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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".

CRI Training Course on Detection of Environmental Pollutants and Monitoring of Health Effects

26-30 October 1998

Her Royal Highness Princess Chulabhorn, President of Chulabhorn Research Institute (CRI), opened the training course on Detection of Environmental Pollutants and Monitoring of Health Effects on 26 October 1998. This course is part of the Chulabhorn Research Institute's regional program in capacity building in environmental toxicology, technology and management to promote sustainable development in countries in the Asia and Pacific region.

The training comprised a one week course of lectures and laboratory exercises on chemical, physical and biological methods recently developed to detect and monitor important changes in the health of populations exposed to environmental pollutants.

Participants in the course came from Cambodia, Indonesia, Lao People's Democratic Republic, Malaysia, Mongolia, Myanmar, Philippines and Vietnam, as well as from Thailand.

The course was taught by a team of experts from the German Cancer Research Center, the University of Kaiserslautern, Germany, and by CRI faculty members.

Funding for the course was supported by the United Nations Development Programme and the Department of Technical and Economic Cooperation of the Royal Thai Government.

In her opening address, Her Royal Highness Princess Chulabhorn stated that the subject of this training course was of the greatest importance to sustainable development in the Asia Pacific region and to the enhancement of quality of life through protection of the physical environment and human health.

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Health Risks from Mercury Exposure

There is general agreement that exposure to mercury, particularly to the organic form methylmercury, causes damaging health effects. Humans are exposed to methylmercury primarily through eating fish that have accumulated amounts of the compound in their muscle tissue. Global industrial development has given rise to increased release of mercury due to higher demands for electricity. Mercury tends to spread widely and easily because it can remain suspended in the atmosphere for up to a year. The organic forms of mercury such as methylmercury are the more dangerous to humans because these forms tend to bioaccumulate, as opposed to the inorganic forms, which tend to be less well absorbed and more easily discarded by the body.

There have been two major studies on the health effects of exposure to methylmercury. A study conducted in Iraq in the 1970s collected data on mother-child pairs and found that the presence of mercury in the mother's hair at levels over 10 parts per million appears to be related to developmental and/or neurological abnormalities in her offspring. More recently, a follow-up study was designed and conducted in the Seychelle Islands. The purpose of this follow-up study was to test the Iraqi findings on a population that was both much larger than in the Iraqi study and that received its mercury through the most common route of consumption of fish. (Subjects in the Iraqi study had eaten contaminated grain.)

The findings of the Seychelles study, published in 1995, found no evidence that prenatal methylmercury exposure is linked to childhood defects. However, a companion study of subjects from the Faroe Islands, published in 1997, indicated that methylmercury exposure *in utero* does cause negative health effects, although not at the level indicated in the Iraqi study. The following table compares the design and findings of the two major studies.

Comparison of two primary studies on exposure to methylmercury

	Iraqi study	Seychelles study
Study type	Retrospective study	Prospective longitudinal study
Number of participants	Approximately 80 mothers with infants	Over 700 mothers with infants
Medium of exposure	Ingestion of tainted grain	Ingestion of tainted fish
Exposure duration	One exposure episode lasting several months; few low-level exposures	Low-level, long-term exposures, including exposures during pregnancy and lactation
Method of collecting exposure data	Used samples of scalp and non-scalp hair	Used only scalp hair
Method of collecting health data	Self-reporting by participants	Collected by health professionals using neurobehavioral tests
Methylmercury levels found in maternal hair	10 to several hundred parts per million	0.5 – 26.7 parts per million

Source: Environmental Health Perspectives, Vol. 106, No. 2, February 1998

An Effective Antidote in Methylmercury Poisoning

Methylmercury is a ubiquitous environmental pollutant and a potent neurotoxin.

Human exposure to methylmercury occurs mostly through consumption of fish and other seafood, although several major inadvertent exposures have also occurred, including epidemics in Japan (Minamata disease), Iraq, Pakistan, and Guatemala.

Individuals poisoned with methylmercury exhibit severe neurological disturbances, including paresthesia, ataxia, sensory and speech impairment, and visual field constriction. These clinical symptoms become evident only after a relatively long latent period of 1-2 months. Because the damage to the central nervous system appears to be irreversible, treatment must be initiated promptly after exposure. The only way to prevent or ameliorate toxicity once methylmercury has been ingested is to accelerate its elimination from the body.

