $PM_{2.5}$ than a cancer-free population.

Certain chemotherapies are linked to short- and long-term immunosuppression. The immunosuppressive effects of $PM_{2.5}$ are well documented and $PM_{2.5}$ is a primary risk factor for respiratory infections in children through immune suppression.

The findings support the hypothesis that immunosuppression from chemotherapy may be further exacerbated by $PM_{2.5}$, resulting in respiratory infection. The odds of $PM_{2.5}$-related respiratory ED visits and respiratory infections were highest among survivors diagnosed at age ≤3 years compared to survivors of older age groups.

This is the first study to report significant associations between $PM_{2.5}$ and respiratory healthcare encounters in childhood cancer survivors.

Chemotherapy-treated survivors displayed the highest odds of hospitalization due to $PM_{2.5}$ exposure. Their risk was significantly higher than the cancer-free group.

Exposure to certain chemotherapies at a young age is linked to long-term pulmonary dysfunction and diffusion abnormalities in up to 65% of childhood cancer survivors. Pulmonary dysfunction and immunosuppression related to chemotherapy may explain the increase in risk for the respiratory infections seen among survivors diagnosed at age ≤3 years in this study. Further follow-up is needed to confirm the association between leukemia and post-treatment $PM_{2.5}$-related respiratory problems.

The results showed that the majority of the hospitalizations and ED visits occurred when the 24-h $PM_{2.5}$ levels were below the 24-h standard (35.4 $\mu g/m^3$) considered acceptable by both national and statewide agencies. In Utah, winter inversions raise the $PM_{2.5}$ above the 35.4 $\mu g/m^3$ standard.

Healthy survivorship is a priority for a growing number of survivors of childhood cancers in the United States. Although medical interventions are critical to the long-term care of childhood cancer survivor, this study provides evidence that the respiratory morbidity of cancer survivors may be impacted by the environment in which they reside.

Since childhood cancer survivors often complete therapy before adolescence, most have decades of life remaining after treatment ceases. To prevent future respiratory morbidity, childhood cancer survivors should take action to avoid air pollution exposure. Survivorship guidelines and health agencies should consider revising current policies and guidelines to include cancer survivors as a vulnerable population.

As respiratory morbidity is a leading cause of non-cancer death in this population, providing adequate guidelines for preserving the health of cancer survivors and identifying post-treatment factors that affect survivors' health may be key to preventing future morbidity.

Source: International Journal of Environmental Research and Public Health, Vol. 16, No. 6, Page 1081, March 2019.

Prenatal Exposure to PAHs in E-waste Recycling Areas and Birth Outcomes

Polycyclic aromatic hydrocarbons (PAHs) have long been known to be carcinogenic endocrine disruptors.

Emitted from diverse sources, semi-volatile PAHs composed of two or more fused aromatic rings are typical. They are hydrophobic with low solubility, which makes them difficult to degrade.

PAHs exist ubiquitously in the environment. People typically ingest these chemicals via contaminated food or water or when they breathe polluted air.

Once ingested or inhaled, PAHs are easily metabolized into more hydrophilic and polar metabolites that pass out of the body in the urine and feces.

Their pervasiveness and their many intermediate byproducts, mostly in the formation of PAH-DNA adducts, have aroused much concern. Numerous studies *in vitro* and *in vivo* have already identified specific mixtures of PAHs as carcinogenic.

Difficulty in properly dealing with electronic waste (e-waste) has been aroused growing cause of global concern especially in the face of 41.8 million tonnes of e-waste in 2014 and as much as 65.4 million tonnes by 2017.

China and the United States are the largest producers of e-waste, creating twice as much as any other single industrialized country.

Guiyu, located in southern China, is one of the largest e-waste destinations in the world. In the informal recycling of e-waste, wire is burned to recover copper, circuit boards are heated over honeycombed coal blocks, and acidic chemical stripping agents are used to recover gold and other metals.

These processes release large amounts of toxicants into the local environment through multiple pathways, potentially impacting human health and the ecosystem.

Previous studies have found that soil samples from two e-waste areas, one in China and one in Nigeria, are highly contaminated with the toxic PAHs associated with concentration-dependent increases in DNA damage in human peripheral blood lymphocytes.

These results point to a considerable quantity of toxic PAH residue in local surroundings. As such, there is a potential health risk to folks living there, particularly for individuals sensitive to toxicants.

