CRI/ICEIT
NEWSLETTER

VOL. 23 NO. 4 – October 2013
ISSN 0858-2793
BANGKOK, THAILAND

Chulabhorn Research Institute

INTERNATIONAL CENTRE FOR ENVIRONMENTAL AND INDUSTRIAL TOXICOLOGY (ICEIT)

CRI's ICEIT has been designated as a
"UNEP Centre of Excellence for Environmental and Industrial Toxicology".

CRI collaborates with the Universiti Brunei Darussalam for capacity building on "Risk Assessment and Management of Chemicals" in Brunei Darussalam from October 14-18, 2013

Professor Dr. Her Royal Highness Princess Chulabhorn Mahidol, President of the Chulabhorn Research Institute (CRI), as Course Director, led a team of international faculty to conduct in-country training on Risk Assessment and Management of Chemicals in collaboration with the Universiti Brunei Darussalam (UBD) from October 14-18, 2013.

CRI's teaching faculty included Professor Herman Autrup from Aarhus University, Denmark, Professor Martin van den Berg from Utrecht University, the Netherlands, and Professor David MacIntosh, from Harvard School of Public Health, USA, as well as Drs. Mathuros Ruchirawat, CRI Vice-president for Research and Academic Affairs, Jutamaad Satayavivad, CRI Associate Vice-president for Scientific Affairs, and Daam Settachan, research scientist from CRI's Laboratory of Environmental Toxicology.

The CRI has a vast experience with providing training for participants within the SEA region, having trained participants from Brunei Darussalam, Cambodia, India, Indonesia, Laos, Malaysia, the Maldives, Myanmar, Nepal, the Philippines, Sri Lanka, Thailand, Timor Leste and Vietnam, amongst others. This training course was conducted as part of CRI's role as the WHO-SEARO designated Regional Training Centre for Chemical Safety in South-East Asia Region.

The collaboration between CRI and UBD in the organization of this training course underscored the close and cordial relations between Thailand and Brunei Darussalam, and reflected the long established bond of friendship between the two Royal families. The training course on Risk Assessment and Management of Chemicals is an important step in the bilateral cooperation, since it involves the integration of science and policy in the areas of chemical safety, public health and economic development, reflecting the shared commitment of the two countries to improve the quality of life of their people.

The management of chemicals and the assessment of the risks involved in their effective and beneficial use in industry and agriculture is an area of specialization in which CRI has developed considerable

(Continued on page 2)

CRI collaborates with the Universiti Brunei Darussalam for capacity building on "Risk Assessment and Management of Chemicals" in Brunei Darussalam from October 14-18, 2013

(Continued from page 1)

expertise, both through the education and research programs and through the close collaborations with eminent scientists and researchers from renowned universities in other countries, as well as from international organizations such as the WHO.

As part of the training, two complimentary tools for providing guidance on conducting risk assessment of chemicals were introduced to the participants. The first is the WHO IPCS Human Health Risk Assessment Toolkit, and the second is an electronic distance learning tool on risk assessment and risk management of chemicals, which CRI played an important role in developing, along with its collaborating partners: WHO's International Programme on Chemical Safety; the University of Ottawa, Canada; and Utrecht University, the Netherlands, and which was officially launched by Professor Dr. Her Royal Highness Princess Chulabhorn Mahidol on the occasion of an official visit to the WHO's Regional Office for South-East Asia in New Delhi in February 2013.

Seventy participants attended the in-country training course from various different agencies, including: Universiti Brunei Darussalam, the Ministry of Health (including the two major hospitals in Brunei Darussalam), the Department of Labour, the Public Work Department, the Fire and Rescue Department, the Agrifood Safety Division, Brunei Shell Petroleum Company Sendirian Berhad, and Brunei Methanol Company, as well as one international participant from the Philippines.

