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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".

Interuniversity Postgraduate Education Program in Environmental Toxicology, Technology and Management – Signing of the Memorandum of Understanding

Her Royal Highness Princess Chulabhorn presided over the signing ceremony of a memorandum of understanding between the Asian Institute of Technology (AIT), Mahidol University (MU) and the Chulabhorn Research Institute (CRI) which took place at the Institute's Convention Hall on 16 December 2002.

As President of the Chulabhorn Research Institute, HRH Princess Chulabhorn was the signatory for the Institute with Professor Dr. Jean-Louis Armand, President of the Asian Institute of Technology and Professor Dr. Pornchai Matangkasombut, President of Mahidol University, signatories for AIT and MU respectively.

This collaborative venture represents the effective pooling of the resources of three of Thailand's leading teaching and research institutions and was made possible by a grant award from the Ministry of University Affairs supported by a loan from the Asian Development Bank.

The tripartite agreement is the result of many years planning and close cooperation established in two earlier bilateral

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Interuniversity Postgraduate Education Program in Environmental Toxicology, Technology and Management – Signing of the Memorandum of Understanding

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agreements, the agreement between Mahidol University and Chulabhorn Research Institute which was signed on 7 December 1995 and the agreement between the Asian Institute of Technology and Chulabhorn Research Institute which was signed on 12 June 1996.

In its initial planning stages, support by the United Nations Development Programme (UNDP) enabled CRI to spearhead the development of an innovative interdisciplinary curriculum, the design of which has received international acclaim.

In her opening address at the signing ceremony, Her Royal Highness stated:

"With the assistance of a team of renowned international experts, we designed the curriculum for a postgraduate program in Environmental Toxicology, Technology and Management, which was especially tailored to the needs of developing countries.

The curriculum is a model of an interdisciplinary program that crosses traditional subject boundaries and combines the disciplines of toxicology, environmental technology and engineering. The special strengths and expertise of our tripartite team have made the launch of this innovatory program possible: AIT in Environmental Engineering, Mahidol University in Life Sciences, and CRI in Environmental and Industrial Toxicology.

Through the effective pooling of our resources as leading teaching and research institutions, we are able to contribute more effectively to the social and economic development of the nation and of the region."

Cigarette smoking and the risk of breast cancer in women

The clear association between tobacco smoking and lung cancer has led researchers to postulate that cigarette smoking could represent a risk factor for breast cancer. This hypothesis is supported by experimental evidence that the carcinogen benz(a)pyrene, present in tobacco smoke, induces neoplastic transformation of human breast epithelial cells. However, this association remains controversial, mainly because breast cancer is hormone-dependent, and evidence indicates that cigarette smoking has an anti-oestrogenic effect in women.

The results of research studies show that the effect of cigarette smoking on the risk of breast cancer differs between premenopausal and postmenopausal women. In premenopausal women, risk of breast cancer is raised in those who smoke before a first pregnancy, but only when smoking is initiated within 5 years of the onset of menarche, and among nulliparous women. These results, which suggest that human breast tissue is most sensitive to environmental carcinogens during periods of rapid cell proliferation when differentiation is incomplete (puberty), and when complete cellular differentiation is never achieved (nulliparity), add epidemiological evidence to experimental studies, relating susceptibility to carcinogenesis to the biology of breast development.

Now, in a recent study, investigators have tested the hypothesis that cigarette smoke exerts competing effects on breast-cancer risk.

In postmenopausal women, cigarette smoking was not associated with an increased risk of breast cancer, irrespective of pregnancy status or age at which smoking was initiated. A significantly reduced risk was noted in women who started to smoke after a first full term pregnancy and whose Body-Mass Index (BMI) increased since early adulthood, but not among those whose BMI did not change from age 18 to the present. These results suggest that carcinogenic events that lead to breast cancer in postmenopausal women are unrelated to perimenarchal exposure to tobacco carcinogens, and that under specific circumstances of exposure to cigarette smoke the risk might be reduced. Postmenopausal risk of breast cancer is significantly associated with circulating oestrogen concentrations, which in turn are highly correlated with increased BMI, as a result of raised oestrogen production from aromatisation of adrenal androgens in adipose tissue; presence of aromatase in breast tissue might also lead to increased synthesis of oestradiol *in situ.* Compounds in cigarette smoke inhibit aromatisation of androgens into oestrogens and enhance