Extensive investigations have been carried out to assess the sources of human exposure to PAHs and the resulting health outcomes. Because of the diversity and fluctuating concentrations of PAHs, efforts have been directed to characterize single or multiple metabolites as PAH exposure biomarkers.

Urine has been recognized as an effective biological matrix for human exposure to PAHs in the environment. Urinary 1-hydroxypyrene (1-OHPyr) is associated with genotoxicity and can serve as a biomarker for internal exposure.

Urinary 1-OHPyr is associated with increased malondialdehyde and 8-hydroxyl-deoxyguanosine, indicative of oxidative stress, in workers and in the general population.

Numerous studies have associated prenatal or postnatal exposure to PAHs with harmful physiological effects, such as global alteration of DNA methylation in cord blood, lower birth weight, smaller head circumference and preterm birth.

On the other hand, only a limited number of studies have examined the effects of PAH exposure and their impact on the developing fetus during pregnancy.

The present study aimed to determine the hydroxylated PAH (OHPAH) metabolite concentrations in maternal urine collected from the e-waste-contaminated area of Guiyu and the reference area of Haojiang, China, and to evaluate their health effects on birth outcomes.

The results show that total and individual urinary PAH metabolites in a polluted e-waste area are higher than those in a non-polluted area. However, both groups have similar exposure profiles and trends for all PAH metabolites, especially for exposure to 2-hydroxy-naphthalene (2-OHNap) and 1-OHPyr.

This suggests that residents in e-waste-polluted areas are exposed to higher concentrations of PAHs.

In total, in this typical e-waste area, the results show PAH metabolites in maternal urine at higher levels than those reported for some European countries and the United States. 2-OHNap and 1-OHPyr are the dominant compounds.

Standardized mean difference revealed that compared to low PAH metabolite levels, high PAH metabolite levels, especially for 1-OHPyr, ΣOHPAHs and sometimes hydroxylphenanthrene compounds, presented a reduced size in birth outcomes, including head circumference, body mass index (BMI) and Apgar 1 score, and increased height.

These findings suggest that high exposure to PAHs during pregnancy in e-waste areas, poses a potential threat to neonatal development, a threat which likely can be attributed to local e-waste recycling activities.

Therefore, continuous monitoring to assess prenatal or postnatal health outcomes is needed in highly polluted areas.

Ongoing studies should be continued to monitor human exposure and health, in particular the health of vulnerable individuals in e-waste-polluted areas.

Source: Environmental Pollution, Vol. 245, Pages 453-461, February 2019.

Butyrylcholinesterase - A Potential Plasma Biomarker in Manganese-induced Neurobehavioral Changes

Drinking water contaminated with metals has created an environmental disaster in Bangladesh. The presence of toxic level of arsenic (As) in groundwater is one of the most serious challenges for pubic health in Bangladesh and in India's West Bengal as well.

Unsafe levels of lead (Pb), nickel (Ni), and chromium (Cr) have been detected in some areas of Bangladesh. Water samples from a large number of deep and shallow wells also contain excess amounts of manganese (Mn) beyond permissible limits.

Mn, an essential trace element, plays a key role in the development and function of the brain. Excess Mn exposure, on the other hand, has been associated with complex neurological disorders.

In humans, as a cofactor of several enzymes involved in neurotransmitter synthesis and metabolism, including glutamine synthetase, arginase, pyruvate decarboxylase, and mitochondrial superoxide dismutase, Mn plays an important role in the development and functioning of the brain.

However, too much Mn, whether through polluted air or drinking water has been shown to be toxic and can produce cognitive deficits in humans. In animal models, neurobehavioral studies focusing on locomotor activity have shown that overexposure to Mn can lead to progressive, permanent neuro-degenerative damage.

Excessive Mn injures the central nervous system within the hippocampus, causing cognitive impairment. Many recent studies have shown that alterations in the biology of gamma-aminobutyric acid-ergic (GABAergic), glutamatergic, and dopaminergic systems are involved in the etiology of Mn-induced neurotoxicity.

Excessive accumulation of Mn in the brain affects the cholinergic system, whose dysfunction is related to Alzheimer's disease (AD).

Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) hydrolyze the cholinergic neurotransmitter acetyl-choline in the circulatory system.

