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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".

WHO – CRI ONGOING COLLABORATION ON REGIONAL CHEMICAL SAFETY

Official Visit of Professor Dr. Her Royal Highness Princess Chulabhorn Mahidol to the World Health Organization's Regional Office for South-East Asia, New Delhi, India

On February 14th, 2013, Professor Dr. Her Royal Highness Princess Chulabhorn Mahidol, President of the Chulabhorn Research Institute (CRI), paid an official visit to the World Health Organization Regional Office for South-East Asia (WHO SEARO) to review progress on collaborative activities between WHO SEARO and CRI, carried out under CRI's International Centre for Environmental Health and Toxicology (ICEHT), a WHO Collaborating Centre for Capacity Building and Research in Environmental Health Science and Toxicology since 2005.

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WHO – CRI ONGOING COLLABORATION...

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One ongoing collaborative activity is the development and use of an **Electronic Distance Learning Tool (eDLT) on Risk Assessment and Risk Management of Chemicals** in training at the regional level.

CRI has been involved in capacity building in the region, particularly in the areas of toxicology, chemical safety and risk assessment, for the past 20 years. Through out this time, and despite the large effort expended in this area, it is apparent that there is still a clear lack of critical mass in terms of qualified personnel in the area of risk assessment and risk management of chemicals. Thus, to build up this critical mass by, for example, addressing the major obstacles of the lack of time and financial resources to attend training courses in foreign countries, CRI and its collaborating partners developed an eDLT on Risk Assessment and Risk Management, which can be accessed from the user's own home or office and at the user's own convenience.

This eDLT is a web-based, interactive tool that was developed under a SAICM Quick Start Programme (QSP) project entitled, "Development of course materials and a distance learning tool for the assessment of risk from the use of chemicals to support SAICM's capacity building efforts in developing countries". The project was carried out by CRI as the implementing agency, in collaboration with the University of Ottawa, Canada, Utrecht University, the Netherlands and WHO's International Programme on Chemical Safety (WHO IPCS). The development of this eDLT was completed in early 2013.

Professor Dr. Her Royal Highness Princess Chulabhorn Mahidol officially launched the eDLT on Risk Assessment and Risk Management of Chemicals, at a specially organized ceremony at WHO SEARO on February 14th, 2013 as part of the official visit. **The eDLT can be accessed through a website developed specifically for it (http://www.chemDLT.com)**. This website provides background information regarding the project and the 8 modules of the eDLT, and is the access point to the eDLT for users who have been registered with CRI.

Another major collaborative activity is **capacity building in Environmental Health and Toxicology** to assist human resource development in the region.

CRI organizes several short-term training courses on an annual basis. These courses are open to participants, primarily from the Asia Pacific region, and are taught by international experts from world-renowned academic and research institutions with a wealth of teaching experience in the region.

In 2012, three training courses were organized at CRI: Principles of Toxicology, Environmental Toxicology, and Environmental and Health Risk Assessment and Management of Toxic Chemicals. WHO SEARO provided fellowships for 11 participants from the SEA region to attend the training course on risk assessment in December 2012. In 2013, in addition to the Environmental Toxicology and Environmental and Health Risk Assessment and Management of Toxic Chemicals courses, CRI will organize a new course on Occupational and Environmental Medicine, in collaboration with Mt. Sinai School of Medicine, a WHO Collaborating Centre in Children's Environmental Health. WHO SEARO will also be providing fellowships for participants in the SEA region to attend this course.

Those who are interested in applying for a fellowship can check the calendar of events at http://www.cri.or.th/en/ac_actcalendar.php.

Research in Environmental Health and Toxicology represents another major collaborative activity.