THE BIOLOGICAL METABOLIC FINGERPRINT AND IMPACT ON HEMATOPOIESIS OF DIETARY EXPOSURE TO A LOW DOSE OF PESTICIDES ALONE OR IN A MIXTURE

The use of pesticides has been crucial for agricultural development and the control of food resources. Pesticides destroy undesirable plants, insects and/or fungi which are vectors of diseases or toxin producers. Although more than 700 pesticides have been withdrawn from use for this reason, many are still in use; in France 310 active substances are currently used in 3215 authorized commercial preparations. The use of pesticides in agriculture and in the maintenance of road networks and parks has led to the contamination of the environmental compartments (air, water and soil) and therefore our food. Accordingly, the European Food Safety Authority (EFSA) recently reported that 49.5% of fruit and vegetables contain pesticides.

Consumers are exposed to a mixture of pesticides through their food intake. These compounds are considered risk factors for human health, and the impact of dietary exposure to low doses of pesticide mixtures remains poorly understood.

To address this issue researchers developed a mouse model that mimics consumer exposure and compared the impact and metabolic fingerprint of pesticides both alone and in combination at low doses corresponding to the Acceptable Daily Intake (ADI). Female mice were exposed to pesticides throughout gestation and lactation. After weaning pups were fed the same pesticide-enriched diet their mothers had received for an additional 11 weeks. A metabonomic approach using 1H NMR-based analysis of plasma showed that exposure to each pesticide produced a specific metabolic fingerprint in adult offspring.

Studies on the fertility of C57BL/6 mice following pesticide exposure showed no significant changes in the number of pregnant mice, nor in the number of pups compared to non-exposed mice. In contrast, the number of living pups was higher in all the groups exposed to pesticides through food and this increase was significant in the endosulfan-exposed group. The explanation for this was that dams from the control group were eating more of their pups than in the other groups, especially the endosulfan-exposed mice. Thus it was hypothesized that dietary exposure of pregnant animals to low doses of endosulfan induced behavior alterations (such as increased tolerance of pups) that would have otherwise been suppressed. Behavior alterations have recently been reported following exposure of rats to chlorpyrifos and have been related to hyperphosphorylation of GSK-3β in the hippocampus and throughout the striatum of the exposed animals.

The health impact of human exposure to low doses of pesticide mixtures is of great concern. The interactions between several types of pesticides may result in multiple responses depending on their impact on xenobiotic metabolism enzymes, their toxicokinetics, and their molecular and cellular targets. Predicting risk from exposure to pesticide mixtures is complex as these compounds may interact at different levels. For some pesticide mixtures the effect may be more or less than what would be expected from combining the effects of the individual components.

The results of the present study demonstrate that a metabonomics approach is a reliable method to characterize dietary exposure to low doses of pesticides. Moreover it is clear that maternal exposure to pesticides can be detected in the plasma of pups. This approach could indeed be a potentially useful tool in human population studies. Moreover, this study shows that dietary exposure to a very low dose of endosulfan from fetal development until adult age leads to great changes in plasma glucose levels and hematopoietic disorders, suggesting that even when contaminants do not exceed the reference dose (MLR/ADI/NOAEL) food safety may still be a serious issue.

Source: Toxicology, Vol. 308, Pages 74-87, June 2013.

Intrauterine Exposure to Fine Particulate Matter: A Risk Factor for Increased Susceptibility to Acute Broncho-pulmonary Infections in Early Childhood

Over the last decades many epidemiologic studies have considered the morbidity patterns for respiratory diseases and lung function of children in the context of ambient air pollution usually measured in the postnatal period. The main purpose of the present study is to assess the impact of prenatal exposure to fine particulate matter ($PM_{2.5}$) on the recurrent broncho-pulmonary infections in early childhood.

The study included 214 children who had measurements of personal prenatal $PM_{2.5}$ exposure and regularly collected data on the occurrence of acute bronchitis and pneumonia diagnosed by a physician from birth over the seven-year follow-up.

While most of the previous studies were mainly concerned with the effect of the postnatal ambient exposure to particulate matter on respiratory morbidity in children, this is the first study of its kind that has evaluated the association between the individual prenatal $PM_{2.5}$ and the recurrent broncho-pulmonary episodes as an indicator of children's susceptibility to respiratory tract infections. It is important to mention that the estimates of the effect remained significant after adjustment for a set of potential confounders. The impact of prenatal exposure to $PM_{2.5}$ on the risk of recurrent broncho-pulmonary infections during early childhood appeared to be independent of the effects of environmental tobacco smoke (ETS), residence area and sensitization to common domestic aeroallergens, which were a proxy of quality of postnatal indoor/outdoor air quality.

