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Chalabhorn 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".

TRAINING COURSE ON ENVIRONMENTAL & HEALTH RISK ASSESSMENT AND RISK MANAGEMENT OF TOXIC CHEMICALS 20 - 25 NOVEMBER 2000



As part of the capacity building program in Environmental Toxicology, the Chulabhorn Research Institute in collaboration with the International Programme on Chemical Safety (IPCS) and the World Health Organization (WHO) Geneva organized a six day training course focusing on health risk assessment and risk management of toxic chemicals at the Institute's Conference Center in Bangkok.

The course was supported by the United Nations Development Programme and attended by participants from 14 countries.

The course coordinator was Dr. Mathuros Ruchirawat, Vice President of Chulabhorn Research Institute, and the international faculty was composed of experts from Europe and North America.

The opening lecture on "The process of human health risk assessment" was given by Dr. Maged Younes of the

World Health Organization's International Programme on Chemical Safety. Throughout the course, the lectures explaining the theoretical concepts and principles of hazard identification, doseresponse assessment, environmental risk assessment and risk management and reduction were supported by practical examples which included dietary risk assessment cases, air pollution, cancer risk assessment cases, dioxins, and the setting and enforcement of environmental health standards.

Biological effects of estrogenic chemicals

A 36-member panel of experts appointed by the U.S. Environmental Protection Agency (EPA) has found that estrogenic chemicals can cause biological effects at levels below those normally found safe, but the implications for human health are unclear.

The work that triggered this inquiry was conducted by a group of researchers at the University of Missouri, Colombia. Published in 1997, the team's two studies found that at levels below the normal testing threshold, the potent chemical diethylstilbestrol (DES) had peculiar effects on the male offspring of pregnant mice. At some very low doses, it enlarged a fetal mouse's prostate, but levels above this had the opposite effect. If low doses of other chemicals produced effects with this same humped curve, then tests conducted at higher doses might

be missing biological effects, the researchers suggested.

The second of the two studies was more controversial. It found that the plastics ingredient bisphenol A enlarged the prostate in mouse fetuses at the extremely low levels to which humans are typically exposed.

(Continued on page 8)

Link between tooth decay and childhood lead exposure

Epidemiological studies suggest a link between lead exposure and dental caries.

Using a retrospective cohort design, a team of American researchers have conducted a new study to establish whether children with a higher lead exposure in infancy had more dental caries at school age than children with a lower lead exposure.

Despite declines in recent years, the prevalence of elevated blood lead levels remains a concern in the United States. The second part of the Third National Health and Nutrition Examination Survey (NHANES III). conducted from 1991 estimated that 4.4% of children 1-5 years of age have blood lead levels > $0.48 \ \mu mol/L \ (\geq 10 \ \mu g/dL)$. approximately 890,000 children in the United States have blood lead levels exceeding the threshold defined by the Centers for Disease Control and Prevention (CDC). Many of these children are urban, minority children. This same population of children also has the highest rates of dental caries in the United States. This disproportional burden of caries and lead exposure in urban, minority populations suggests a potential association.

Results of animal-model studies report an association between lead

exposure and caries. In a recent study, pregnant rats were randomized to receive either lead-contaminated water or lead-free water: the exposure was continued until the rat pups were weaned. The mean smooth surface and sulcal surface caries scores were higher among the lead-exposed rat pups than the nonexposed rat pups.

Human epidemiologic studies also report an association between lead exposure and caries. Studies report a positive association between lead level in teeth and caries. Gil et al [Gil F, Facio A, Villanueva E, Pérez ML, Tojo R, Gil A. The association of tooth lead content with dental health factors. Sci Total Environ 192: 183-191 (1966)]. reported that a high tooth lead level is significantly associated with levels of plaque and Lactobaccilli (odds ratio 2.79 and 2.52, respectively), both known risk factors for caries. However, this study was cross-sectional, and thus could not establish the sequence of exposure and disease.

The new study examined children attending second and fifth grades in the public schools in the city of Rochester, New York for dental

caries through a program conducted by the Eastman Dental Center. subjects in the study were identified from the 1995 - 1996 and 1996 -1997 academic school years. of schoolchildren sample were examined for caries through a dental screening program which assessed the number of decayed, missing, or filled surfaces on permanent teeth (DMFS). and the number of decayed or filled surfaces on deciduous teeth (dfs). The number of surfaces at risk (SAR) was also recorded.