As a well-known and respected research institution in the international arena, including in the areas of environmental health and toxicology, CRI currently has on-going research in several areas, for example: (a) urban and indoor air pollution and potential health effects in traffic police, street vendors, and temple workers; (b) liver cancer and cholangiocarcinoma, and (c) health impacts of climate change. A key area of particular interest is how environmental exposures can impact on vulnerable groups such as children, with previous research at CRI related to traffic-related air pollution indicating that they may be particularly susceptible to health effects from exposures. CRI currently has collaborations with the National Institute of Occupational and Environmental Health, Vietnam (WHO Collaborating Centre for Occupational Health), Columbia University, and the Massachusetts Institute of Technology (MIT) in the area of the health impacts of arsenic. An additional area in which WHO SEARO will look into the possibility of collaborations with CRI is e-waste and children's environmental health.

Chemical safety is becoming an increasingly important issue in the region. However, there is an ever-widening gap between developed and developing countries in their respective capabilities for the sound management of chemicals. To address the issue, CRI and WHO SEARO jointly initiated a **Regional Chemical Help Desk, or Chem HelpDesk**, as another important area of collaboration.

The Chem HelpDesk provides basic cost-free advice on technical questions, sources of expertise, policy guidance, capacity building opportunities, guidelines and funding related to chemical safety through a weblog developed, operated and maintained by CRI and supported by a network of experts (http://www.chemhelpdesk.org). The key items of discussion at WHO SEARO were how to expand the service to a larger base of registered users, e.g. to include national SAICM focal points from the Asian region, as well as to coordinate with national poison centers in the SEA region to develop national chemical help desks that could be tailored to a country's specific needs, e.g. in their national languages. A regional workshop on chemical safety is scheduled for June 2013 at CRI, and will include a session on the Chem HelpDesk, including further discussions on the possibility of national poison centers in helping to address broader chemical safety needs of countries and providing a source of chemicals expertise and information.

SIGNING OF AGREEMENT FOR ACADEMIC EXCHANGE AND COOPERATION BETWEEN CHULABHORN RESEARCH INSTITUTE, CHULABHORN GRADUATE INSTITUTE AND NAGOYA UNIVERSITY

On February 22nd, 2013 an agreement was signed by Her Royal Highness Princess Chulabhorn, President, Chulabhorn Research Institute and the Council of the Chulabhorn Graduate Institute, Thailand and Professor Michinari Hamaguchi, President, Nagoya University, Japan.

The aim of this agreement is to develop academic exchange and cooperation in education and research between the participating institutions based upon the principles of respect for each other's independence and promotion of mutual benefit.

Under the terms of the agreement each institution may arrange for Faculty members and research staff to visit the other institution for purposes of teaching and research. Such collaboration will enable each institution to benefit from the other's expertise and create a broader vision in both research and teaching.

The agreement also provides for the exchange of students. Exchange students will undertake to comply with the requirements and respect the regulations and culture of the host institution.

The overall purpose of student exchanges is to promote cultural understanding and to forge lasting ties at the personal as well as institutional levels.

Effects of Environmental Cadmium Exposure on Liver Function in Adults

Cadmium is a metal widely used in many industries. Cadmium emissions to the air, water and soil have increased dramatically during the twentieth century. This metal is a well-known persistent environmental pollutant.

Once it has been absorbed by the human body, the biological half-life of cadmium is beyond 10 years. It has been reported that cadmium exposure in the population is associated with osteoporosis, renal dysfunction, diabetes, cancer, blood pressure and reproduction.

The greatest body accumulation of cadmium occurs in the liver and kidney. It has been well established that environmental exposure to cadmium may induce kidney dysfunction in the general population.

However, less attention has been paid to the possibility that cadmium exposure may also cause dysfunction in the liver. It has previously been shown in experimental animals that cadmium is toxic to the liver after repeated or even a single-dose administration. Most epidemiologic studies, to date, have reported that there are no significant associations. Overall, there is inconsistency in the observation among the positive results of animal studies and the negative results of epidemiological studies regarding the effects of cadmium exposure on liver function.