The biological mechanism whereby prenatal exposure to prenatal $PM_{2.5}$ may lead to the increased susceptibility is yet unclear. $PM_{2.5}$ is a proxy for a wide spectrum of environmental hazards, such as constituents of tobacco and wood smoke, organic compounds, sulfates, polycyclic aromatic hydrocarbons (PAHs), metals and many other chemicals, which may be implicated in generating oxidative stress. Fine particles containing a very high proportion of organic carbon add to the biologic oxidative potency of these particles. While inhaled particles of 2.5 µm are linked to bronchial inflammatory effects, smaller particles (0.25 µm or less) are thought to move beyond the respiratory system and reach the bloodstream across placenta.

It is believed that the one of the key mechanisms by which air pollutants is linked with the increased risk of respiratory infections is the inhibition of the production of immunocompetent cells contributing to immunosuppression. On the other hand, transplacental exposure of newborns to higher prenatal $PM_{2.5}$ and its compounds may result in the production of an "allergic response" typified by the proliferation of Th2 type T lymphocytes which secrete proinflammatory cytokines in the body tissues. As the Th2 cytokines promote allergen-specific IgE antibody and induce eosinophile-dominated inflammatory tissue responses, allergic reactions are enhanced within the bronchial tract and lead to an increased susceptibility of newborns and young infants to pulmonary infections.

A strength of this study is the prospective birth cohort design that also enabled researchers to limit measurement error in estimating prenatal exposure to fine particles by assigning an individual prenatal personal exposure level to each child. The personal monitoring of ambient $PM_{2.5}$ exposure is a relevant measure incorporating outdoor and indoor exposures. Good agreement between the personal $PM_{2.5}$ measurements across all trimesters of pregnancy carried out in a subsample of 80 subjects provided evidence that the measurements of fine particles in the second trimester is also a good reflection of mean exposure level over pregnancy.

The study suggests that prenatal exposure to $PM_{2.5}$ increases susceptibility to respiratory infections and may program respiratory morbidity in early childhood. The observed effect of the increased susceptibility to respiratory infections may result from cytokine deregulation and an "allergic response" phenotype possibly established in the fetal period as a result of transplacental exposure to fine particulate matter. The study also provides evidence that the daily exposure below 20 µg/m^3 may better protect unborn babies than that proposed by EPA (35 µg/m^3). However, the proposed standard value would be very close to the 24-h mean limit of 25 µg/m^3 recommended by the present WHO guidelines (Air quality guidelines for Europe, 2000).

Source: International Journal of Hygiene and Environmental Health, Vol. 216, Issue 4, Pages 395-401, July 2013.

INITIATIVES, PRACTICES AND CONSEQUENCES IN HANDLING E-WASTE

Electronic products become e-waste when they are deemed at the end of their useful life. Nonfunctioning or obsolescent TVs, computers, printers, photocopiers, cell phones, fax machines, home appliances, lighting equipment, games and such, when no longer wanted, become e-waste. These electronic products contain many materials requiring special end-of-life handling, most prominently lead, mercury, arsenic, chromium, cadmium, and plastics capable of releasing, among other compounds, dioxins and furans.

The fate of e-waste is guided in vastly different ways, both physically and in policy, in different parts of the world. Developed countries have gone to great lengths to devise fairly complex, high-cost systems to handle e-waste, following directives written to spare the environment – although the majority of e-waste across Europe and North America still goes unrecycled. Elaborate collection systems are deployed, backed by information campaigns. Especially developed clean recovery technologies are used, from disassembly stations to plasma furnaces carefully engineered to prevent release of dioxins. In systems at the other end of the scale, in developing and transition countries for which China, India, Pakistan, and Nigeria may be taken as the archetypes, common practice is to smolder plastic off cables, as the cheapest means known of recovering their copper. Precious metals may be leached by acid baths from circuit board components and the used acid, laden with toxic metals, dumped into the ground or nearby stream. The surrounding population may be largely unaware of any danger from toxicity.