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WELL-SWITCHING: A STRATEGY TO REDUCE THE CRISIS OF ARSENIC IN DRINKING WATER IN BANGLADESH

Hand-pumped tube wells have been promoted in Bangladesh as a means of reducing childhood mortality from water borne microbial diseases caused by drinking contaminated surface waters. However, it is feared that cancers of the skin, liver, lungs and other organs, as well as diabetes and cardiovascular diseases caused by the presence of arsenic in tube-well water will constitute a major human tragedy in the future. National and international programs to reduce arsenic exposure in the population have to date been largely ineffective.

To find possible strategies for the mitigation of the impending crisis, a team of researchers from the United States and from Bangladesh have carried out a survey of wells within an area 25 km east of Dhaka that encompasses patterns of geographical variability that are similar across broad regions of Bangladesh. This survey holds hope for a viable strategy for reducing exposure since results indicate that, while the nature of the arsenic distribution complicates intervention, the high degree of spatial variability between wells also presents an opportunity for remediation that should be more widely promoted in future.

The contiguous wells that were sampled in the survey cover an irregularly-shaped area of approximately 21 km^2 and serve a population of approximately 55,000. The wells are clustered in villages separated by open rice fields. The number of wells in the study area has roughly doubled every 5 years, with an annual growth rate of 15%, more than five times greater than that of the annual population increase in Bangladesh.

There is considerable variation in the proportion of safe and unsafe wells within the study area, with a higher proportion of safe wells in the central region and very few safe wells to the east and to the west. Similar patterns of variability on a local scale have been reported elsewhere in Bangladesh.

Because the position of all wells was determined in the present study, the distance from each unsafe well to the nearest safe well could be calculated. This analysis revealed that even though only half the inhabitants of the study area had access to safe water from their own well, 88% resided within 100 m of a safe well and 95% within 200 m. Even for a subset of 515 contiguous wells of which only 18% were safe, 73% of the villagers concerned lived within 100 m of a safe well and 89% within 200 m. The implication of this finding is that well-switching could drastically reduce arsenic exposure in the study area, and possibly in many other parts of the country, at least in the short term.

Range of concentration of arsenic in water from 4,997 tube wells in the survey area.

Arsenic concentration (mg/l)	% of wells
< 5-10	28
11-50	20
51-100	17
101-900	35

Source: Bulletin of the World Health Organization, Vol. 80, No. 9, 2002.

Effects on human health of arsenic in drinking water

Chronic ingestion of arsenic-contaminated drinking water poses a significant risk to human health.

In humans, arsenic is primarily associated with tumors of the bladder, lung, and skin. Most regulatory activities are focused on arsenic's potential to cause cancer, but characterization of risk from noncancer effects such as cardiovascular disease is also needed to assure adequate protection of public health. Epidemiological studies have revealed that chronic arsenic exposure in many countries caused the increased risk of mortality associated with cardiovascular disease, but a plausible explanation for the development of arsenic-induced cardiovascular disease has not been previously examined.

A recent study carried out by researchers from the College of Pharmacy of the Seoul National University, Korea, investigates the hypothesis that altered platelet aggregation could be a causative factor in cardiovascular diseases observed in human populations that have chronically ingested arsenic-contaminated drinking water.

In the study, the effects of arsenic on platelets were examined *in vitro* and in a drinking water study using a rat animal model.

Trivalent inorganic arsenic (arsenite) induced *in vitro* aggregation when platelets were exposed to subthreshold challenge by thrombin and several other agonists in a concentration-dependent manner, with arsenite being the most potent form tested. Arsenite also induced significant increases in serotonin secretion, thromboxane A_2 formation, and adhesion protein expression in platelets. Consistent with the *in vitro* studies, 4-week ingestion of arsenite-contaminated drinking water resulted in enhanced arterial thrombosis. Human platelets showed similar responses, suggesting that the effects seen in animal experiments are applicable to humans. These results will provide new insights into the mechanism of arsenic-induced cardiovascular disease. They will also allow regulatory agencies to estimate risk from arsenic-induced cardiovascular disease and to determine if drinking water regulatory levels based on human cancer studies will protect against noncancer effects associated with cardiovascular diseases.