At present, no effective strategy exists to promote the rapid clearance of methylmercury from poisoned individuals. A number of sulfhydryl-containing complexing agents have been evaluated extensively and found to be only marginally effective.

Now, however, a new research study has demonstrated that oral administration of *N*-acetylcysteine (NAC), a widely available and largely nontoxic amino acid derivative, produces a profound acceleration of urinary methylmercury excretion in mice.

Mice that received NAC in the drinking water (10 mg/ml) starting at 48 hr after methylmercury administration excreted from 47 to 54% of the ^{203}Hg in urine over the subsequent 48 hr, as compared to 4-10% excretion in

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ARSENIC EXPOSURE – A RISK FACTOR FOR DIABETES MELLITUS

An increased risk for diabetes mellitus has been reported among people exposed to arsenic through drinking water. This form of exposure is a serious problem that has been reported in a number of countries including Argentina, Bangladesh, Chile, Taiwan, and the United States. The April 1998 issue of this Newsletter reported on the seriousness of arsenic pollution of ground water in Bangladesh. Particularly high arsenic levels have also been reported in West Bengal, an Indian province bordering Bangladesh. West Bengal and Bangladesh form a geologic continuity, and the occurrence of arsenic in drinking water seems to depend on arsenic-rich sediments. Withdrawal of a large quantity of ground water may decrease the level of moisture in the soil. This facilitates penetration of oxygen into the ground with subsequent oxidation of arsenic-containing minerals and the release of arsenic into the aquifers.

Since previous studies had suggested a link between arsenic exposure and diabetes mellitus, a new study has been carried out by Swedish and Bangladeshi researchers on the occurrence of this disorder among people in western Bangladesh, who were drinking tubewell water containing arsenic.

This study was designed as a comparison of the prevalence of diabetes mellitus among subjects living in areas where there was exposure to arsenic and subjects in areas where there was no evident exposure through the drinking water supply. For the first group, only subjects with keratosis were enrolled to ensure definite arsenic exposure. The prevalence of diabetes mellitus was compared for this group versus the population with uncontaminated water supply.

In this study, a significantly higher prevalence of diabetes mellitus was found among subjects with keratosis compared with subjects who did not have keratosis. A significant trend in risk beween an approximate, time-weighted arsenic exposure and the prevalence of diabetes mellitus was interpreted as strengthening the possibility of a causal association. However, the lack of a comprehensive, systematic, long-term sampling of the water supplies in the study area is an acknowledged limitation of the study since directly measured individual exposure data over time would have been desirable for more conclusive evidence.

It is, moreover, currently unclear whether the risk of contracting diabetes mellitus also operates at the low exposure levels that may cause cancer, and a mechanism through which inorganic arsenic would induce diabetes mellitus is unknown. To investigate more precisely the likely diabetogenic effect of arsenic, different sources of exposure might need to be considered in future studies.

Source: American Journal of Epidemiology, Vol. 148, No. 2, July 1998.

The "Lethal Factor" in Anthrax

Anthrax toxin, produced by the bacterium Bacillus anthracis, is composed of three proteins, protective antigen (PA), edema factor (EF) and lethal factor (LF). LF and PA together form a toxin referred to as lethal toxin which is the dominant virulence factor produced by B. anthracis and is the major cause of death of infected animals.

Scientists have long suspected that LF is a protease, an enzyme that cuts other proteins, but they have not been able to identify its targets. Now, however, a research team at the National Cancer Institute in Frederick, Maryland has made a discovery that may one day lead to a new countermeasure against the disease. The research team has found that LF cleaves and inactivates an enzyme in one of the cell's key signaling pathways, the mitogen-activated protein kinase (MAPK) pathway, which helps control cell growth, embryonic development, and the maturation of oocytes into eggs.

The new research has shown that the LF toxin prevents frog oocytes from maturing into eggs, indicating possible blockage of the MAPK pathway. This blockage apparently occurs because LF clips off a piece of the enzyme responsible for activating MAPK, thereby rendering it inactive. When the researchers sequenced two forms of this enzyme – MAPK kinase (MAPKK) – from LF-treated cells, they found that the amino terminals of the proteins were missing either seven or nine amino acids.