The practices are widely different yet the official policies and regulatory guidelines in developing countries show much influence from those of the developed world. While waste import bans are common in the developing world, the topography of recycling and disposal costs seems to assure a flow of e-waste out of the developed world down to the points of lowest-cost disposal.

The purpose of the present study is to characterize the e-waste situation at the present, in terms of intervention attempts made to keep it where it may be safely handled, and its fate when exported.

Discarded electronic goods contain a range of toxic materials requiring special handling. Developed countries have conventions, directives, and laws to regulate their disposal, most based on extended producer responsibility. Manufacturers take back items collected by retailers and local governments for safe destruction or recovery of materials. Compliance, however, is difficult to assure, and frequently runs against economic incentives. The expense of proper disposal leads to the shipment of large amounts of e-waste to China, India, Pakistan, Nigeria, and other developing countries. Shipment is often through middlemen, and under tariff classifications that make quantities difficult to assess. There, despite the intents of national regulations and hazardous waste laws, most e-waste is treated as general refuse, or crudely processed, often by burning or acid baths, with recovery of only a few materials of value. As dioxins, furans, and heavy metals are released, harm to the environment, workers, and area residents is inevitable.

The faster growth of e-waste generated in the developing than in the developed world presages continued expansion of a pervasive and inexpensive informal processing sector, efficient in its own way, but inherently hazard-ridden.

Source: Science of the Total Environment, Vol. 463-464, Pages 1147-1153, October 2013.

Relationship between Ambient Fine Particles and Ventricular Repolarization Changes and Heart Rate Variability in The Elderly

Multiple epidemiological studies have showed that ambient particulate matter (PM) is associated with increased cardiovascular hospital admission, morbidity and mortality in the exposed population. Among all people, elderly individuals with underlying cardiopulmonary disease are at the greatest risk. Although this association has been well established, the underlying physiological mechanisms are still not fully understood. At present, poor myocardial substrate (current state of the myocardium), myocardial vulnerability and altered cardiac autonomic function (sympathetic activation or/and parasympathetic withdrawal), which are known as the "cardiac death triangle", are believed to be key factors leading to cardiac events. It has been postulated that PM might be a trigger of these factors, especially among vulnerable subjects.

Changes in myocardial substrate can be detected by analyzing the features of electrical activity in myocardium using electrocardiogram (ECG) methods such as repolarization/depolarization parameters. A previous study found that repolarization duration in 56 males with ischemic heart disease increased significantly in response to exposure to $PM_{2.5}$ observed that elevated $PM_{2.5}$ could lead to longer ventricular repolarization but have no immediate impact on ventricular depolarization in samples of nonsmoking adults who lived in communities in central Pennsylvania. However, to date, epidemiologic evidence linking exposure $PM_{2.5}$ to repolarization/depolarization parameters is still limited.

Heart rate variability (HRV) is a measure of cardiac autonomic function. It has been reported to be a predictor of increased risk of population mortality, myocardial infarction and other cardiovascular diseases. Evidence for a positive association between PM and alterations in HRV have been illustrated; however, some studies have also observed negative or zero association

(Continued on page 5)

Relationship between Ambient Fine Particles and Ventricular Repolarization Changes and Heart Rate Variability in The Elderly

(Continued from page 4)

between ambient $PM_{2.5}$ level and HRV. The inconsistency of these findings highlights the need for further exploration to gain a better understanding of the relationship between ambient $PM_{2.5}$ and HRV in exposed populations.

To explore the effects of PM less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$) on heart repolarization/depolarization and HRV. Researchers conducted a panel study for elderly subjects with heart disease in Beijing from 2007 to 2008. $PM_{2.5}$ was measured at a fixed station for 20 h continuously each day while ECG indexes were also recorded repeatedly.

Significant adverse effects of $PM_{2.5}$ on ECG indexes reflecting HRV were observed statistically. However, there were no associations between $PM_{2.5}$ and ECG indexes reflecting heart repolarization/depolarization. Additionally, the effects of $PM_{2.5}$ on subjects with hypertension were larger than on the subjects without hypertension.