BChE is a nonspecific cholin-esterase enzyme that hydrolyses many different choline-based esters and is involved in cholinergic regulation, both in the central and peripheral nervous systems. BChE is found in blood, in the liver, and in the central and peripheral nervous systems.

BChE is the major acetylcholine-hydrolyzing enzyme in the circulation. It maintains the normal cholinergic pathway in AChE knockout mice. In addition, it has been reported that BChE activity changes in the plasma in pregnancy, liver disease, poor nutrition, cancer, and AD patients's brain.

BChE is used as an organo-phosphate poisoning biomarker. Its activity reveals the strength of the cholinergic anti-inflammatory response as well as changes in sympathetic/ parasympathetic balance.

A higher level of Mn in drinking water (> 300 μg/l) is associated with reduced intellectual function in children. Although there is evidence of neurotoxicity in children due to the presence of higher levels of Mn in drinking water, there is no ideal blood biomarker for evaluating neurotoxicity associated with Mn exposure.

Furthermore, while the cholinergic system is reported to be affected by Mn, BChE activity in Mn exposure has not clearly been documented.

This study was designed to establish the BChE as a biomarker in Mn-induced neurobehavioral changes through human and animal experiments.

The study found an exceptionally large presence of Mn above permissive limits in the tube-well water of Rajshahi and Naogaon districts in Bangladesh.

Higher levels of Mn in hair and nail samples, and a decreasing level of BChE activity were detected in plasma samples of human subjects recruited from Naogaon district.

Mn concentrations in water, hair, and nails were negatively correlated with the plasma BChE levels in Mn-exposed populations.

To compare and validate these human studies, an animal model was used to determine the *in vivo* effects of Mn on neurobehavioral changes and blood BChE levels.

In an elevated plus maze, time spent was significantly reduced in open arms but increased in the closed arms of Mn-exposed mice, compared to in control group.

The mean latency time to find the platform was significantly less for control mice, compared to Mn-treated group during 7 days testing in a Morris water maze test. The Mn-exposed group also spent significantly less time in the desired quadrant, as compared to the control group in a probe trial.

BChE activity was significantly reduced in Mn-exposed mice compared to control mice.

The results of this human and animal study clearly suggest that prolonged consumption of Mn-contaminated water is linked to the reduction of plasma BChE activity.

This study also demonstrates that consumption of Mn-contaminated drinking water induces anxiety-like behavior and causes learning and memory impairment.

Neurobehavioral changes and reduced blood BChE activity in both Mn-exposed humans and animals indicate that plasma BChE levels may serve as a reliable biomarker of Mn-induced neurotoxicity related to behavioral change.

Further study is needed to explore the pathophysiological mechanism of Mn-induced BChE activity reduction and its impact on neurobehavioral alterations.

Source: Environmental Science and Pollution Research, Vol. 26, Issue 7, Pages 6378-6387, March 2019.

DDT and Breast Cancer: Induction Time and Susceptibility Windows

Prior findings in the Child Health and Development Studies (CHDS) are consistent with experimental evidence showing that the timing of environmental exposures during susceptible windows, including *in utero*, in childhood, puberty, or pregnancy cause varying dys-regulation of breast or mammary gland development that can result in cancer later in life.

Most epidemiological studies to date have not shown an association between DDT and breast cancer, but they have been based on exposures measured in mid-life blood samples obtained after DDT use was banned.

Less accurate estimations of the toxic affects for women of exposure to the active insecticide are like due to differences in the period in which exposure occurred.

Perimenopause and menopause may be particularly relevant in assessing breast tissue changes and mammary carcinogenesis because this is a period when the breast tissue is changing in structure and in function.

Two independent nested prospective case-control samples within the CHDS were conducted to investigate whether DDT associations with breast cancer depend on both timing of exposure (exposure window) and timing of disease (outcome window).

The first study in the CHDS investigated breast cancers in women diagnosed prior to age 50. During the premenopausal outcome window for all the subjects, there was a statistically significant *p,p'*-DDT association with breast cancer.

While this association depended on the age of the subject at first exposure and was present only in women exposed before puberty, the *p,p'*-DDT-breast cancer association was strongest for women exposed *in utero* or in infancy.

These results are consistent with experimental evidence that early life is an important window of susceptibility for mammary cancer where the induction period from first exposure to breast cancer was about 40 years.

In the second prospective, nested case-control study, observation was extended to breast cancer diagnosed during early postmenopause (ages 50-54 years) to determine whether age at diagnosis modifies the interaction of DDT with age at exposure.