Lead exposure was defined as the mean of all blood lead levels collected between 18 and 37 months of age by fingerstick [provided the blood lead level was < 0.48 µmol/L (< 10 µg/dL)] or venipuncture. A total of 248 children (197 second graders and 51 fifth graders) were examined for caries and had a record of blood lead levels to define lead exposure. The mean dfs was 3.4 (range 0-29); the mean DMFS was 0.5 (range 0-8). Logistic regression was used to examine the association between the proportion of children with DMFS \geq 1,

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New Estimates of Possible Carbon "Sinks" and their Effects on Climate Change

A special report on Land Use, Land-Use Change, and Forestry has been brought out by the United Nations-sponsored Intergovernmental Panel on Climate Change (IPCC).

he 460-page report runs through a dozen types of land uses, such as regenerating forests or converting cropland to grassland, spelling out just how much carbon might be socked away in each. The answer is, a lot. The report, informally known as the "sinks" report, suggests that, at first glance, the 41 developed countries could meet their Kyoto goals of cutting 200 megatons of carbon emissions per year entirely through land use changes rather than by reducing emissions from fossil fuels.

However, the report cautions that there are certain problems inherent in following this route, one being the difficulty of measuring precisely how much carbon can be stored in this way.

The report also discusses the feasibility of allowing developed countries to offset emissions by planting, protecting, or managing forests in developing countries. Such mechanisms can have "benefits", but there are risks, for instance, that displaced people will deforest lands elsewhere.

Moreover, researchers at the Hadley Centre for Climate Prediction and Research of the UK Met Office have warned that the overall impact of forestation on climate will also depend on other effects associated with the creation of new forests. In particular, the albedo of a forested landscape is generally lower than that of cultivated and, especially in snow covered areas, and decreasing albedo exerts a positive radiative forcing on climate. Studies carried out at the centre simulate the radiative associated changes in surface albedo as a result of forestation in temperate and boreal forest areas, and translate these forcings into equivalent changes in local carbon stock for comparison estimated carbon sequestration potentials. results suggest that in many boreal forest areas, the positive forcing induced by decreases in albedo can offset the negative forcing that is expected from Some carbon sequestration. high-latitude forestation activities may therefore serve to increase climate change, rather than reduce it as intended.

Source: Science, Vol. 288, No. 5468, May 2000 and Nature, Vol. 408, No. 6809, November 2000.

HOW INCREASING CO₂ EMISSIONS AFFECTS PLANTS

One of the unforeseen consequences of industrialisation has been the steady increase in the amount of carbon dioxide in the atmosphere. Plants have responded to this increase by having fewer stomata, the paired cells found mainly on the surface of leaves, that control the uptake and release of gases. Thus, over the past 200 years, the number of plant stomata has decreased in response to increasing CO₂ levels.

However, a new study has shown that the small mustard plant *Arabidopsis thaliana* has a gene that prevents changes in the number of stomata in response to further atmospheric CO_2 enrichment. This gene has been named high carbon dioxide (HIC). Laboratory experiments show that even doubling the current CO_2 levels in the atmosphere has no effect on the stomatal index in the leaves of at least one strain of *Arabidopsis*.

The experiments also show that plants with a loss of function mutation in the HIC gene exhibit a large increase in this index when grown in higher concentrations of CO_2 .

An important implication of these experiments is that the response of the stomatal index to CO_2 in many plant species is now close to saturation. It seems, therefore, that plants may continue to make enough stomata, regardless of how much more CO_2 is released into the atmosphere as a result of anthropogenic emissions.

Source: Nature, Vol. 408, No. 6813, December 2000.

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CONCERNS OVER DECLINES IN AMPHIBIAN POPULATIONS

Biologists from the U.S. Geological Survey are attempting to determine why amphibians are disappearing in the United States and around the globe. These die-offs are of great concern because amphibians are good barometers of significant environmental changes that may go initially undetected by humans. This is because amphibians, unlike people, breathe at least partly through their skin, making them much more sensitive to environmental insults.