The identification of an LF target molecule represents the first step towards development of an antidote to the toxin.

To try to show directly that MAPKK inactivation is responsible for the physiological effects of LF, the researchers are also investigating whether a MAPKK mutant that resists cleavage by LF can protect cells from the toxin. At the same time, the team is looking for other cellular substrates of LF.

Source: Science, Vol. 280, No. 5364, May 1998.

In-depth Study Into the Pfiesteria Problem

Men who work along the Pocomoke River and adjacent waterways on the eastern shore of the Chesapeake Bay in Maryland, U.S.A., began complaining of health problems such as fatigue, headaches, diarrhea and weight loss as early as 1996. At the same time the fish they caught in these waterways began appearing with lesions and sores.

In 1997, studies were carried out and Pfiesteria was implicated. Pfiesteria is a one- celled organism which is harmless unless something triggers it to change form and emit poison that attacks fish, allowing the organism to feed on them until they die. Species in the toxic Pfiesteria complex had previously been identified as the cause of similar lesions and wide-scale fish kills in North Carolina, with laboratory studies showing that the neurological symptoms and skin lesions in fish were associated with the release of specific toxins into the water.

A recent study has assessed 24 people who had contact with the affected waterways, and data has been collected on their exposure history and symptoms. Neuropsychological screening has been performed on 13 of the subjects of the study to make a complete medical and laboratory assessment. Performance on neuropsychological measures was compared with a matched control group. The study showed that people with high exposure were significantly more likely than occupationally matched controls to complain of neuropsychological symptoms, including new or increased forgetfulness; headache; and skin lesions. Exposed people had significantly reduced scores on the Rey Auditory Verbal Learning and Stroop Color-Word tests and the Grooved Pegboard task. There was a dose-response effect with the lowest scores among people with the highest level of exposure. However, by 3-6 months after cessation of exposure, all those assessed had test scores that had returned to within normal ranges.

This in-depth study provides scientific evidence that people with environmental exposure to waterways in which Pfiesteria toxins are present are at risk of developing a reversible clinical syndrome characterized by difficulties with hearing and higher cognitive functions. Risk of illness is directly related to the degree of exposure, with the most prominent symptoms occurring among people with chronic daily exposure to affected waterways.

Mechanisms responsible for the observed neuropsychological symptoms remain to be defined and more data are needed on the type and degree of exposure necessary to cause clinical symptoms.

The present study also highlights the need to explore the environmental basis for the emergence of the new pathogen with its propensity for killing fish in the Chesapeake Bay region, and its relation to toxic Pfiesteria-like dinoflagellates in other coastal areas.

Source: The Lancet, Vol. 352, August 1998.

Inherited Radiation Damage

Considerable controversy exists over whether radiation-induced mutations occurring in the male germ line can be the cause of a predisposition to cancer in subsequent generations. This has been a subject of debate since the late Martin Gardner of the University of Southampton suggested in 1990 that some children at Seascale, the site of the Sellafield nuclear plant in the United Kingdom, had developed leukaemia because their fathers were exposed to radiation while working at the plant.

Now a recent study conducted by researchers at the Paterson Institute for Cancer Research in Manchester and the Medical Research Council's Radiation and Genome Stability Unit at Harwell, UK, has produced the first evidence from animal experiments that two "hits" by carcinogens, one to a father and one to his offspring, can trigger leukaemia.

The study has shown that 90 per cent of the offspring of male mice injected with plutonium developed either leukaemia or a lymphoma after they were exposed to a powerful chemical carcinogen, methyl-nitroso-urea. Only 68 per cent of mice whose fathers were not injected with plutonium contracted one of the two diseases after exposure to the chemical.

The mice whose fathers had been irradiated developed leukaemia or lymphomas up to 28 days earlier than mice whose fathers were not irradiated. In addition, the pattern of cancers in pups of irradiated fathers differed from that of pups of non-irradiated fathers, with the former developing twice as many leukaemias and half as many lymphomas. These findings suggest that a father's exposure to radiation can be instrumental in causing cancer in offspring.

While there are no grounds for suggesting that these results explain the Seascale phenomenon, the researchers believe that the current study is the first to describe the enhanced induction of lympho-haematological disorders following preconceptional paternal irradiation.