The results showed a similar induction period of about 40 years between first DDT exposure and onset of breast cancer. However, in contrast to the earlier study, this association was accounted for women first exposed after infancy, pointing to the dependence of *p,p'*-DDT associations with breast cancer on both exposure and outcome windows.

These observations, taken in the same cohort for different outcome windows suggest that intrauterine and infant DDT exposure increases risk of premenopausal breast cancer, whereas DDT exposure after infancy increases breast cancer risk in the early postmenopausal years.

In conclusion, *p,p'*-DDT was a risk factor for breast cancer through age 54 among women in the founding generation in the CHDS (born 1915 to 1950), regardless of age at first exposure. However, risk patterns depended both on age at first exposure and timing of diagnosis.

When first exposure occurred before puberty, there was greater susceptibility for breast cancer before age 50. they also found long induction period (about 40 years) between first DDT exposure and onset of breast cancer, regardless of age at first exposure.

Associations with *p,p'*-DDT depended on exposure and outcome windows that encompass critical shifts in endocrine function, suggesting that DDT affects breast cancer as an endocrine disruptor.

Source: Journal of the National Cancer Institute, Vol. 111, No. 8, February 2019.

Hexachlorobenzene and Endometriosis Progression in a Rat Model

Hexachlorobenzene (HCB) is a dioxin-like compound and a weak ligand of the aryl hydrocarbon receptor (AhR), a transcription factor which triggers membrane and nuclear functions modulating processes such as inflammation, proliferation and migration.

It has been suggested that AhR is involved in the normal function of the endometrium, possibly by modulating cellular proliferation in response to hormones.

Endometriosis development and maintenance depends on the recruitment of blood vessels to endometriotic lesions through angiogenesis. Angiogenic vascular endothelial growth factor (VEGF) increases in the peritoneal fluid of women with endometriosis, as compared to healthy women.

Cyclooxygenase (COX) is the rate-limiting enzyme in the conversion of arachidonic acid to prostaglandins (PGs). COX-2 is induced in response to inflammatory stimul. Its over-expression in endometriosis has been documented.

Matrix metalloproteinases (MMPs) are essential in the physiological function of the endometrium. Endometriosis is primarily associated with the degree of expression or activity of MMP-2 and MMP-9.

COX-2 decreases the migration and invasion of endometriotic epithelial and stromal cells by suppressing MMP-2 and MMP-9 activity relative to the decrease of prostaglandin E2 (PGE2) levels.

However, the PGE2 receptors EP2/EP4 pathway promotes phosphory-lation of c-Src kinase, triggering MMP activation. Tumor necrosis factor-α (TNF-α) is a major pro-inflammatory cytokine which is also implicated in endometriosis. It induces endometrial cell proliferation and adhesion to

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Noncommunicable Diseases and Air Pollution

Air pollution is the second leading cause of deaths from noncommunicable diseases (NCDs) after tobacco smoking, according to World Health Organization (WHO).

Around the world every year, household and ambient air pollution cause 7 million people to die prematurely. This number includes more than 5 million deaths caused by the NCDs associated with air pollution. In the WHO European Region, more than 550,000 deaths in 2016 were attributable to the joint effects of household and ambient air pollution.

Tackling air pollution will be a key factor in reducing premature mortality. Indeed, at the United Nations High-level Meeting on NCDs in September 2018, air pollution was included as a fifth risk factor for NCDs.

The main NCDs associated with air pollution include ischaemic heart disease, stroke, chronic obstructive pulmonary disease and lung cancer. Substantial epidemiological evidence links air pollution with diverse health outcomes., Extensive research has been conducted to advance understanding of the underlying mechanistic pathways.

Among the complex mixtures of air pollutants, particulate matter is a prime public health concern. Interventions to reduce exposure to air pollution and improve air quality have huge potential for protecting health and reducing the burden of NCDs. Creating healthier environments which reduce NCDs can result in a host of multiple benefits for health, climate change and the environment.

There is substantial evidence concerning the health impacts on the public of air pollution and its magnitude as an environmental risk. Any intervention will require cooperation between many sectors of society and the active support of multiple levels of government. However, concerted efforts can give multiple benefits.