Over the last twenty years, have accumulated of reports frog severe reductions in populations and unusual deformities in amphibians. There has been evidence that ultraviolet-B radiation, an iridiovirus, a chytrid fungus, and fluke parasites could each be responsible for damage to amphibian populations. One recent study has shown that a species of frog disappeared when lakes in the California Sierras were stocked with non-native trout. Another study showed that tadpoles carry much higher loads of parasites in the presence of predatory fish.

Researchers from the US Geological Survey and the US Department of Agriculture have found that pesticides used by Californian farmers can disrupt an enzyme that regulates the nervous system of frogs and may be eroding once-healthy frog populations in the pristine mountain areas of California.

However, other research shows that rural areas and farms may be friendlier to frogs and toads than urban areas. Research on populations of these amphibians in two midwestern states shows that frog and toad abundance and species richness were

low in urban areas but near normal in agricultural areas. Stopping declines in amphibian populations is now a national priority in the United States, and scientists with the U.S. Geological Survey are examining how various landscapes relate to frog and toad populations. Their research may benefit natural research managers who have been given the task of promoting healthy and diverse amphibian populations.

Source: Nature, Vol. 408, No. 6814,

EFFECTS OF CADMIUM TOXICITY ON WILDLIFE SPECIES

Cadmium is known to be both extremely toxic and ubiquitous in natural environments. It occurs in almost all soils, surface waters and plants, and it is readily mobilized by industrial activities such as mining. As a result, cadmium is a potential health threat to wildlife species.

According to a recent study made of cadmium toxicity among wildlife in the Colorado Rocky Mountains, the white-tailed ptarmigan, a member of the grouse family, may be the first of several wildlife species to feel the effects of cadmium toxicity.

While the toxicity of cadmium is already established through short-term lethal dose experiments, the present study is the first to show the subtler effects of chronic exposure to the metal in a plant-based diet.

The study found that willows, a plant eaten by birds particularly in winter when other foods are scaree, concentrated cadmium since the trees acted as biological pumps increasing concentrations of cadmium by two orders of magnitude, which was then passed along to the ptarmigan population. Many North American herbivores also eat large quantities of willow. These include wapiti (*Cerous*

elaphus), moose (Alces alces), mule deer (Odocoileus hemionus) beaver (Castor canadensis) and snowshoe hare (Lepus americanies).

The study postulates, therefore, that chronic cadmium poisoning may be more widespread and that herbivores, particularly those that eat willow, should receive priority in future studies of cadmium toxicity in the Rocky Mountains and elsewhere around the world where natural cadmium levels are high.

Source: Nature, Vol. 406, July 2000.

Studies on effective repellents against insect vectors

A report by researchers from Lund University, Sweden, suggests that garlic may be an effective insect repellent.

Lyme borreliosis is the most common vector-borne disease in Sweden, and as many as 10000 individuals are thought to be affected each year. Recent studies have suggested that individual variability in vector attachment may be linked to different body odors. Other studies suggested that diethyltoluamide is the best repellent against insect vectors and permethrin against ticks, in particular. However, insect repellents may have adverse effects on humans and animals.

Because military personnel are at particularly high risk for tick bites and tick-borne diseases, a prospective, randomized, double-blind intervention trial of garlic (*Allium sativum*) was conducted among Swedish marines.

Of 100 individuals in Swedish military service in 1998, 50 consumed 1200 mg/d Allium sativum in capsule form and 50 consumed placebo for 8 weeks, followed by a washout period of 2 weeks, and then a crossover to placebo or Allium sativum consumption for another 10 weeks. All participants wore the same type of uniforms, consumed approximately the same diet, participated in similar activities, and spent equal amounts of time in tickendemic areas. Tick bites were recorded in a diary after daily self-inspection of the skin. Written informed consent was obtained from all participants.

In the intention-to-treat analysis, 66 (66%) of 100 participants recorded tick bites vs 55 (69%) of 80 participants in the per-protocol analysis. A total of 286 tick bites were recorded by the participants. On average, the participants recorded 0.2 tick bites per week during military service, compared with 0.03 tick bites

during leave. There was significant reduction in tick bites when consuming garlic compared with placebo in perprotocol analysis (Wilcoxon test, P=.04). A greater number of the participants were bitten by ticks during placebo consumption (normal approximation of binomial assumption, relative risk by intention to treat, 0.79 [95% confidence interval {CI}, 0.65-0.96]; relative risk per protocol, 0.70 [95% CI, 0.54-0.90])

Swedish marine conscripts are at high risk of tick bites during military service. Preventive measures, including vaccinations against tick-transmitted diseases, should be considered. However, the results suggest that garlic may be considered as a tick repellent for individuals and populations at high risk for tick bite, rather than other agents that might have more adverse effects.