Source: Toxicology and Applied Pharmacology 179, No. 2, March 2002.

EFFECTS OF LEAD EXPOSURE ON MALE REPRODUCTIVE HORMONES: CLINICAL IMPLICATIONS

Lead exposure is commonly associated with defects in neurologic growth. Lead exposure in men has been associated with abnormalities of spermatogenesis, with an inverse relationship between blood lead and sperm concentration being reported. Animal studies have tended to support the conclusion that lead exposure disrupts the reproductive hormones but clinical studies have so far been inconclusive.

The reproductive axis is composed anatomically of the hypothalamus, pituitary, and testes in males, and physiologically by gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, and inhibin. GnRH, a peptide hormone, is produced in the medial basal portion of the hypothalamus. GnRH stimulates the pituitary gland to produce and secrete LH and FSH. LH is primarily responsible for stimulating testicular Leydig cell secretion of testosterone. FSH acts on the Sertoli cells of the testes to stimulate spermatogenesis and inhibin.

In the animal model, lead has a primary toxic effect on the hypothalamic-pituitary unit, a primary effect on the testes, and acts at all levels of the reproductive axis. Using the rat model, it has been demonstrated that lead exposure produces a dose-response suppression of serum testosterone and spermatogenesis, accompanied by no significant changes in circulating gonadotropin levels. However, mRNA levels of GnRH in the hypothalamus and LH in the pituitary are increased with lead exposure. This reported endocrine disruption was noted at blood lead levels > 30 µg/dL after exposure times of 2-8 weeks. Limited data are available on the toxic effects of lead at lower exposure concentrations and for longer periods of exposure. Increasing the length of exposure to 8 weeks seems to allow the adult animal to normalize its responses. Other data suggest that the lead-exposed animal is able to adapt to the metal's toxic effects.

It has been previously reported that exposure to lead acetate in relatively high dose ranges for 3 weeks increased mRNA levels of GnRH and LH as well as stored levels of LH. Consistent with the conclusion that the reproductive axis adapts to the toxic effects of lead was the finding that the increase in GnRH, mRNA, and β-LH concentration plateaued once the animal's blood lead levels reached 50 µg/dL.

Now a new study has been designed to determine whether exposure to lower levels of lead acetate over a longer time would produce a similar pattern of adaption to toxicity at the molecular level in the male rat, and whether changes in GnRH mRNA are mirrored by changes in circulating levels of GnRH.

The data from this study show that low doses of lead for long periods of time alter the rat hypothalamic-pituitary axis in a manner similar to that previously reported at higher doses for shorter periods of time. These results agree with previous findings that indicated a significant positive correlation between lead dose and expression of GnRH mRNA levels in the hypothalamus. Furthermore, the data support the hypothesis that lead exposure initially induces an increase in intracellular levels of GnRH mRNA in a dose-related manner, but with an attenuation in message production at higher levels of blood lead. The attenuation of the increase in GnRH mRNA levels with a greater dose of lead exposure, without a significant change in the levels of plasma GnRH and LH, support the conclusion that the male rat adapts to the toxic effects of lead on the hypothalamus, and that alterations in GnRH production at the molecular level do not translate to increases in circulating GnRH or LH levels.

These findings of perturbed GnRH mRNA expression at low levels of lead exposure are of potential clinical importance. Cognitive and behavioral development may be altered in children exposed to these low levels of lead. A recent clinical study evaluating the impact of lead exposure on normal reproductive development suggests that boys with marginally increased blood lead levels may mature sexually at a later age and have smaller testicular volume.

The exact mechanism by which this occurs clinically is not fully understood but the present study using an animal model has yielded results that suggest that disruptions in GnRH production and release may be involved.

Source: Environmental Health Perspectives, Vol. 110, No. 9, September 2002.