Source: British Journal of Cancer, Vol. 78 (3), 1998.

Chemical Landfills and Birth Defect Risks

Waste-disposal sites are a potential hazard to health. People who live near landfill sites may be exposed to chemicals released into the air, water, or soil. Air contamination includes off-site migration of gases, dust, and chemicals bound to dust and other particulates. Local surface water and groundwater can become contaminated, leading to the contamination of potable water supplies. Chemical contamination of air, water or soil may also affect locally grown food produce, making landfill sites a health risk for local residents and their children.

To date, however, there has been little epidemiological evidence on which to base health-risk assessments of landfill sites. The potential teratogenicity of many of the chemicals dumped in these sites, such as heavy metals, pesticides, and solvents, is known, but chemical dose may have to reach a threshold level before significant teratogenic effects become evident.

Now a study carried out by a team of European investigators focusing on the health of 3,455 children born within a 7-kilometer radius of 21 European chemical landfill sites before 1994 has reported that pregnant women living within 3 kilometers of a chemical landfill have a 33% higher risk of having a child with a birth defect when compared with women living further away from such sites. The authors of the study found that residence within 3 kilometers of a landfill site was associated with a significantly raised risk of congenital defects, for three defects in particular- brain deformities like spina bifida, heart malformations, and abnormalities of major blood vessels.

Data for the study were collected from seven research centers in five European countries – Belgium, Denmark, France, Italy and the United Kingdom. The research centers maintain regional population-based registers of congenital anomalies that include data on livebirths, stillbirths, and termination of pregnancy after prenatal diagnosis.

The landfill sites under study were located in areas covered by the registers of congenital anomalies and contained hazardous waste of non-domestic origin, as defined in the EC Directive on Hazardous Waste.

A total of 21 landfill sites was studied of which 9 sites closed before the start of the study period and ten were in operation for more than 20 years before the end of the study period.

The researchers who carried out the study found little difference in risk between individual landfills. However, they did find a consistent decrease in risk for birth defects as the distance of residence from the sites increased.

The authors of the study caution, however, that random clusters of abnormality often appear in these types of geographically-focused studies, and separating these random clusters from those in which there is a common underlying cause is difficult.

The degree of environmental hazard of a landfill site may be more a result of geology, engineering, and waste disposal management practices than of the type or amounts of the chemicals dumped there. Moreover, the study team also note that landfill sites cannot be easily classified according to the chemicals they contain, because each site contains a range of chemicals and information is in any case usually incomplete.

The next step is to rank landfill sites according to hazard potential by expert consensus, with concealment of risk status. A dose-response effect, in which sites of highest hazard potential are associated with the highest risk of congenital anomaly, would strengthen the case for a causal association between risk of congenital anomaly and residence near sites. Direct measurement of exposure to chemicals for residents near landfill sites would also help in assessing whether the association is causal, but this research has not yet been done.

Source: The Lancet, Vol. 352, No. 9126, August 1998.

An Effective Antidote in Methylmercury Poisoning

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control animals. When NAC-containing water was given from the time of methylmercury administration, it was even more effective in enhancing urinary methylmercury excretion and at lowering tissue mer-cury levels. In contrast, excretion of inorganic mercury was not affected by oral NAC administration. The ability of NAC to enhance methylmercury excretion when given orally, its relatively low toxicity, and its wide availability in the clinical setting indicate that it may be an ideal therapeutic agent for use in methylmercury poisoning.

