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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".

The Chem HelpDesk: a joint initiative of the Chulabhorn Research Institute (CRI) and the World Health Organization Regional Office for South-East Asia (WHO SEARO)

The Regional Chemical Help Desk, or Chem HelpDesk, is a joint initiative between WHO SEARO and CRI, through the WHO Collaborating Center for Capacity Building and Research in Environmental Health Science. The main aim is to further empower countries in the SEA Region to manage the import, manufacture and processing, storage, distribution, transport, use, recycling and disposal of chemicals, in ways that minimize significant adverse impacts on the environment and human health. This is done through providing basic cost-free advice on technical questions, sources of expertise, policy guidance, capacity building opportunities, guidelines and funding related to chemical safety and chemicals management through a website (http://www.chemhelpdesk.org), where general information related to chemical safety and links to additional resources are also provided. The Chem HelpDesk provides advice in (a) toxicology/ecotoxicology, (b) international programs/activities related to chemical safety and chemicals management, (c) funding opportunities, (d) best practices related to chemical safety/ chemicals management, (e) national and international opportunities for collaboration, (f) multilateral environmental agreements (MEAs), and (g) enhancing sustainability of capacity for chemicals management, through international experts who are part of a Community of Practice.

The Chem HelpDesk recently hosted the International Workshop to Strengthen the Capacities for Sound Chemicals Management in SEA Region on 24 – 27 May 2011 which was attended by 23 delegates from the Ministries of Health and the Environment from Bhutan, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, and Timor Leste. Delegates from WHO country offices in India and Thailand, as well as resource persons from WHO Headquarters, the WHO South-East Asia Regional Office, the Strategic Approach to International Chemicals Management (SAICM), the WHO collaborating Centre for Public Health Management of Chemical Incidents (University of Wales Institute, Cardiff) and the WHO Collaborating Centre for Capacity

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The Chem HelpDesk: a joint initiative of the Chulabhorn Research Institute (CRI) and the World

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Building and Research in Environmental Health Science (CRI) also attended.

The workshop was officially opened by Dr. *Khunying* Mathuros Ruchirawat, Vice-President for Research and Academic Affairs, CRI, and the opening remarks were delivered by Dr. Maureen Birmingham (WR Thailand), with the introduction of participants by Dr. Salma Burton, Regional Adviser-Occupational Health, WHO SEARO. Delegates also introduced themselves, highlighting the pressing issues related to chemical safety and chemicals management in the countries they represented.

The objectives of the workshop were to promote and strengthen the role of public health for the sound management of chemicals focusing on the recently developed WHO Human Health Risk Assessment Toolkit and the use of the Chem HelpDesk. The workshop built on CRI's collaboration with WHO, as well as on work at the WHO Collaborating Centre in Cardiff, Wales on development of WHO training and teaching material for the public health management of chemical incidents, and the important work already initiated on the WHO Risk Assessment Toolkit, with examples of how the toolkit is used.

A further highlight of the workshop was the presentation of case studies by international resource persons on public health and chemical incidents, as well as the training provided on using the Chem HelpDesk. Delegates participated in group discussions to prioritize chemical safety issues in the region, and provided input on how to maximize the usefulness of the Chem HelpDesk weblog and question and answer service in addressing these issues.

This is one of the first workshops of its kind, bringing together delegates from the ministries of health and the environment from countries in the region to discuss issues related to chemical safety and chemicals management. The delegates had the opportunity to exchange information and experiences from their own countries, including needs and possible solutions. They also had the chance to familiarize themselves with some of the international tools available to assist them in their efforts to address chemical safety issues in their respective countries.

ASSOCIATIONS OF LOW-LEVEL URINE CADMIUM WITH KIDNEY FUNCTION IN LEAD WORKERS: A KOREAN STUDY

Low-level, environmental cadmium exposure, resulting in urinary cadmium <2.0 µg/g creatinine, is widespread. Similar to lead, cadmium is a kidney proximal tubular toxicant that accumulates in the body resulting in chronic endogenous exposure. A known cause of chronic kidney disease in the occupational setting, recent data indicate nephrotoxicity at lower levels of exposure. Furthermore, in a recent US general population analysis, participants with higher levels of both blood lead and cadmium had increased risk of an estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m^2 compared to those with lower levels of both metals. Thus, environmental cadmium co-exposure may contribute to nephrotoxicity in lead workers. To address this hypothesis, researchers performed a cross-sectional analysis examining associations between urine cadmium, a measure of cumulative dose, and kidney function in 712 current and former lead workers in the Republic of Korea.