The study results showed that elevated $PM_{2.5}$ induced decreased HRV in elderly people with heart disease. It did not affect HR, QRS complex and QTc. The effects of $PM_{2.5}$ on HRV were strengthened by hypertension.

The findings provide additional evidence for the statements that $PM_{2.5}$ can affect cardiac autonomic function in elderly individuals with heart disease and people with hypertension appear to be more susceptive to autonomic dysfunction induced by $PM_{2.5}$. The cardiac autonomic dysfunction is a major cause of cardiac death. In contrast, these findings cannot provide evidence about the influence of $PM_{2.5}$ on myocardial substrate.

Source: Biomedical and Environmental Sciences, Vol. 26, Issue 8, Pages 629-637, August 2013.

Gut Microbiota Limits Heavy Metals Burden Caused by Chronic Oral Exposure

Inorganic cadmium (Cd) and lead (Pb) ions are the most representative toxic non-essential elements which can contaminate food, water or air. In industrial areas, occupationally exposed workers as well as environmentally exposed populations can experience moderate to severe health perturbations due to the chronic ingestion of heavy metals. It has been shown that a significant fraction of inhaled Cd (60%) ends up in the gastrointestinal tract, as a result of mucocilliary clearance and subsequent ingestion. Following oral entry of Cd and Pb, the body burden of these metals has been clearly linked to various sorts of diseases based on various mechanisms, including those involved in oxidative stress and extended toxicity such as genotoxicity and carcinogenesis.

The gut microbiota is likely an important mediator of the bioavailability and toxicity of environmental pollutants including heavy metals. On the one hand, the microbiota by itself may interact with metals inside the gut, either by active uptake or by passive ad- or absorption. On the other hand, intestinal barrier integrity, as the first line to control the entry of ingested toxic metals, also depends on microbial-host interactions that involve epithelial junctions and physical impediments of the mucous layer. Finally, the gut microbiota and its metabolites will also impact on environmental parameters such as pH, oxidative balance, detoxification enzymes, and xenobiotic-metabolizing and transporting host proteins, all of which may highly influence the bioavailability of chemicals in the gut lumen. The microbial status furthermore affects hepatic and renal metabolism.

In a recent study, researchers confirmed the essential role of the intestinal microbiome to limit heavy metal body burden by using germ-free mice following 6-weeks oral exposure. Germ-free animals are, however, physiologically different from conventional specific pathogen free (SPF) individuals and thus may show differences in the *in vivo* handling of xenobiotics. Significant increases of Cd and Pb absorption and dissemination in blood and target organs were measured in germ-free mice when compared with SPF mice. Besides the "barrier" function of the luminal microbiota, this may involve specific host-genes such as metallothioneins, which are differentially expressed in the gastrointestinal tract of each group of mice. Considering genes relevant for divalent metal transporters and oxidative pathways, significant differences in basal gene expression were measured between control and germ-free mice. Moreover, the magnitude of induction of these genes upon stimulation by heavy metals varied greatly depending on the dose and type of metal as well as the microbial status of the animal.

The results clearly show that mice lacking an intestinal microbiota are more susceptible to the accumulation of heavy metals in their blood and target organs, and this in a dose dependent way. Several facts, including the particular physiological and morphological properties of germ-free animals as well as a distinct basal expression and regulation of key genes involved in uptake and transport of metals, can explain this observation. Another intervening factor could be the direct interaction with consecutive immobilization and/or uptake of minerals and metals by the microorganisms from the microbiota, with apparent lowering of the availability of the minerals and metals for the host.

Little is known about the impact of chronic ingestion of heavy metals on the digestive system itself, especially in the small intestine and the colon. The part of the ingested xenobiotics that are efficiently absorbed in healthy subjects is highly variable, depending on factors such as age, fasting and/or meal composition as well as speciation form and salt conjugates. The role of the diets and the composition of essential metals competing with transporters are also critical. Collectively, the main results of the study provided evidence that the gut microbiota controls the distribution of heavy metals throughout the body by several ways, quantitatively and maybe qualitatively. This observation could be of importance for either susceptible individuals exposed to increased levels of heavy metals or for subjects using of broad spectrum antibiotic exposed to this type of pollutants.