It has been reported that the mean blood concentration of cadmium among the Koreans (1.27 µg/l) is lower than that for the Japanese (2.13 µg/l), but higher than the levels for many other countries, such as in Germany (0.38 µg/l), Belgium (0.42 µg/l), Sweden (0.35 µg/l) and the USA (0.3 µg/l).

Researchers in the present study assumed that the data from a population with higher cadmium levels could provide a better opportunity to evaluate the possible effects on the liver.

This cross-sectional study evaluated adult participants without liver disease from the Korean National Health and Nutrition Examination Survey for 2008-2009. Multiple linear regression was conducted to investigate the association between blood cadmium concentration and the serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) adjusting for age, sex, body mass index and the amount of alcohol consumption.

The study found cadmium exposures are associated with an elevated liver enzyme level based on the data representative of the Korean adult population. Prevention of cadmium exposure, for instance, in cigarette smoking or environmental and occupational exposures, could reduce the potential for the development of preclinical liver dysfunction, which may have important implications for health policy and disease prevention.

Source: Occupational and Environmental Medicine, Vol. 70, Issue 4, Pages 268-273, April 2013.

Toxic Mechanisms of Cardiovascular System Injuries Induced by Ozone and Fine Particulate Matter

The pathophysiologic consequences of particulate matters and ozone exposure have been extensively studied in pulmonary systems, and it is clear that both of them can induce or exacerbate lung diseases in humans. In fact, extra-pulmonary and systemic functions could also be affected by these two air pollutants.

Epidemiologic studies have demonstrated that both fine particulate matters ($PM_{2.5}$) and ozone are associated with the increased incidence of cardiovascular morbidity and mortality in western populations. In Chinese populations, strong evidence was indicated that $PM_{2.5}$ caused significant increase of the total, cardiovascular and respiratory mortality. It is possible that pulmonary oxidant stress mediated by particulate matters and/or ozone exposure can induce downstream perturbations in the cardiovascular system due to the intricate association between pulmonary and cardiovascular systems. Despite the obvious adverse cardiovascular effects observed after exposure to $PM_{2.5}$, the mechanisms by which $PM_{2.5}$ affect cardiac functions remain unclear. Part of the potential mechanisms were suggested that, in short-term exposure to $PM_{2.5}$, an increase in arterial blood pressure within hours to days was triggered, and for long-term exposure, many of the pro-inflammatory/oxidative reactions, the vascular dysfunction and the imbalance of autonomic nervous system (ANS) control were instigated by $PM_{2.5}$ which may prompt the chronic development of obvious hypertension. For ozone pollutant, aspects of the mechanisms influencing cardiovascular system, increase of oxidative stress, activation of a considerable systemic inflammatory responses mediated by cytokines, modification of endothelial function and vascular vasomotricity, and alterations in autonomic control of cardiac frequency may be associated to ozone exposure.

In practice, people are usually exposed to multiple air pollutants during a limited time. Studies examining multi-exposures to ambient compounds may be more relevant for evaluating the risks of human health. However, the adverse cardiovascular health effects of co-pollutants have not been suitably investigated. Until now, only a few studies considered the effects of co-exposure to ozone and fine particles on cardiovascular impairments.

In order to understand the toxic mechanisms of cardiovascular system injuries induced by ambient $PM_{2.5}$ and/or ozone, a subacute toxicological animal experiment was designed. Wistar rats were exposed to inhalation of ozone and / or intratracheal instillation of ambient $PM_{2.5}$ twice a week for 3 continuous weeks. Heart rate (HR) and electrocardiogram (ECG) was monitored at approximately 24-h both after the 3rd exposure and the last (6th) exposure, and systolic blood pressure (SBP) was monitored at approximately 24-h after the 6th exposure. Biomarkers of systemic inflammation and injuries [C-reactive protein (CRP), interleukin-6 (IL-6), lactate dehydrogenase (LDH), and creatine kinase (CK)], heart oxidative stress [malondialdehyde (MDA), superoxide dismutase (SOD)] and endothelial function [endothelin-1 (ET-1) and vascular endothelial growth factor (VEGF)] were analyzed after the 6th exposure. Additionally, myocardial ultrastructural alterations were observed under transmission electron microscopy (TEM) for histopathological analyses.