Researchers evaluated associations of urine cadmium, a measure of cumulative dose, with 4 glomerular filtration measures and N-acetyl-β-D-glucosaminidase (NAG) in the cohort. Recent and cumulative lead doses were assessed via blood and tibia lead, respectively.

The results revealed that in 712 lead workers, urine cadmium was positively correlated with tibia lead and age but negatively correlated with blood lead. However, when examined by worker status, urine cadmium remained associated with age in all three groups but was only correlated with the lead biomarkers in younger, current workers; both associations were positive. After adjustment for age, sex, body mass index, urine creatinine, smoking, alcohol, education, annual income, diastolic blood pressure, current or former lead worker job status, new or returning study participant, and blood and tibia lead, higher ln-urine cadmium was associated with higher calculated creatinine clearance, eGFR and ln-NAG but lower serum creatinine.

A number of hypotheses for the paradoxical associations (higher urine cadmium with lower serum creatinine and higher glomerular filtration) observed in these data must be considered. Given the similarities between lead and cadmium, it is possible that these associations represent cadmium-induced hyperfiltration.

These unexpected associations were present in participants in the highest as well as the lowest eGFR tertiles and remained even in former workers in whom lead-related hyperfiltration was not apparent. Potential explanations for these results include a normal physiological response in which renal filtration affects urine cadmium levels, the impact of adjustment for urine dilution with creatinine in kidney outcome models, and cadmium-related hyperfiltration. Additional research is required to determine which of these hypotheses is involved; analyses using specific gravity to adjust for urine dilution, cystatin C outcomes, and other metals to assess the potential impact of metal protein binding would be very helpful as would analysis of prospective data. These associations have important implications for cadmium risk assessment related to kidney outcomes but may also have relevance for any toxicant research involving associations between urine biomarkers and kidney outcomes.

Source: Occupational and Environmental Medicine, Vol. 68, No. 4, Pages 250-256, April 2011.

Cytogenetic Damage in Chronic Arsenic-exposed Individuals

Chronic arsenic exposure through contaminated drinking water is a major environmental health issue. Chronic arsenic exposure is known to exert its toxic effects by a variety of mechanisms, of which generation of reactive oxygen species (ROS) is one of the most important. A high level of ROS, in turn, leads to DNA damage that might ultimately culminate in cancer. In order to keep the level of ROS in balance, an array of enzymes is present, of which catalase (CAT) and myeloperoxidase (MPO) are important members. Hence, this study, sets out to determine the activities of these two enzymes in the sera and chromosomal aberrations (CA) in peripheral blood lymphocytes in individuals exposed and unexposed to arsenic in drinking water. Arsenic in drinking water and in urine was used as a measure of exposure.

In addition to its well known ability to induce a variety of cancers, arsenic exposure also gives rise to a plethora of precancerous and non-cancerous dermatological symptoms. However, these symptoms develop long after the initial exposure, sometimes requiring more than 10 years of chronic exposure. In addition, chronically exposed individuals develop a wide variety of non-dermatological diseases, which might appear much earlier than the development of classical dermatological symptoms. Thus, exposed individuals devoid of arsenic-induced skin lesions are at higher risk of developing non-dermatological symptoms. So, in addition to the classic dermatological biomarkers of chronic arsenic toxicity, novel biomarkers which will enable researchers to predict impending disease are needed.

Several mechanisms have been proposed to explain the mechanism of arsenic-induced toxicity and carcinogenicity. An ever accumulating body of evidence demonstrates that generation of ROS is one of the paramount mechanisms behind chronic arsenic toxicity and subsequent carcinogenicity. It has been shown that arsenic exposure leads to a rapid production of superoxide radicals in the system and also extracellular H_2O_2. Furthermore, during metabolism, arsenic can give rise to reactive intermediary products, such as $(CH_3)_2AsOO^{\bullet}$ and reactive byproducts like superoxide radicals.