Source: Toxicology Letters, Vol. 222, Issue 2, Pages 132-138, October 2013.

DIETARY CADMIUM EXPOSURE AND INCIDENCE OF KIDNEY STONE

Cadmium exposure is associated with increased urinary calcium excretion. Hypercalciuria is recognized as a major risk factor for kidney stone formation. Increased prevalence of kidney stones among those occupationally exposed to cadmium has previously been suggested. Food is the main source of cadmium exposure in the general population with tobacco representing an important additional source among smokers.

A recent study aimed to assess the association between dietary cadmium exposure and kidney stone incidence in two large population based prospective cohorts of men and women (Cohort of Swedish Men (COSM), Swedish Mammography Cohort (SMC)). The analysis was conducted with and without stratification by smoking status (ever/never). In both cohorts researchers have previously observed an increased risk of fracture in relation to dietary cadmium exposure as well as increased risks of breast, endometrial and prostate cancers.

During an average of 13 years of follow-up researchers ascertained 707 incident cases of kidney stones among men (in 421,611 person-years) and 290 cases among women (in 403,575 person-years). The mean estimated dietary cadmium exposure in the cohort of men was 19 µg/day and 13 µg/day among women. Both men and women in the highest tertile of dietary cadmium exposure were more likely to be never smokers, to have a lower dietary intake of calcium and higher intake of iron, magnesium, potassium, vitamin B6 and vitamin C.

No association was observed between dietary cadmium exposure and kidney stone incidence in either men or women. Additional adjustment for hypertension, tea and coffee consumption and use of vitamin C supplements did not change the results. In stratified analyses, it was observed that among men in the highest tertile of exposure multivariable-adjusted hazard ratio (HR) for never smokers and HR 1.06 for ever smokers. The corresponding results among women were HR 0.72 for never smokers and HR 1.30 for ever smokers.

This study is the first to prospectively assess the risk of kidney stones associated with cadmium exposure in a non-occupationally exposed population. In this large population-based cohort no increased risk of kidney stones in relation to dietary cadmium exposure in men or women, was observed.

One possible explanation for the lack of an association is simply that the exposure levels were not high enough to have sufficient effect on urinary composition. There are, however, several limitations to consider which may also account for the null findings. The dietary cadmium exposure estimates are based on self-report, inevitably leading to some degree of measurement error and subsequent exposure misclassification, any association would therefore likely be biased towards the null. The range of exposures in this study population is relatively narrow and may, therefore, not provide sufficient differentiation between high and low exposures for an effect to be identified. Owing to insufficient, reliable data on the oxalate content of various foods researchers were not able to adjust for dietary oxalate, which may represent a potential source of confounding. Kidney stones are highly recurrent and by excluding those with a previous diagnosis of stones researchers may be excluding those who are most susceptible as well as reducing the power of the study. This study had the power (>80%) to detect increased HR of 1.3 in men and 1.4 in women.

The results do not support a strong association between dietary cadmium and kidney stone risk at the exposure levels seen in the general population. This may suggest that any effect of cadmium exposure on kidney stone risk is only relevant at occupational exposure levels.

Source: Environment International, Vol. 59, Pages 148-151, September 2013.

Particulate Matter and Cardiovascular Disease: Microvascular Changes

Particulate matter (PM) has been consistently associated with cardiovascular disease development and progression and is believed to contribute to development either indirectly through the autonomic nervous system or inflammatory responses, or directly via entry into systemic circulation and subsequent damage to blood vessels. However, it is unclear whether changes in the microcirculation – the small veins (venules) and arteries (arterioles) that compose the majority of the circulatory system – might also contribute.

A new study explores the impact of PM on small blood vessels by studying the retina. The objective was to study the effect of short-term air pollution exposures and microvascular changes in 84 healthy adults (22–63 years of age) using a repeated-measures design.