Study of tumour initiation and promotion potential of cypermethrin on mouse skin

Cypermethrin (CYM) is a synthetic pyrethroid insecticide widely used because of its high bio-efficacy and low mammalian toxicity. However, results from a recent study carried out in Lucknow, India, using a mouse skin model of carcinogenesis, revealed that CYM possesses complete carcinogenic as well as tumour initiating and promoting potential in both the sexes of Swiss albino mice.

The mouse skin model of carcinogenesis is a well-established protocol to test the carcinogenic and co-carcinogenic potential of test compounds. The results of the present investigation revealed that topical application of CYM at the tested doses and durations were capable of initiating, as well as promoting the transformation of mouse skin

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CAUSES OF ELEVATED BLOOD LEAD CONCENTRATIONS IN CHILDREN IN KARACHI, PAKISTAN

Sources of lead in the environment that have been shown to contribute to elevated blood lead concentrations include petrol, paint, water, food, cosmetics and lead-glazed ceramics. Automobile emissions are recognized as an important source of lead exposure for urban residents, particularly in areas of frequent traffic congestion.

The lead from these emissions is deposited in dust, soil and other ecosystems.

A recent cross-sectional study has been carried out of children living in different parts of Karachi in order to identify which types of exposure to lead contribute most to elevated blood lead levels.

A total of 430 children aged 36-60 months were selected through a geographically stratified design from the city center, two suburbs, a rural community and an island situated within the harbour at Karachi. Blood samples were collected from children, and a pre-tested questionnaire was administered to assess the effect of various types of exposure. Cooked food, drinking-water and house dust samples were collected from households.

About 80% of children had blood lead concentrations >10 µg/dl, with an overall mean of 15.6 µg/dl. At the 5% level of significance, houses nearer to the main intersection in the city center, application of surma, a cosmetic widely used in Pakistan, to children's eyes, father's exposure to lead at workplace, parents' illiteracy and child's habit of hand-to-mouth activity were among variables associated with elevated lead concentrations in blood.

Since most children in Karachi are likely to suffer some degree of mental impairment as a result of environmental lead exposure, this situation is of the greatest concern to public health. The current study shows that there is an urgent need for appropriate interventions in reducing the lead burden in the environment, due to the various factors associated with this toxic element.

The population of Karachi is largely unaware of the hazards and health consequences of lead exposure, and they therefore lack prevention strategies.

Source: Bulletin of the World Health Organization, No. 80, October 2002.

RAPID DIAGNOSIS OF PLAGUE

A test using dipsticks for the rapid diagnosis of plague, developed and evaluated at the Pasteur Institute in Madagascar and in Paris, now makes it possible to detect this disease in fifteen minutes at a patient's bedside. This research represents considerable progress in monitoring and combating this re-emerging disease, which is often fatal without early treatment. A small production unit for this test is already in place in Madagascar.

The test developed by the Pasteur teams is very easy for medical personnel to use: by simply putting a sample in contact with a dipstick capable of detecting the presence of a specific antigen of the plague bacillus, antigen F1, it is possible to establish an accurate diagnosis in fifteen minutes, instead of the two weeks required by bacteriological methods.

It is thus possible to give warning quickly and to instigate necessary control measures: antibiotic therapy for the patient, preventive measures for those in contact and disinsecting of the environment to kill the vector fleas of the disease. This is a considerable step forward in the fight against plague, which, in the absence of early treatment, can kill the infected person in several days.

These rapid-diagnosis dipsticks can detect bubonic plague as well as pneumonic plague, a less frequent but more serious form, which rapidly leads to death if treatment is not undertaken in the 24 hours following the first symptoms. This extremely serious form, directly communicable from human to human, would be the one observed in case of a bioterrorist use of *Yersinia pestis*.

This diagnostic test also has the advantage of being usable in the most remote and least electrified areas: the transportation and storing of the dipsticks do not necessitate constant refrigeration and performing the test does not require any specific equipment.

Furthermore, these tests can also be performed on samples from rodents, in the case of abnormal mortality of these animals in the villages, thus making it possible to give very early warning, and to take necessary preventive measures (disinsecting and preventive treatment for subjects in contact) in order to avoid the first human cases.