Depending on the level of the ROS generated, they can give rise to toxic and subsequently carcinogenic outcomes in a variety of ways. Usually, at low doses, ROS induce abnormal gene expression patterns by acting as second messengers, whereas at higher doses, ROS can directly cause cellular death through oxidative damage. Another potent mechanism by which ROS induce their toxic effect is the generation of DNA damage. Arsenic induces DNA adducts through calcium-mediated production of peroxynitrite, hypochlorous acid and hydroxyl radicals. Also, it has been shown that chronic arsenic exposure gives rise to oxidative DNA adducts like 8-hydroxy-2-deoxyguanosine (8-OHdG).

It has been speculated that such damage to DNA in the tumor suppressor genes or protooncogenes might lead to the initiation of cancer.

Cells have an arsenal of enzymes which keep ROS levels in balance. CAT and MPO are two such opposite acting enzymes, which help in keeping the level of ROS in check. Previous studies have used CAT to show that it can alleviate the toxic effects of chronic arsenic exposure on DNA damage. However, no previous study has looked at the effect of chronic arsenic exposure on the activities of serum CAT and serum MPO in human subjects. As the level of H_2O_2 increases in the system due to arsenic exposure, researchers expect that the activity levels of CAT will be induced by the increase in substrate concentration. Similarly, for MPO as well, researchers expect a higher activity level with the increase in its substrate (H_2O_2) concentration. The results are consistent with this hypothesis. Researchers find that activities of both these enzymes in serum are significantly increased in subjects chronically exposed to arsenic. Also, it is interesting to note that there exists a moderate positive correlation between arsenic concentration in urine with specific activity levels of serum CAT and serum MPO. The correlation, however, was not significant with arsenic content in drinking water. This is not an anomalous observation though, because urine arsenic represents body burden and drinking water arsenic merely the exposure. In order to strengthen the findings, researchers also studied induction of DNA damage in exposed and unexposed individuals inferred from CA analysis. Since individuals chronically exposed to arsenic have a higher amount of ROS in the system, researchers expect that they will have a greater amount of DNA damage as well. The results of the present study demonstrate that indeed, the exposed individuals have a significantly higher CA/cell as also % aberrant cells consistent with higher DNA damage.

In conclusion, it can be said that chronic arsenic exposure increases the activity of both serum CAT and serum MPO as a consequence of increased ROS. This elevated ROS, and also its active byproducts, subsequently cause elevated amounts of DNA damage reflected in high incidence of CA. It is also interesting to speculate that the serum activity levels of these enzymes might be used as putative biomarkers to detect the early effects of arsenic exposure in conjunction with other parameters like water and urinary arsenic content. The observation of a significant increase in activities even at low levels of chronic arsenic exposure (>10 to ≤100 µg/water arsenic concentration; >50 to ≤200 µg/L urine arsenic concentration) indicates that these are early events in response to chronic arsenic exposure. Thus, activity levels of these enzymes in the serum could act as biomarkers of impending disease from chronic arsenic exposure, much before the appearance of typical dermatological symptoms, which are considered to be the hallmarks of arsenic toxicity.

Source: Toxicology and Applied Pharmacology, Vol. 249, Issue 1, Pages 47-54, November 2010.

NEUROBEHAVIORAL EFFECTS OF LONG-TERM EXPOSURE TO PESTICIDES: RESULTS FROM THE 4-YEAR FOLLOW-UP OF THE PHYTONER STUDY

There is growing evidence that pesticides may harm humans and cause cancers and neurological diseases and have reproductive effects.

However, it is still controversial whether long-term neuropsychological sequelae occur and if permanent abnormalities follow acute toxic episodes. Epidemiological data are also very limited on the long-term effects of chronic exposure without acute symptoms, although some studies have demonstrated lower cognitive performances in subjects chronically exposed to pesticides. Regarding acute effects, most studies have focused on cholinesterase inhibitors. The question of long-term disturbances such as neurodegenerative diseases can only be answered by follow-up studies of exposed populations. In 1997, a cohort was recruited from among French vineyard workers for a study of the link between long-term pesticide exposure and neurobehavioral impairment. The first phase of this study demonstrated lower neuropsychological performances in people directly or indirectly exposed to pesticides.