The key finding of this repeated measurements study in a panel of healthy adults is that an acute narrowing of retinal arterial vessels, a marker for arteriolar damage, was associated with particulate matter air pollution. Based on the analysis, the estimated effect on central retinal arteriolar equivalents (CRAE) associated with a 10-µg/m^3 increase in average PM_{10} during the 24 hr before the retinal examination was equivalent to the change in CRAE associated with a 1.5-year increase in age. This microvascular response to air pollution might contribute to the development or progression of cardiovascular diseases and complications, as seen in epidemiological studies. These findings add new evidence to the cardiovascular health effects of short-term exposure to air pollution in healthy persons and suggest a mechanistic pathway through which air pollution can act as a trigger of cardiovascular events at

(Continued on page 8)

The Relationship between Cadmium in Kidney and Cadmium in Urine and Blood in an Environmentally Exposed Population

Cadmium (Cd) is a serious environmental contaminant which accumulates in the kidney and can potentially affect human health at relatively low concentrations. It is toxic to the kidney, especially the proximal tubular cells, but can also cause bone demineralization. Soil and water are contaminated through airborne deposition, and soil concentrations are further increased by the use of fertilizers or sewage sludge on agricultural farm fields. Cadmium from the soil is accumulated in the crops, and diet is the main source of Cd exposure in the general population. For smokers, tobacco consumption is also an important route of exposure. Gastrointestinal Cd absorption in humans from dietary exposure is 3–5%, while Cd absorption from inhalation is 10–50%. When absorbed, Cd binds to proteins in the blood and is transported to the liver where it is bound to metallothionein. The Cd-metallothionein complex is filtered in the renal glomerulus, reabsorbed in the tubular cells, and accumulated in the kidney with a biological half-time ranging from10 to 30 years. Approximately 50% of the total Cd body burden is accumulated in the kidney. Absorbed Cd is excreted in urine and feces.

Urinary Cd (U-Cd) and blood Cd (B-Cd) are widely used as biomarkers to assess exposure or body burden of Cd in the general population. U-Cd is considered to reflect the kidney burden and body burden of Cd, while B-Cd is considered to be the most valid marker of recent exposure. Close relationships between the concentrations of Cd in the kidney, urine, and blood are anticipated at steady state. If a linear relationship between kidney Cd (K-Cd) and U-Cd is assumed, a U-Cd concentration of 2.5 µg/g creatinine corresponds to a concentration of about 50 µg/g in the kidney, giving a U-Cd/K-Cd ratio of about 1:20.

Until now, information about the relationship between K-Cd, U-Cd, and B-Cd has mainly been collected by *in vivo* measurements using X-ray fluorescence (XRF) or neutron activation, or by autopsy studies. However, most *in vivo* studies have been performed in occupationally exposed workers, and the techniques are not sensitive enough for investigating the relationship between K-Cd and biomarkers of Cd at the low-level exposure occurring in the general population. Autopsy cases may not be representative of the healthy part of the population, and Cd levels in urine and blood may change post mortem. Moreover, data concerning diet and smoking habits may be uncertain in autopsy studies.

The present study is the first to provide empirical data on Cd levels in the kidney cortex, urine, and blood of healthy individuals from the general population with low-level Cd exposure, using analytical methods which can precisely quantify kidney Cd at very low concentrations. The aims for this study were to determine the relationship between Cd in kidney and Cd in urine, and thereby estimate the elimination half-time of Cd in kidney, and to investigate factors affecting U-Cd excretion and the relationships between Cd in kidney, urine, and blood.

In the study kidney cortex biopsies, urine, and blood samples were collected from 109 living kidney donors. Cd concentrations were determined and the relationships between K-Cd, U-Cd, and B-Cd were investigated in regression models. The half-time of K-Cd was estimated from the elimination constant.

There was a strong association between K-Cd and U-Cd adjusted for creatinine, while the association with B-Cd was weaker. The relationship between K-Cd and U-Cd was non-linear, with slower elimination of Cd at high K-Cd. Estimates of the K-Cd half-time varied between 18 and 44 years. A K-Cd of 25 µg/g corresponds to U-Cd of 0.42 µg/g creatinine in overnight urine (U-Cd/K-Cd ratio: about 1:60). Multivariate models showed Cd in blood and urinary albumin as determinants for U-Cd excretion.

In healthy individuals with low-level Cd exposure, there was a strong correlation between Cd in kidney and urine, especially after adjustment for creatinine. Urinary Cd was also affected by Cd in blood and urinary albumin. Previous estimates of the U-Cd/K-Cd ratio may underestimate K-Cd at low U-Cd.