Responsible for three historic, extremely deadly pandemics, plague remains fixed in human memory as a particularly horrifying synonym of pestilence. Usually confined to some isolated areas of the world, plague is currently re-emerging, with the number of cases increasing in several world regions. For example, in Madagascar, 1,000 to 1,500 suspected cases were declared annually during the last decade compared to 200 to 300 cases throughout the 1980s. Approximately twenty other countries are affected, mainly in Africa, but also in Asia, and industrialized nations, like the United States (14 cases in 1994 and 4 cases in 1997) are not being spared.

The possible spread of plague by rapid forms of transportation constitutes a potential danger which must not be underestimated. Furthermore, current fears of international bioterrorism are restoring major interest in studies on plague and its means of diagnosis.

Source: The Lancet, January 2003.

URGENT NEED TO CONTROL THE USE OF PESTICIDES IN THE DEVELOPING WORLD

In parts of the developing world, pesticide poisoning causes more deaths than infectious diseases. Use of pesticides is poorly regulated and often dangerous; their easy availability also makes them a popular method of self-harm. In 1985, the UN Food and Agriculture Organisation (FAO) produced a voluntary code of conduct for the pesticide industry in an attempt to limit the harmful effects of pesticides. Unfortunately, a lack of adequate government resources in the developing world makes this code ineffective, and thousands of deaths continue today. WHO has recommended that access to highly toxic pesticides be restricted — where this has been done, suicide rates have fallen.

WHO's model essential drugs list was initiated in 1977 to support rational use of drugs. Today, the model list contains over 300 drugs that satisfy the health needs of most people for most of the time. In countries that have used the essential drugs list to develop their own essential drugs programme, it has led to better supply and use of important drugs.

At present, the situation with pesticides has some similarities to that of drugs in the 1970s. Hundreds of active ingredients and thousands of formulations are available in an uncontrolled fashion and promoted by both manufacturer and distributor as being essential for crop production.

It is argued that there is now an urgent need for a model minimum, rather than essential, pesticide list in order to address the many short and long-term health problems resulting from the agricultural use of pesticides.

The model list would give governments who are under-resourced information to allow them to determine which pesticides suit their agricultural needs. Unbiased assessment and comparison of pesticides, using an explicit and transparent evidence-based approach, would be very useful for governments and small-scale farmers.

Although enforcement of legislation would still often be difficult, a greatly reduced number of pesticides should simplify this process. A model list would allow legislators to decide which few pesticides should be used in their region and then actively register them; other pesticides would not be registered, removing a large number of obsolete and dangerous pesticides from circulation.

A minimum pesticide list may go some way to preventing the deaths of hundreds of thousands of people worldwide every year from pesticide poisoning. Such a goal can only be achieved, however, if the safest and most effective pesticides are used in combination with ways to control their use, such as prescriptions to restrict sales and increased funding for the effective training of farmers in pest management.

Source: The Lancet, Vol. 360., October 2002.

Vitamin D receptor as an intestinal bile acid sensor

A recent study provides insights into the epidemiologic relation between colon cancer, vitamin D and a high-fat diet. The study finds that a receptor for vitamin D (VDR) in the intestine also binds a bile acid called lithocholic acid (LCA). Increased amounts of LCA are associated with a fat-high diet, and because it is poorly reabsorbed, it passes into the colon. Binding to the vitamin D receptor stimulates the expression of CYP3A, an enzyme that can catabolize LCA.

To explore the role of LCA and VDR in the activation of CYP3A, the promoters of the mouse, rat and human CYP3A genes were investigated for potential VDR-PXR (Pregnane X receptor) heterodimer binding sites.