929 workers affiliated to the health insurance system for farmers in the Bordeaux area of south-western France were enrolled in the study in 1997-1998. They were contacted for a first follow-up in 2001-2003. Participants completed a questionnaire and nine neurobehavioral tests. They were classified according to their life-long pesticide exposure, as directly exposed, indirectly exposed or non-exposed. Educational level, age, sex, alcohol consumption, smoking, psychotropic drug use and depressive symptoms were taken into account in the analysis.

614 subjects were available for investigation at follow-up. Follow-up analysis confirmed that the risk of obtaining a low performance on the tests was higher in exposed subjects, with ORs ranging from 1.35 to 5.60. Evolution of performances over the follow-up period demonstrated that exposed subjects had the worst decreases in performance. The risk of having a two-point lower score on the Mini-Mental State Examination was 2.15 in exposed subjects.

In the present study subjects were categorized into groups of exposure from information provided in detailed job calendars including history of treatment tasks. It remains questionable whether indirectly exposed subjects in contact with treated plants really experienced lower cumulative levels than those directly exposed through treatment tasks, as re-entry tasks in vineyards are carried out on more days per year than treatment tasks, especially since the impact on cognitive effects did not differ much between these two categories of subjects.

The prospective design of this study demonstrated that the difference in performances between the exposed and non-exposed subjects was sustained. In some tests, the decrease in performances appeared significantly worse in exposed workers, and was even worse if they had better performances at baseline. It should be underlined that some subjects, mostly those who were non-exposed, also had better results at follow-up than at baseline, which might be attributable to the well-known effect of practice when tests are repeated.

The data suggest that the effects observed cannot be fully explained by acute exposure. Indeed, low performances were not associated with the reporting of acute poisoning, taking the tests during the treatment season did not influence performances, and about half of the subjects were no longer exposed at the time of interview. Even taking major confounders into account, researchers cannot definitely rule out the possible role of suspected (solvents, metals, etc) or as yet unidentified risk factors in the neurobehavioral effects observed.

The analysis did not focus on specific pesticides. Indeed, a pilot stage revealed that workers did not know the names of the pesticides they were using, a situation partly explained by the fact that they were not in charge of purchasing them. Moreover, wine production requires many treatments, especially against various fungi. Considering that the oldest farmers started their occupational exposure in the 1970s and that latency is important, pesticides used in vineyards during the 1970s and 1980s are of primary concern for the effects the researchers observed. During that period, the most probable fungicides used were dithiocarbamates, phtalimides, dicarboximides, triazoles and inorganic substances (copper, sulphate, arsenic) with, to a lesser extent, insecticides (organophosphates, organochlorines and carbamates) and some herbicides (triazines or sulfamides). To date, most studies on the neurological impact of pesticides have examined organophosphates and carbamates, whose neurotoxicology has been largely elucidated. Research in animal models recently underlined that cholinesterase inhibitors are not the only pesticides likely to produce long-term neurological effects in animals. Overall, 13 of the 16 animal studies addressing cognitive impairment demonstrated a positive association with pesticide exposure.

The mild impairment observed raises the question of the potentially higher risks of injury in this population and also of possible evolution towards neurodegenerative diseases such as Alzheimer's disease or other dementias.

Source: Occupational and Environmental Medicine, Vol. 68, No. 2, Pages 108-115, February 2011.

MATERNAL EXPOSURE TO AMBIENT BENZENE LINKED TO SPINA BIFIDA IN INFANTS

Occupational exposure to hazardous air pollutants such as benzene has been linked in some studies to neural tube defects (NTDs), yet to date no one had studied whether exposure to ambient levels of benzene may similarly lead to adverse outcomes. A new study now reveals a positive association between exposure to ambient benzene in outdoor air and increased prevalence of spina bifida.

NTDs are a common type of birth defect. They arise when the neural tube fails to close during fetal development, leading to spina bifida (incomplete spinal column formation) or anencephaly (incomplete brain and skull formation). Both genetic and environmental factors, particularly inadequate folic acid intake, appear to play a role in NTDs.

This study was conducted in Texas, a state that ranks number one in the United States for benzene levels in ambient air and accounts for 48% of all benzene emissions in the nation.