Source: JAMA, Vol. 284, No. 7, Aug 2000.

Health Risks from Exposure to Lead in Candles

Although the candle industry in the United States agreed with the Consumer Product Safety Commission (CPSC) in 1974 to voluntarily stop making candles with wicks containing а survey conducted physicians in the Washington based Public Citizen's Health Research Group in February 2000, found that lead from burning candles was still an appreciable health risk particularly in young children. Blood lead levels as low as $0.43 \mu mol/L$ (10 $\mu g/dL$) in children can result in developmental and behavioural problems. However. many physicians are unaware that household candlewicks may include lead as a stiffener and thus pose a health risk in the home. In the survey, 285 types of candle were tested of which 86 (30%) contained metallic wicks and 9 of these (10%) contained lead, for an overall 3% leadwick prevalence.

Total lead content per wick ranged from approximately 24000 μg to 118000 μg (33%-85% lead by weight). When the rate equations are solved, these 9 candles are calculated to result in average 24-hour air lead concentrations ranging from 15.2 to 54.0 $\mu g/m^3$ which is 10.1 to 36.0 times the US Environmental Protection Agency standard of 1.5 $\mu g/m^3$

Because each 1- μ g/m³ increase in ambient air lead concentration in this range can increase a child's blood lead level by 0.22 μ mol/L (5 μ g/dL), chronic exposure to only 1.5 μ g/m³ could raise a child's blood lead level from 0.13 μ mol/L (2.7 μ g/dL) (the median for US children younger than 5 years) to 0.48 μ mol/L (10 μ g/dL), which is the upper limit recommended by the Centers for Disease Control and Prevention. Thus, all 9 candles that were tested have at least 10 times enough lead to achieve this increase.

It was estimated that the candle containing the least lead would produce an average air lead concentration of $30.6~\mu g/m^3$ during 3 hours of burning; a 6-year-old, inhaling $0.66~m^3$ of this air per hour during average daily activity would exceed the CPSC's recommended daily lead limit for children (15 μ g) in 45 minutes.

According to the National Candle Association, \$2.3 billion worth of candles were projected to be sold in 1999, a figure that is increasing by 10% to 15% annually. Physicians should therefore warn patients that burning candles with lead-containing wicks may cause lead poisoning and that there is no reliable method to distinguish metallic candlewicks containing lead from those that do not.

Source: JAMA, Vol. 284, No. 2, July 2000.

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HEALTH EFFECTS OF LONG-TERM ARSENIC EXPOSURE

A study carried out in Taiwan has found that the prevalence of diabetes mellitus was twice as high in villages on the southwestern coast where individuals are exposed to high levels of inorganic arsenic from artesian well water than in Taipei City and the Taiwan area in general.

In the study, researchers examined the association between long-term arsenic exposure and the incidence of diabetes mellitus using a biannual 75 g oral glucose tolerance test to follow a cohort of subjects who were free from diabetes mellitus for a period of 4 years.

The study area included three villages located on the southwestern coast of Taiwan where arseniasis was hyperendemic. Because of the high salinity in the water of shallow wells, residents in these villages used artesian well water for drinking and The median arsenic concooking. centration of artesian well water ranged from 0.70 to 0.93 mg/L. A tap water supply system using surface water was implemented in the 1960s, but few people had access to this water until the late 1970s. standard for arsenic in drinking water set by the U.S. Environmental Protection Agency is 0.05 mg/L.

During a follow-up period of 1499.5 person-years, 41 of 446 subjects developed diabetes mellitus in the arseniasis-hyperendemic villages. The calculated incidence rate was 27.4/1, 000 person-years. The follow-up rate was 70.6%

The results of this study thus support the assocation between a long-term arsenic exposure and diabetes mellitus and the health hazards of arsenic in groundwater.

Source: Environmental Health Perspectives: Vol 1081, No. 9, Sep 2000.