Source: WHO/Europe News. Publication Date: March 2019. (http://www.euro.who.int/en/health-topics/environment-and-health/air-quality/news/news/2019/3/noncommunicable-diseases-and-air-pollution)

Hexachlorobenzene and Endometriosis Progression in a Rat Model

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peritoneal cells, regulates MMPs, and stimulates angiogenesis.

Aromatase is the key enzyme in the biosynthesis of estrogen, the essential hormone for the establishment and growth of endometriosis. In endometriosis cells, aromatase expression is induced via the COX-2-PGE2 pathway.

Estradiol also stimulates COX-2 expression by generating a positive feedback loop. Aberrant expression and signaling of estrogen and progesterone receptors (ER, PR) have been associated with the progression of endometriosis, which is commonly referred to as estrogen-dependent and progesterone-resistant.

Previous studies have found that HCB increases MMP-2 and MMP-9 activities in the human endometrial stromal cell line T-HESC and in primary cultures of endometrial stromal cells from eutopic endometrium both in women who were the control group and in patients with endometriosis.

Given that rat endometriotic tissues are similar to human lesions *in vivo*, rat models permit the study of mechanisms in a controlled manner, free from confounding influences such as individual patient variation.

The present study was conducted to investigate the impact of HCB on the endocrinal, invasive and inflammatory parameters in a surgically induced rat endometriosis model. Female rats were exposed to HCB (1, 10 and 100 mg/kg b.w.) for a period of 30 days.

Results showed that HCB increases endometriotic-like-lesions (L) with volume in a dose-dependent manner. In L, HCB10 increases micro-vessel density (immunohisto-chemistry) and the vascular endothelial growth factor (VEGF), cyclooxygenase-2 (COX-2) and AhR levels (Western Blot), while HCB1 enhances aromatase expression (Western Blot).

In addition, in eutopic endometrium (EU), HCB10/HCB100 augments micro-vessel density, VEGF and MMP-9 expression, while HCB1/HCB10 increases tumor necrosis factor-α (TNFα) content in peritoneal fluid (ELISA).

It is noteworthy that both L and EU from HCB-treated rats exhibited higher estrogen receptor α (ERα) (immunohisto-chemistry) and metalloproteases (MMP)-2 and -9 levels (Western Blot), as well as lower progesterone receptor (PR) expression (immunohistochemistry) than in control rats.

In the present study, several parameters (VEGF, COX-2, aromatase and ERα expression) were enhanced at lower doses (1 and 10 mg/kg b.w.) than at higher HCB doses. This is interesting, since it suggests that environmental concentrations of HCB are sufficient to induce changes in endometrial cells.

The researchers proposed a mechanism of action of HCB in

CALENDAR OF EVENTS

International Training Courses at Chulabhorn Research Institute
Schedule for 2019

	Training Course	Date	Duration	Closing Date
1.	Environmental and Health Risk Assessment and Management of Toxic Chemicals	December 6-18, 2019	2 weeks	October 15, 2019

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

Course Description:

Environmental and Health Risk Assessment and Management of Toxic Chemicals (December 6-18, 2019)

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.

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

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More information and application:
please visit - http://www.cri.or.th/en/ac_actcalendar.php

Hexachlorobenzene and Endometriosis Progression in a Rat Model

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endometrial stromal and epithelial cells. HCB enters to cells, binds to the AhR-c-Src complex, triggering: 1) a membrane pathway, where c-Src stimulates growth factor receptors (GFR, such as VEGFR); and activates MMPs, promoting cell proliferation and invasion; and 2) a nuclear pathway, where HCB-AhR complex translocates to the nucleus, binds to the AhR nuclear translocator protein (ARNT) and leads COX-2, VEGF and TNFα gene expression [xenobiotic response elements (XRE) in theirs promoters].

This increase in COX-2, VEGF and TNFα expression could induce cell proliferation, inflammation and angiogenesis, contributing to the progression or worsening of endometriosis.

In conclusion, the present results show for the first time that environmentally relevant HCB doses alter inflammatory, endocrinal invasive parameters in eutopic endometrium and endometriotic like-lesions in a rat endometriosis model.

Environmentally relevant concentrations of HCB could thus have a potential role in the progression of this illness. The HCB would act as a xenoestrogen, inducing a proliferative and invasive profile, and a peritoneal proinflammatory and proangiogenic microenvironment contributing to the development and progression of the disease.

Source: Food and Chemical Toxicology, Vol. 123, Pages 151-161, January 2019.

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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