Data on live births, stillbirths, and electively terminated fetuses with NTDs (spina bifida and anencephaly) delivered between 1 January 1999 and 31 December 2004 were obtained from the Texas Birth Defects Registry (*n* = 1,108). The registry is a population-based, active surveillance system that has monitored births, fetal deaths, and terminations throughout the state since 1999. Researchers selected a stratified random sample of unaffected live births delivered in Texas between 1 January 1999 and 31 December 2004 as the control group, using a ratio of four controls to one case. Controls were frequency matched to cases by year of birth because of the decreasing birth prevalence of NTDs over time. This yielded a group of 4,132 controls.

Researchers found a significant association between the prevalence of spina bifida in offspring and maternal exposure to ambient levels of benzene as estimated from the 1999 U.S. Environmental Protection Agency's Assessment System for Population Exposure Nationwide (ASPEN) model. The association was greatest for those in the highest exposure group. Positive associations between benzene and spina bifida were also observed in lower exposure categories; however, there was no monotonic dose-response relationship. The finding that the risk of having a spina bifida-affected infant more than doubled for mothers living in census tracts with estimated benzene levels of ±3 μg/m^3 is in keeping with a report classifying individuals living in areas with benzene levels >3.4 μg/m^3 as being at the greatest risk for adverse health effects. There were also associations with toluene, ethylbenzene, and xylene and between benzene, toluene, ethylbenzene, and xylenes (BTEX) and anencephaly; however, these associations were not statistically significant.

The association between benzene levels and spina bifida appears to be nonlinear. This is supported by studies reporting nonlinear associations between personal exposure to benzene and various biomarkers (i.e., urinary metabolites and albumin adducts) of exposure using data collected on occupationally and environmentally exposed individuals, whereby exposure-metabolite curves became steeper at higher exposure levels.

Despite the strong correlations between the BTEX compounds, a significant association with spina bifida was seen only with benzene.

Benzene is known to cross the placenta and has been found in cord blood at levels equal to or higher than maternal blood. Moreover, benzene can lead to genetic toxicity by covalently binding to DNA and forming DNA adducts, which, if not repaired, disrupt the micro-environment of the cell, leading to inhibition of important enzymes, cell death, and alteration of other cells. If this occurs during the critical window of development, the complex cellular processes involved in neurulation (e.g., folate metabolism, cell proliferation, cellular adhesion, and vascular development) may be disturbed, resulting in NTDs.

Oxidative stress could also play a role in the teratogenic effect of benzene. Reactive oxygen species (ROS) formed after benzene exposure lead to DNA strand breakage and fragmentation leading to cell mutation.

A potential limitation of this study is related to the exposure assessment, which relied on modeled predictions of ambient air levels of BTEX (i.e. the ASPEN model) and this may have resulted in misclassification.

However, strengths of the study include the use of a population-based birth defects registry that employs an active surveillance system to ascertain cases throughout the state of Texas. This should limit the potential for selection bias. Furthermore, the Texas Birth Defects Registry includes information on pregnancy terminations, reducing any potential bias due to the exclusion of these cases. An additional strength was the use of a relatively small (census tract-level) measure of exposure. Using larger geographic units to estimate exposure (e.g., counties) may not capture the spatial variability of benzene. Furthermore, separate analyses were conducted for spina bifida and anencephaly, as opposed to combining the groups into a single phenotype. This is important, as the effects of some exposures appear to be heterogeneous across the subtypes of NTDs.

This study provides the first assessment of the relationship between maternal exposure to ambient levels of BTEX and the prevalence of NTDs in offspring. The analyses suggest that maternal exposure to ambient levels of benzene is associated with the prevalence of spina bifida among offspring. Researchers believe that future investigations of air pollutants and NTDs should include additional measures of exposure (e.g., air pollutant monitoring and biomarker data) and additional covariate information (e.g., genotypes and nutrient status).

Source: Environmental Health Perspectives, Vol. 119, No. 3, Pages 397-402, March 2011.