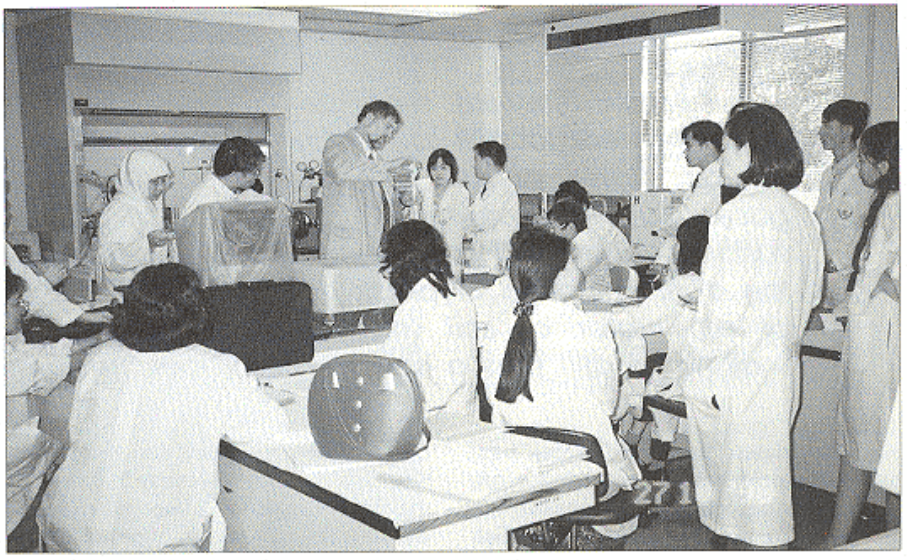
Source: Environmental Health Perspectives, Vol. 106, No. 5, May 1998.

CRI Training Course on Detection of Environmental Pollutants and Monitoring of Health Effects

(Continued from page 1)

The detection and identification of environmental pollutants was the key to successful management of toxic chemicals providing the basis for effective protection of the environment and human health.

Her Royal Highness commented that health monitoring, which was the major focus of the training course, was all too often overlooked by environmental specialists. However, without adequate monitoring and accurate identification of toxic compounds in the environment there could be no guarantee that the health of the industrial workforce could be effectively protected.



The lecture program for the course focused on different aspects of toxicology, the occurrence of toxic compounds in the environment and their effects on man, analytical methods in environmental toxicology, the fate and distribution of chemicals in the body, host factors affecting toxicity, and the testing of toxicity in chemicals.

In the practical sessions, participants conducted experiments in qualitative and quantitative determination of toxic compounds in the environment focusing on nitroaromatic compounds in air, lead in roadside dust samples, arsenic in drinking water, aflatoxins in food, polychlorinated biphenyl (PCB), polycyclic aromatic hydrocarbon (PAH) in air and N-nitrosamines.

There were also sessions on the determination of toxicity covering oxidative status (MDA), cytotoxicity and genotoxicity.

At the end of the course, Dr. N. Frank of the German Cancer Research Center speaking on behalf of his colleagues offered his comments on the success of the training program.

"The program of the training course was particularly relevant to the countries of Southeast Asia facing a number of environmental problems. These include air pollution mainly due to motor vehicles, energy production and uncontrolled industrial emissions, as well as the extensive use of pesticides, and localized contaminations with metals etc. in industrial zones.

According to these problems, a number of topics were selected such as the determination of exposure to aromatic nitro compounds, PAHs, PCBs, dioxins, and metals. In addition, the increasingly relevant effects of these environmental pollutants on living organisms were discussed. Participants received practical training in toxicity testing and biomonitoring in the hope that this will enable them to evaluate pollution-related, problems specific to their own countries.

The facilities provided by the CRI were of a very high standard, and the overall organization of the course was excellent. During the practical part, the outstanding skills and helpfulness of the CRI staff were highly appreciated.

We were impressed with the high motivation of all participants to improve their theoretical and practical knowledge in Environmental Toxicology. They were very eager to apply the newly acquired skills in order to improve the environmental situation in their countries".

Chulabhorn Research Institute
CAPACITY BUILDING PROJECT ACTIVITIES
for Southeast Asian Countries

We are pleased to announce the following schedule of project activities for the period 1999-2000.

Date	Subject Area	Course	City/Country
1999			
May*	Environmental Toxicology	Practical Training Course on Detection of Environmental Pollutants	Hanoi/VIETNAM
August*	Environmental Toxicology	Executive Seminar on Environmental Toxicology	Bangkok/THAILAND
August 16-27	Environmental Toxicology	Training Course on Environmental Toxicology Pollution Control and Management	Bangkok/THAILAND
December 6-10	Biotechnology	Training Workshop on Risk Assessment and Risk Management in Biotechnology	Bangkok/THAILAND
2000			
February*	Environmental Toxicology	Training Course on Environmental Toxicology Pollution Control and Management	Hochiminh City and/or Hanoi VIETNAM
October*	Environmental Toxicology	Training Workshop on Environmental and Health Risk Assessment and Risk Management of Toxic Chemicals	Bangkok/THAILAND

* dates to be announced

PESTICIDE DETOXIFICATION

The intensive use of pesticides in modern agricultural systems has resulted in serious environmental problems. The pesticides that have received particular attention include pentachlorophenol (PCP), *s*-triazines, organophosphates and carbamates, because they are highly persistent compounds and are biodegraded very slowly.