Results showed that $PM_{2.5}$ alone exposure could trigger the significant increase of CRP, MDA, CK, ET-1 and SBP and decrease of heart rate variability (HRV), a marker of cardiac ANS function. Ozone alone exposure in rats did not show significant alterations in any indicators. Ozone plus $PM_{2.5}$ exposure, however, induced CRP, IL-6, CK, LDH and MDA increase, SOD and HRV decrease significantly in a dose-response way. Meanwhile, abnormal ECG types were monitored in rats exposed to $PM_{2.5}$ with and without ozone and obvious myocardial ultrastructural changes were observed by TEM. In conclusion, the study found $PM_{2.5}$ alone exposure could cause inflammation, endothelial function and ANS injuries, and ozone potentiated these effects induced by $PM_{2.5}$.

Source: Toxicology Letters, Vol. 217, Issue 1, Pages 23-33, February 2013.

THE EFFECT OF MIXTURES OF ORGANOPHOSPHATE AND CARBAMATE PESTICIDES ON ACETYLCHOLINESTERASE

Pesticides are used extensively in agriculture and many of these pesticides contaminate rivers and water sources through run-off. While pesticides may target a particular insect or pest, they are often also toxic to humans and animals while also suspected to be endocrine disruptors. The rapid detection of pesticides in the environment is therefore very important for protection of humans and animals who may consume such contaminated water.

Organophosphates (OPs) and carbamates (CPs) pesticides are designed to inhibit acetylcholinesterase (AChE), a ubiquitous enzyme that is responsible for the breakdown of acetylcholine into acetic acid and choline, controlling the transmission of nerve impulses. OPs inhibit AChE by the phosphorylation of the serine residue in the active site, whilst CPs carbamylate this residue.

Enzymatic detection methods using AChE are nonspecific for pesticides such as OPs and CPs and therefore detect total anticholinesterase activity. Although this may be useful as a screening method, identification of individual pesticides could be useful. Some studies have therefore explored the use of chemometrics for data analysis to identify individual pesticides in

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THE EFFECT OF MIXTURES OF ORGANOPHOSPHATE AND CARBAMATE PESTICIDES ON ACETYLCHOLINESTERASE

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mixtures. Artificial neural networks (ANNs) often form the basis of chemometrics and are mathematical models that model the functionality of the brain, thus are able to deal with non linear and imprecise data and have been used in several studies to identify individual pesticides in mixtures.

Therefore on the present study, researchers examined the effect of five different pesticides (carbaryl, carbofuran, parathion, demeton-S-methyl, and aldicarb) on AChE activity to determine whether combinations had an additive, synergistic, or antagonistic inhibitory effect. Results indicated that the mixtures had an additive inhibitory effect on AChE activity. The data from the assays of the mixtures were used to develop and train an ANN which was then utilized successfully for the identification of pesticides and their concentrations in mixtures. This study is significant because it evaluated mixtures of OPs and CPs where previous studies focused on either OPs or CPs. Previous studies have only examined up to three pesticides while this study evaluated mixtures of five pesticides simultaneously. This is also the first study where an ANN was able to utilize data from the inhibition of a single enzyme to differentiate five different pesticides and their concentrations from mixtures.

Future work should include the investigation of this method in complex matrices and the types of interferences that may occur in such matrices.

Source: Environmental Monitory and Assessment, Vol. 185, Issue 3, Pages 2315-2327, March 2013.

Pre- and Postnatal Impacts of Polybrominated Diphenyl Ether Exposures

Polybrominated diphenyl ether (PBDEs) flame retardant chemicals, used in the manufacture of furniture, infant products, and electronics, are ubiquitous in U.S. households. An unintended consequence of California's Technical Bulletin 117 (TB 117) a fire safety law promulgated in the 1970s which requires that furniture, baby, and other household products resist open flame – is that PBDE concentrations in California children are now among the highest measured worldwide.