Blood Lead Levels as a Cause of Preterm Labor: A Study Conducted in Three Teaching Hospitals in Tehran

During pregnancy, long-term fetal exposure to lead via the mother causes lead accumulation in fetal tissues and may result in irreversible damage. Studies have shown that maternal blood lead levels ≤10 µg/dl may cause complications during pregnancy, including increased risk of pregnancy hypertension, reduced length of gestation, miscarriage, spontaneous abortion and preterm delivery. Recently, adverse pregnancy outcomes have been reported even at mean blood lead levels of <5 µg/dl. In addition to exogenous lead exposure, lead in the bone can be a potential endogenous source for increasing blood lead concentrations in previously exposed women. This discharged lead can freely cross the placenta and affect the fetus.

Preterm labor can cause perinatal morbidity and mortality and long-term handicap in surviving infants. It may be induced by many factors, including gestational hypertension, multiple pregnancy, intrauterine growth restriction, maternal stress, heavy physical work and smoking. Environmental factors combined with inherent genetic susceptibility may contribute to an increased risk of preterm labor in some women. The incidence of preterm birth in most countries is less than 10% of live births, but, in both developed and developing countries, this rate has tended to rise in recent decades. In Iran the frequencies of reported preterm delivery ranges from 3% to 39%.

Previous reports on the effects of low levels of lead on pregnancy outcome have investigated the pathways of exposure, duration of exposure, and individual differences among subjects. A recent study aims to clarify the effects of low levels of blood lead measured in early pregnancy and at preterm delivery in apparently healthy women and is part of a longitudinal study project which began in October 2006 in three teaching hospitals in Tehran, Iran.

Blood samples were collected from 348 singleton pregnant women, aged 16-35 years, during the first trimester of pregnancy (8-12 weeks) for lead measurement by inductively coupled plasma-mass spectrometry. Subjects were followed up and divided into two groups (preterm and full-term deliveries) according to duration of gestation.

The results revealed blood lead level was significantly higher in mothers who delivered preterm babies than in those who delivered full-term babies. Logistic regression analysis demonstrated a significant association between increased blood lead levels and risk of preterm labor.

These results support previous findings of adverse pregnancy outcomes at blood lead levels lower than the currently 'acceptable' levels, although this study may be the first to attribute preterm deliveries to low levels of blood lead (mean <5 µg/dl). On the other hand, it is possible that in the present study blood lead levels may serve as a proxy for some other unmeasured factor responsible for the increased risk of premature delivery (such as an underlying inflammatory state causing premature delivery as well as increased bone resumption resulting in increased blood lead). As few studies have focused on associations between human blood lead concentrations and preterm birth, the results of the current study should be considered by future studies.

Source: Occupational and Environmental Medicine, Vol. 68, No. 3, Pages 231-234, March 2011.

Uptake and Cytotoxicity of Chitosan Nanoparticles in Human Liver Cells

Despite extensive research into the biomedical and pharmaceutical applications of nanoparticles, and the liver being the main detoxifying organ in the human body, there are few studies delineating the hepatotoxicity of nanoparticles. Now a new study has been conducted of the biological interactions between liver cells and chitosan nanoparticles, which have been widely recognised as biocompatible.

The hepatic cytotoxicity profile of chitosan nanoparticles was evaluated in this study in human liver progenitor cells with corresponding chitosan molecules as control. The nanoparticles were less cytoadhesive than the chitosan molecules, but were rapidly internalised by the bi-potential human liver (BHAL) cells, a human liver cell line derived from non-tumorous tissues. Uptake and cytoadhesion was well-correlated to the zeta potential and size of the chitosan nanoparticles and molecules *in situ*. The internalised nanoparticles caused a reduction in cell viability and proliferation, while the extracellularly associated chitosan molecules appeared to promote cell proliferation. BHAL cells showed poor cell membrane integrity after exposure for 4 h to chitosan nanoparticles at concentrations ≥0.5% w/v, which correlated to a higher leakage of alanine transaminase from the cells into the extracellular space. Both the chitosan molecules and nanoparticles induced CYP3A4-mediated activity in the BHAL cells, but the chitosan molecules exhibited a concentration-independent effect while the nanoparticles showed a concentration-dependent effect within the concentration range of 0.01 to 1%. These results are again in agreement with the cellular internalisation data of the nanoparticles and molecules. The increase in CYP3A4 activity illustrates a possible defence mechanism. Electron microscopy revealed significant damage in the nucleus and cytoplasm following exposure to the chitosan nanoparticles that were suggestive of necrotic cell death. Hence drug delivery strategies using chitosan nanoparticles as a vehicle need to consider its adverse effect on an important cell which is often induced to proliferate in chronic liver disease.