By binding to VDR, both LCA and vitamin D may activate a feed-forward catabolic pathway that increases CYP3A expression and leads to the detoxification of LCA. These findings suggest a model to explain how the enteric system could protect itself from the potentially harmful effects of LCA and why vitamin D is protective against colon cancer under normal physiologic conditions. Protection provided by VDR activation may become compromised when the detoxification pathway is overwhelmed (e.g., by increased levels of LCA due to sustained high-fat diets) or under clinical conditions of vitamin D deficiency (e.g., rickets / oesteomalacia). Consistent with this model, there is an epidemiologic relation between the incidence of colon cancer and Western-style, high-fat diets, and the highest death rates from colon cancer occur in areas with a high prevalence of rickets. Furthermore, mice lacking VDR not only have rickets but also display enhanced cellular proliferation in the colon. Thus, this work should provide the impetus for further studies addressing the role of diet, bile acids, and vitamin D in colorectal cancer.

Source: Science, Vol. 296, May 2002.

New research promises effective protection against anthrax

The dormant and durable spore form of Bacillus anthracis is an ideal biological weapon of mass destruction. Once inhaled, spores are transported by alveolar macrophages to lymph nodes surrounding the lungs, where they germinate; subsequent vegetative expansion causes an overwhelming flood of bacteria and toxins into the blood, killing up to 99% of untreated victims. Natural and genetically engineered antibiotic-resistant bacilli amplify the threat of spores being used as weapons, and heighten the need for improved treatments and spore-detection methods after an intentional release.

Now, new research work is focusing on a technique for tackling bacterial infections using bacteriophage – viruses that infect and lyse specific bacteria. Researchers have exploited a single key enzyme of bacteriophage γ, a virus commonly used in the laboratory to identify *B. anthracis.* This enzyme, PlyG, is a type of lysin which, in the normal course of the bacteriophage life cycle, destroys the bacterial cell wall so as to allow the release of progeny phage.

Lysins are typically highly specific for particular species or strains of bacteria, because their binding regions are directed towards cell-wall carbohydrate structures that vary greatly among species and strains. Accordingly, the PlyG lysin described by the researchers was highly effective in killing *B. anthracis,* but did not affect most strains of the closely related species *Bacillus cereus* and *Bacillus thuringiensis.*

Although bacteriophage lysins are made inside bacteria and normally cause lysis from within, the authors of the study showed that PlyG added externally had strong lytic activity towards all the *B. anthracis* strains tested when they were grown on solid or liquid media. Most importantly, it was also found that when mice were injected with PlyG 15 minutes after being infected with a close relative of *B. anthracis,* about 80% of the animals were rescued from otherwise certain death. An obvious concern is that some of the mice might have died because PlyG-resistant mutants of *B. anthracis* had arisen. However, a controlled test showed that PlyG-resistant mutants were not generated in *B. anthracis* cultures, even when the cultures were treated chemically in a way that increased the percentage of mutants resistant to standard antibiotics.

The researchers suggest that the development of resistance to PlyG is due to the fact that any mutational change to the cell wall structure that prevents binding to PlyG would kill the bacterium. This targeting of phage lysins to an essential bacterial structure gives them an advantage over the small-molecule antibiotics to which bacteria rather easily become resistant.

There is still much to be done to develop PlyG into an effective drug. For example, it would probably need to be administered intravenously in a formulation that would give adequate concentrations in the blood, because that is where the bacteria grow rapidly during the dangerous final stage of infection. Nonetheless, the new research has introduced a potential treatment for anthrax that might be useful either alone or in combination with other therapies.

Source: Nature, Vol. 418, No. 6900, 2002

Cigarette smoking and the risk of breast cancer in women

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the formation of oestradiol metabolites with minimum oestrogenic activity. The possible protective effect of cigarette smoking on breast-cancer risk could, therefore, be mediated through mechanisms that reduce production of endogenous oestrogens in postmenopausal women who initiate smoking during a fairly refractory window to carcinogen exposure.

The findings have public-health consequences and implications for the design of studies to investigate effects of carcinogenic and hormonally active agents in breast cancer. This new evidence of the detrimental effect of cigarette smoking on the most frequent sex-specific cancer in women should reinforce the importance of smoking prevention, especially in early adolescence. Attention should be paid to the timing of exposure in relation to susceptibility and refractory windows when planning to investigate associations between environmental carcinogens or putative endocrine disruptors and breast cancer risk. Premenopausal women who smoke in early adolescence should be the target population for studies to assess the effect of carcinogenic agents, whereas investigations of the effect of hormonally active agents on risk of breast cancer should enrol postmenopausal women.