Source: Toxicology and Applied Pharmacology, Vol. 268, Issue 3, Pages 286-293, May 2013.

BPA AS A MAMMARY CARCINOGEN

Perinatal exposure of rodents to low doses of bisphenol A (BPA) has been associated with altered mammary gland development and increased propensity for mammary tumors later in life.

Cumulative exposure to ovarian steroids during a woman's lifetime represents the most well-defined risk factor for the development of breast cancer. Epidemiological studies have suggested that increased estrogen levels in the fetal environment are associated with an increased risk of breast cancer during adult life.

The synthetic estrogen, bisphenol A (BPA), is currently one of the highest volume chemicals produced worldwide. BPA is used in the production of polycarbonate plastics, epoxy resins, dental sealants and composites, and thermal receipt paper. Incomplete polymerization of BPA leads to leaching of the chemical and subsequent human exposure, as evidenced by the detection of BPA in human urine, serum, maternal and fetal plasma, amniotic fluid, placenta, and adipose tissue. The U.S. Environmental Protection Agency (EPA) has calculated an oral reference dose for BPA of 50 µg BPA/kg body weight (BW)/day based on a lowest observed adverse effect level of 50 mg/kg BW/day. A review of more than two dozen biomonitoring studies that used analytical chemistry methods to measure BPA in healthy adults reported the detection of mean unconjugated BPA levels in the range of 1 ng/mL in blood. The distinction between unconjugated and conjugated BPA is especially important in blood because the unconjugated form is considered the active form and has estrogenic activity.

A recent study has aimed to determine whether BPA exposure of dams during gestation only or throughout lactation affects the incidence of mammary gland neoplasia in female offspring.

In the study, pregnant Sprague-Dawley rats were treated with varying amounts of BPA from gestational day (GD) 9 to birth and from GD9 to postnatal day (PND) 21. Mammary glands from BPA-exposed offspring were examined at four time points for preneoplastic and neoplastic lesions. To assess circulating BPA levels, researchers exposed pregnant rats to vehicle or 250 µg BPA/kg BW/day during gestation only or during gestation/lactation and analyzed sera from dams, fetuses, and nursing pups for total and unconjugated BPA.

Total and unconjugated BPA were detected in sera from 100% of dams and fetuses and 33% of pups exposed to 250 µg BPA/kg BW/day. Unconjugated BPA levels in exposed dams and fetuses (gestational) and in exposed dams and pups (gestational/lactational) were within levels found in humans. Preneoplastic lesions developed in BPA-exposed female offspring across all doses as early as PND50. Unexpectedly, mammary gland adenocarcinomas developed in BPA-exposed offspring by PND90.

The study findings suggest that developmental exposure to environmentally relevant levels of BPA during gestation and lactation induces mammary gland neoplasms in the absence of any additional carcinogenic treatment. Thus, BPA may act as a complete mammary gland carcinogen.

Source: Environmental Health Perspectives, Vol. 121, No. 9, Pages 1040-1046, September 2013.

Particulate Matter and Cardiovascular Disease: Microvascular Changes

(Continued from page 7)

least in part through effects on the microvasculature.

The findings may not be generalizable to the adult population as a whole. Subsequent research should therefore aim at confirming the observations in larger and more diverse populations. In addition, it would be informative to study populations that may be more susceptible to microvascular effects of air pollutants due to underlying pathologies that promote chronic inflammation. Persons with diabetes, for example, have been shown to be vulnerable to the effects of air pollution.

Also some exposure misclassification cannot be excluded. Measurements from a monitoring station close to the study site were used to estimate exposures. However, participants may have been exposed to different black carbon (BC) concentrations at their places of residence or while commuting. The amount of time spent driving in traffic, as determined from the questionnaire, was negatively associated with arteriolar diameter, although the association was not statistically significant. Ideally, personal measurements of BC should be used in future studies.

Source: Environmental Health Perspectives, Vol. 121, No. 9, Pages 1011-1016, September 2013.

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

Correspondence should be addressed to:

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

For back issues of our newsletter, please visit:

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