Source: Toxicology and Applied Pharmacology, Vol. 249, Issue 2, Pages 148-157, December 2010.

Road Traffic and Stroke: A Danish Study

Increasing noise from traffic occurs in parallel with urbanization. Acute exposure to noise is believed to activate the sympathetic and endocrine systems, thereby causing changes in blood pressure and heart rate and release of stress hormones. Furthermore, exposure to noise during the night at normal urban levels has been associated with sleep disturbances.

Persistent exposure to noise is believed to increase the risk of cardiovascular disorders. An overview in 2006 of 61 epidemiological studies of the effects of exposure to transport noise (road, air, and rail) on cardiovascular health showed associations with hypertension and ischaemic heart disease in adults. Recently, a meta-analysis indicated that the risk for myocardial infarction with road traffic noise increased in a dose-effect manner; this finding was supported by those of a case-control study that, as the first study of its kind, adjusted for exposure to air pollution.

Stroke is a major cause of disability and death worldwide. There has been no investigation of the relation between exposure to transport noise and risk for stroke, although some of the suspected effects of noise, e.g. increased blood pressure, are associated with risk for stroke. One study of the relation between exposure to road traffic noise and overall cerebrovascular mortality showed no association.

The aim of the present study was to investigate the association between exposure to transport noise and risk for stroke in a cohort after adjustment for air pollution and other important risk factors for stroke.

In a population-based cohort of 57,053 people, researchers identified 1,881 cases of first-ever stroke in a national hospital register between 1993-1997 and 2006. Exposure to road traffic noise and air pollution during the same period was estimated for all cohort members from residential address history. Associations between exposure to road traffic noise and stroke incidence were analysed in a Cox regression model with stratification for gender and calendar-year and adjustment for air pollution and other potential confounders. An incidence rate ratio (IRR) of 1.14 for stroke per 10 dB higher level of road traffic noise (L_{den}) was found. There was a statistically significant interaction with age, with a strong association between road traffic noise and stroke among cases over 64.5 years (IRR: 1.27) and no association for those under 64.5 years (IRR: 1.02).

In this study, residential exposure to road traffic noise was associated with risk for stroke, with a 14% higher risk per 10 dB higher exposure to noise for all participants and a 27% higher risk per 10 dB higher exposure to noise for participants above 64.5 years.

This is the first study on the association between transport noise and risk for stroke, as previous studies on transport noise focused mainly on hypertension and ischaemic heart disease. Exposure to noise is suspected to cause hypertension and ischaemic heart disease through a stress response, with changes in stress hormones and blood pressure, which are also related to the risk for stroke. The results show that the risk for stroke increases in a dose-dependent manner at exposure levels >60 dB among the oldest participants. These results are in accordance with the results of a meta-analysis of case-control and cohort studies on road traffic noise and myocardial infarction, which showed that there appeared to be a dose-response relation starting at noise levels >60 dB. This value may therefore be a threshold with regard to both cerebro- and cardiovascular effects of road traffic noise.

Although one of the most important risk factors for stroke is high blood pressure, the association with road traffic noise persisted after adjustment for systolic and diastolic blood pressures and use of antihypertensive medicine, indicating that other pathways are involved in the effect of traffic noise on risk for stroke.

The relation between exposure to road traffic noise and risk for stroke was strongest among the oldest participants in the present study. Sleep disturbances can contribute to cerebro- and cardiovascular risks, leading to the hypothesis that nocturnal exposure to noise might be more harmful than daytime exposure. The sleep structure generally becomes more fragmented with age, and elderly people are thus more susceptible to sleep disturbances. This could explain why the association between road traffic noise and risk for stroke was mainly seen for the oldest participants. As exposure to road traffic noise during the night (L_n) was highly correlated with L_{den}, researchers could not separate the two effects.