Source: The Lancet, Vol. 360, October 2002.

Toxic effects of cadmium – a study of low dose inhalation exposure in the guinea pig

Inhalation is the most common occupational and environmental exposure of cadmium (Cd) in the general population. However, when Cd exposure occurs, it tends to be at a very low level, close to or lower than the threshold limit value (TLV) of 50 µg/m^3. Unfortunately, many animal studies on Cd placental transfer and its distribution in the maternal-fetal system have used relatively high doses and exposure routes (ex: single intravenous injection of 1.25 mg Cd_2 or subcutaneous injection of 40 µmol/kg $CdCl_2$) other than inhalation.

A recent study of low dose inhalation exposure of Cd has used the guinea pig as the test animal since guinea pigs, compared to other test animals, have a relatively long gestation period and their placenta is largely hemo monochorial like the human placenta.

During pregnancy, the placenta behaves as a very active transporter of essential elements like calcium, copper, zinc and iron to the developing fetus. Low level Cd exposure can interfere with normal placental functions by reducing the transplacental transport of these essential elements to the fetus and thus inducing developmental abnormalities, anemia, and fetal growth retardation.

Human studies on Cd placental transfer using perfused isolated placenta have provided important data on the toxic effects of Cd and its mechanism of transfer, but failed to account for maternal metabolism of this metal during pregnancy.

Now a Canadian study has succeeded in characterizing the precise maternal-fetal distribution of Cd in the pregnant guinea pig following a low dose by inhalation exposure. The study found that the exposure of pregnant guinea pigs to low-level of Cd (53.2 $\pm$ 4.6 µg Cd/m^3) by inhalation during the late stages of gestation led to a transfer from the mother through the placenta and an important deposition of Cd was observed in the fetal brain, liver, and, to a smaller extent, heart. In this context, it was demonstrated that the Cd inhalation by pregnant mothers could have an important effect on the ion deposition in newborn. Future experiments will be needed to elucidate whether the placental transport and fetal distribution of Cd would have been the same at the earlier stages of gestation and also how this distribution would evolve after birth. The treatment did not induce placental MT synthesis and consequently no placental Cd accumulation was observed but a maternal-fetal Cd gradient was generated and the placental calcium level was decreased. These findings confirmed the results of an earlier study both by the absence of MT induction and the inverse correlation between MT expression and Cd accumulation in fetal brain. These results therefore suggest that low level Cd such as 53.2$\pm$4.6 µg Cd/m^3 by inhalation (1 or 5 days period) can interfere with maternal-fetal calcium metabolism even though the placenta still acts as a partial barrier to Cd transfer.

Source: Toxicology Letters 129, No. 3, March 2002.

Study of tumour initiation and promotion potential of cypermethrin on mouse skin

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epidermal cells for the development of skin tumours. It was noted that a single topical application of CYM was found sufficient to initiate the tumourigenesis, and multiple applications of the same were able to induce the tumours at a much higher rate. This difference in tumour initiating potential following single or multiple doses of pesticides is consistent with earlier reports with other pesticides like deltamethrin and quinolphos in two-stage mouse skin model of carcinogenesis. The tumour initiating property of CYM observed in the present study may be attributed to its ability to interact with DNA and damage its structure. Such interactions are critical for the initiation of cells to transform into neoplastic cells. CYM exposure is also reported to induce the frequency of well established markers of genotoxicity such as chromosomal aberrations and micronuclei formation. Commercial formulations of CYM are reported to cause *in vivo* induction of sister chromatid exchange in mouse bone marrow cells.

The results of the present investigation show that CYM, a commonly used synthetic pyrethroid, posseses both tumour initiating and tumour promoting potential along with complete carcinogenic potential in long term *in vivo* carcinogenicity assays on mouse skin. However, further studies are required to provide sufficient evidence, from the regulatory toxicology point of view, for the carcinogenic risk associated with CYM exposure.

Source: Cancer Letters 182, No. 1, August 2002.

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