Side-effects of arsenic trioxide treatment

Research carried out in Japan has demonstrated the effectiveness of arsenic trioxide in patients with acute promyelocytic leukemia. However it has also been reported that cardiac toxicities have occurred in some patients.

After one of their patients developed a prolonged QT interval during arsenic trioxide treatment, the researchers began a prospective study to assess the cardiac effects of this agent. The study included eight patients with relapsed acute promyelocytic leukemia who received 0.15 mg/kg of arsenic trioxide per day for a maximum of 60 days.

Ambulatory electrocardiography was used for continuous monitoring of the patients. Participants also underwent 12-lead electrocardiography at least once a week.

Arsenic trioxide provided substantial benefits, with five patients achieving complete remission, the resarchers report. Four of these patients underwent a second course of therapy.

At baseline, four patients had QT intervals greater than 440 ms. All eight patients had prolonged QT intervals during the first round of arsenic trioxide therapy as did three of the four patients who received a second course.

Other cardiac toxicities included ventricular premature contractions, which were detected during 8 of 12 courses of treatment, and nonsustained monomorphic ventricular tachycardia, which developed in four patients.

Because of its remarkable effectivenes, arsenic trioxide will continue to be widely used for or refractory relapsed acute promyelocytic leukemia. Since such patients have been heavily treated chemotherapeutic agents. including anthracycline and all-trans retinoic acid, cardiac damage is likely to be universal before arsenic trioxide therapy begins. Arsenic trioxide thus might induce arrhythmia. In the Japanese study, although the number of patients was small, ventricular arrhythmias were observed, often through careful monitoring. Therefore, patients taking arsenic trioxide should have frequent electrocardiographic monitoring and, in particular, should be monitored carefully for serious arrhythmias when QT intervals are prolonged. Prophylactic antiarrhythmic drugs that do not prolong the QT interval should be used because previous reports showed an association between fatal ventricular tachycardias and prolonged QT intervals in arsenic intoxication. Electrolyte imbalances, such hypokalemic and hypomagnesemia, also frequently induce arrhythmias and prolonged QT intervals. Anv electrolyte imbalances that develop sould be corrected immediately.

It is recommended that clinicians should carefully monitor cardiac toxicities in patients with acute promyelocytic leukemia during treatment with this promising drug.

Source: Annals of Internal Medicine, Vol. 133, No. 11, December 2000

Link between tooth decay and childhood lead exposure

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and the proportion with dfs \geq 1, and lead exposure [< 0.48 μ mol/L vs. \geq 0.48 μ mol/L (< 10 μ g/dL vs. \geq 10 μ g.dL)] while controlling for SAR, age at examination, and grade in school. For DMFS, the adjusted odds ratio was 0.95 [95% confidence interval (CI), 0.43-2.09; p = 0.89); for dfs, the odds ratio was 1.77 (95% CI, 0.97-3.24; p = 0.07). This study did not

demonstrate that lead exposure > 10 µg/dL as an infant was a strong predictor of caries among school-age children. However, the results should be interpreted cautiously because of limitations in the assessment of lead exposure and limited statistical power.

Source: Environmental Health Perspectives, Vol. 108, No. 11, November 2000.

FROM EXPOSURE TO HEAVY METALS IN DRINKING WATER

Drinking water is a well-recognized pathway of exposure to metals such as arsenic, cadmium and lead, which have been associated with various forms of cancer and cardiovascular disease in humans. To improve understanding of the temporal dimensions of exposure to these metals in drinking water, as part of a longitudinal study, 381 samples of tap water were obtained and self-reported rates of drinking water consumption were collected from 73 members of a stratified random sample in Maryland, U.S.

Data were collected approximately 2-month intervals from September 1995 through September 1996. Concentrations of As (range< 0.2-13.8 µg/L) and Pb (< $0.1-13.4 \mu g/L$) were within the ranges reported for the United States, as were the rates of drinking water consumption (median < 0.1-4.1 L/day). Cd was present at a detectable level in only 8.1% of the water samples. Mean log-transformed concentrations and exposures for As and Pb varied significantly among sampling cycles and among respondents, as did rates of drinking water consumption, according to a generalized linear model that accounted for potential correlation among repeated measures from the same respondent. The intraclass correlation coefficient of reliability was used to attribute the total variance observed for each exposure metric to between-person and withinperson variability. Between-person variability was estimated to account for 67, 81, and 55% of the total variance in drinking water consumption, As exposure (micrograms per day), and Pb exposure (micrograms per day), respectively.