Current methods for detoxifying such pesticides rely on incineration and landfills, although both methods have serious drawbacks. Incineration has met serious public opposition because of the potentially toxic emissions. It is, moreover, a very costly process as it requires large amounts of energy to obtain the high temperatures needed to destroy the pollutants. Landfills carry the risk of the leaching of pesticides into surrounding soil and groundwater supplies. Because of the problems associated with these two methods, there is increasing interest in the use of microorganisms capable of degrading pesticides. Systems based on both natural isolates and genetically engineered strains have been utilized for this purpose.

In systems of detoxification based on natural isolates, bacteria and fungi are the major degraders of pesticides and their breakdown products, and several detoxification processes based on pure or mixed cultures have been proposed.

However, recent advances in genetic techniques have opened up new avenues to move towards the goal of genetically engineering microorganisms to function as "designer biocatalysts" in which certain desirable biodegradation pathways or enzymes from different organisms are brought together in a single host with the aim of performing specific detoxification. The application of genetic engineering and biochemical techniques to further improve and evolve natural biodegradative capabilities will ultimately create "super biocatalysts" capable of degrading several pesticides rapidly and cost-effectively.

Source: Trends in Biotechnology, Vol. 16, February 1998.

Advance Announcement

The Fourth Princess Chulabhorn Science Congress
Impact of Chemicals in the 21st Century
Bangkok, Thailand
28 November – 2 December 1999

The congress marks the turn of a century of global industrial development in which the use of chemicals has had an important impact both on human health and on the environment. The congress looks forward to the next century and to the new technologies which will ensure that our use of chemical substances is optimally beneficial to human health, enhancing our quality of life and safeguarding our environment.

The scientific program of the congress, comprising plenary lectures, workshops, symposia, contributed papers, poster sessions and exhibitions, reflects these 3 main perspectives: health, environment and technology.

Topics to be addressed by the congress will be organized under the 3 categories:

Health
- Bioactive substances
- Diseases on the increase
- Cancer chemoprevention
- Monitoring/assessing toxicological risk

Environment
- Environmental pollutants
- Environmental management
- Regulatory aspects of chemicals

Technology
- Detection and monitoring of chemicals
- Treatment of toxic chemicals and industrial wastes
- Clean-up remediation
- Genetic modifications and chemicals
- Risk management of chemical processes

The congress will bring together experts from a wide range of specializations, so that through the sharing of knowledge new directions for the beneficial and safe use of chemicals can serve as a benchmark for developments in the next century.

For further information, please contact:
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Man-made Reefs to Remove Carbon Dioxide from the Atmosphere

A team of chemical engineers at Louisiana State University have developed an ingenious means of removing carbon dioxide from the atmosphere, which could serve to combat global warming. The researchers have designed concrete hemispheres that could be positioned in estuaries and coastal waters, forming a man-made reef capable of removing large quantities of carbon from the atmosphere. These concrete hemispheres will be colonised by algae which "fix" carbon from the atmosphere and trap it in sediment. The plan is to attract algae that grow 20 times faster than free-floating forms. As they grow and photosynthesise, they extract carbon dioxide from the surrounding waters, which is then replenished by carbon dioxide from the atmosphere. When the algae die, they fall to the seabed and become part of the sediment.

At the moment the idea is being tested in the laboratory using concrete balls 15 centimeters in diameter. However, the next stage will be sinking reef balls in the ocean. A hollow hemisphere or reef ball of 1 meter in diameter could provide about 100 square meters of active surface area for microalgae growth. Each reef hemisphere could remove 200 kilograms of carbon from the atmosphere each year, a process that would continue indefinitely. The researchers say that these balls could eventually be used to dispose of carbon dioxide from fossil-fuel power plants with emissions being pumped into the ocean close to a concrete reef system.

Source: New Scientist, Vol. 158, No. 2139, June 1998.

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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