The study indicated no association between risk for stroke and noise from railways and airports; however, the risk estimate for exposure to airport noise has a very wide confidence interval probably because <1% of the cohort was exposed. Furthermore, the calculations of railway noise were subject to some degree of uncertainty because of missing information on screening by buildings and noise screens. Thus, the possibility that these types of noise also affect the risk for stroke cannot be ruled out.

The present study shows a positive association between residential exposure to road traffic noise and risk for stroke in a general Danish population among people older than 64.5 years of age. As this is the first study of its kind, the results need to be confirmed by other studies before any conclusions can be drawn.

Source: European Heart Journal, Vol. 32, No. 6, Pages 737-744, March 2011.

INDICATIONS OF POSSIBLE BRAIN-TUMOR RISK IN MOBILE-PHONE STUDIES

Mobile-phone use has increased dramatically in most countries since its introduction in the early to mid 1980s. The expanding use of this technology has been accompanied by concerns about health and safety. In the late 1990s, several expert groups critically reviewed the evidence on health effects of low-level exposure to radiofrequency (RF) electromagnetic fields, and recommended research into the possible adverse health effects of mobile telephone use. As a result, a number of studies have been conducted, including a large 13-country collaborative study, Interphone, with over 2700 glioma and 2400 meningioma cases and their matched controls, which was recently published.

Studies on the health effects of mobile phones are very complex, and interpretation of the results necessitates understanding and careful consideration of various aspects including the timing of the study, the exposure variables of relevance and the influence of methodological limitations. Indeed, the results of studies to date, in particular those of the recently published Interphone international analyses, have been interpreted differently by various groups: some have taken them to suggest that mobile phones are safe, others that they cause tumors, while some have suggested that the limitations of the studies were such that no conclusion could be drawn.

Most published studies have found no increased risk (and in many instances even a decreased risk) associated with ever having used a mobile telephone. These studies, however, were conducted at a time when mobile communication was still a relatively new phenomenon with low levels of use compared with today. As an illustration, though the largest study, Interphone, started in 2000, the maximum duration of use among the study participants was about 12 years, and only 5 years had passed from the start of heavier use. For most known carcinogens, however, identification of increased risk of solid tumors (particularly brain tumors) has required long follow-up periods of subjects with substantial exposure. For example, while the atomic bombs were dropped on Hiroshima and Nagasaki in August 1945, an excess risk of solid tumors was reported in the survivors only in the 1960s, and no elevation in risk of brain tumors was noted for about 50 years.

The decision to conduct epidemiological studies of brain tumors in relation to mobile phones under these circumstances was based on the urgency of data regarding possible health effects of this widespread technology and the possibility that the effect of exposure could be seen relatively early after exposure based on the hypothesis that RF might act in the later stages of carcinogenesis.

Although no firm conclusion can be drawn at present, owing to methodological limitations, several studies have found suggestions of an increased risk of brain tumors in relatively long-term users. In Interphone, no such increase was seen in the main analyses; however, in a subanalysis where short-term users (instead of never users) were used as the reference category, an increased risk was seen among long-term users, with an indication of a trend for increasing risk with increasing time since start of use.

The findings in several studies of an increased risk for glioma among the highest users on the side of the head where the phone was used and, in Interphone, in the temporal lobe are important. These are the findings that would be expected if there was a risk, as these are the *a priori* relevant exposure variables.

While more studies are needed to confirm or refute these results, indications of an increased risk in high- and long-term users from Interphone and other studies are of concern. There are now more than 4 billion people, including children, using mobile phones. Even a small risk at the individual level could eventually result in a considerable number of tumors and become an important public-health issue. Simple and low-cost measures, such as the use of text messages, hands-free kits and/or the loud-speaker mode of the phone could substantially reduce exposure to the brain from mobile phones. Therefore, until definitive scientific answers are available, the adoption of such precautions, particularly among young people, is advisable.

Source: Occupational and Environmental Medicine, Vol. 68, Issue 3, Pages 169-171, March 2011.

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Correspondence should be addressed to:

ICEIT NEWSLETTER
Chulabhorn Research Institute
Office of Academic Affairs
Kamphaenge Phet 6 Road
Bangkok 10210, Thailand
Tel: +66 2 574 0615
Fax: +66 2 574 0616
CRI Homepage: <http://www.cri.or.th>

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