The temporal dimension of exposure to these elements in drinking water is of interest because their toxicologic effects, such as cancer, kidney disease,

and impaired cognitive function, are considered to result from chronic exposure rather than short-term exposure. Improved understanding of chronic exposure to As, Cd, and Pb in drinking water can be expected to increase the precision and accuracy of health risk assessments performed for these metals.

The objectives were to measure short-term and prolonged (1-year) average exposure to As, Cd, and Pb from ingestion of drinking water; to characterize the temporal variability of short-term exposure measures; and to evaluate the reliability of short-term measures of exposure to assess longterm average exposure. Exposure to was assessed from metals repeated measurements the analytes in drinking water samples collected from each member of the study population. These data are one component of a longitudinal investigation of chemicals in multiple media: The National Human Exposure Assessment Survey in Marvland (NHEXAS-MD).

The results of this investigation suggest that exposure to As and Pb in drinking water varies significantly and perhaps substantively over time. However, the limited scope of the study requires that the findings be treated with caution. For example, it is difficult to generalize these findings to the sampling domain (i.e., metropolitan Baltimore and Annapolis, MD) because of limited representation of various

subpopulations whose exposure could vary systematically from one and other. Similarly, the degree to which these findings can be generalized to other regions of the United States and other nations is not clear. Further, the longitudinal scope of the present study offers little information on the temporal aspects of exposure over periods of time shorter than 6-8 weeks and longer than 1 year.

Nevertheless. if concentrations of As and Pb in drinking water vary systematically by season for a population, then timing of data collection should be considered in exposure and risk Results of the assessments NHEXAS-MD study suggest that the central tendency of As and Pb exposure via drinking water for a population may vary over time. However, the duration of the study was not sufficient to identify seasonal patterns. The value of additional information on systematic temporal differences in drinking water exposure to As and Pb should be evaluated in comparison to the cost of obtaining that information and the uncertainty about other inputs to the risk assessment procedure.

Source: Environmental Health Perspectives, Vol. 108, No. 8, August 2000.

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ANNOUNCEMENT







Inter University Post-Graduate Education Program on Environmental Toxicology and Management (M.Sc. and Ph.D.) International Program

- · Applications for the academic year 2002 are now being accepted
- Fellowships are available for foreign/Thai students (full scholarship or partial scholarship)
- · All interested applicants should visit the program's web site at

http://203.151.96.5:250/et_postgrad.htm

for detailed information and application form

Please note that the final date for submission of application forms is 30 August 2001.

developing rats or their offspring. But curiously, when the panel picked apart the protocols and data, a summary statement says it found that both University of Missouri studies and the negative ones were credible and sound.

The discrepancies may be attributable to lab animals' exquisite sensitivity to estrogenic chemicals. As scientists noted, many factors—such as whether animals are fed or injected with chemicals, as well as their diet—can influence hormone levels.

Not all panelists, however, were satisfied that the discrepancies have been fully explained, leading some EPA officials to suggest that the agency may postpone modifying its congressionally mandated screening program which is set to begin testing commercial products containing bisphenol A and DES in 2003.

Source: Science Vol. 290, No. 5992, Oct 2000

Calendar of Events

Date	Course	City/Country
Aug. 30-31	Meeting of the Network for Scientific Cooperation in Biotechnology	Bangkok/Thailand
Oct. 8-16 (tentative date)	Training Workshop on Environmental & Health Risk Assessment and Risk Management of Toxic Chemicals	Bangkok/Thailand
Oct. 17-19 (tentative date)	Training Workshop on Environmental & Health Risk Assessment and Risk Management of Toxic Chemicals	Jakarta/Indonesia
Nov. 12-24	Training Course on Detection of Environmental Pollutants and Monitoring of Health Effects	Hanoi/Vietnam

Biological effects of estrogenic chemicals

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However attempts to replicate the University of Missouri study with the same mouse strain, CFI, failed to find any bisphenol A or DES effects.

The negative data included two major new studies by Japanese and industry-supported U.S. groups that found no effects of bisphenol A on

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