The largest study to investigate the effects of human exposure to PBDE flame retardants reports evidence of impaired neurobehavioral development in connection to both prenatal and childhood exposures. Associations were greatest for attention, fine motor coordination, and cognition in school-age children.

The study focused on chemicals associated with pentaBDE, a mixture of PBDEs that was used in polyurethane foam padding in furniture and infant products manufactured before 2005. These flame retardants can be released into home environments throughout products' life spans, and children are disproportionately likely to be exposed to them through hand-to-mouth activity. PBDEs are chemically similar to polychlorinated biphenyls (PCBs), which are associated with similar neurodevelopmental impairments.

The new study included mothers and children participating in the ongoing CHAMACOS (Center for the Health Assessment of Mothers and Children of Salinas) cohort study, which in 1999 and 2000 recruited more than 600 pregnant women living in California's agricultural Salinas Valley. Most of the mothers were Mexican immigrants, and neurobehavioral assessments were conducted by bilingual psychometricians in the dominant language of 310 of the children when they were 5 years old and 323 of the children at age 7. PBDE exposures were estimated based on measurements of maternal blood serum collected during the pregnancies and child blood serum at age 7 years.

In their analysis, the researchers adjusted for other factors that might affect neurodevelopment and be correlated with exposure, including maternal exposures to lead, PCBs, and organophosphate pesticides; they also incorporated assessments from parents and teachers of children's attention, learning, and behavior. They found associations between maternal PBDE levels during pregnancy and evidence of deficits in children's attention, fine motor coordination, and cognitive functioning at both ages. The children's PBDE levels were associated with lower scores for full-scale IQ, particularly processing speed, verbal comprehension, and perceptual reasoning. The researchers also found that each 10-fold increase in the children's total measured PBDE levels was associated with at least 4.5 times higher odds of the child being rated by teachers as at least moderately hyperactive and impulsive.

This study's finding of significant associations of both maternal prenatal and childhood PBDE exposures with poorer attention, fine motor coordination, and cognition in early school-age children contributes to the growing evidence of adverse associations between PBDE exposure and children's neurobehavioral development. Although these results are of particular concern for California children, they are also relevant to other locations, many of which contain products manufactured to meet California's standards. With the phase-out of pentaBDE, other flame retardants have been used to achieve compliance with TB 117. Additional research is needed to determine the potential child health consequences of these new chemical flame retardants.

Source: Environmental Health Perspectives, Vol. 121, No. 2, Pages 257-262, February 2013.

A PROPOSED NOVEL REMEDIATION SYSTEM FOR WELL WATER CONTAMINATED BY ARSENIC AND IRON

It has been estimated that over 200 million people worldwide are exposed to highly toxic elements including arsenic from well drinking water. In fact, more than 25 million patients with arsenicosis have been reported in Bangladesh, where arsenic-mediated health disturbance in humans is the most serious in the world. This worldwide tragedy has been made even more serious by explosive increases in various carcinomas in patients with arsenicosis.

In order to solve this tragedy, it is essential to clarify toxic components including arsenic in drinking water and to develop a low-cost and high-performance remediation system for the components.

Many previous studies have provided evidence of arsenic as a carcinogen. Since skin melanosis and hyperkeratosis develop in patients with arsenicosis, skin is one of the target organs for arsenic. Bowen's disease (carcinoma *in situ*) and skin squamous cell carcinoma (SCC) are known as representative cancers derived from chronic exposure to arsenic.

Multistep carcinogenesis that proceeds through several processes including initiation, promotion, transformation, and progression has been proposed in arsenic-mediated carcinomas including skin cancer. Initiation is the first step of tumor development and is an irreversible process. Promotion is the step of clonal expansion of the initiated cells, resulting in the formation of benign tumors. Transformation is the step of change from benign tumors to malignant tumors. Cells in this step gain hyper-proliferative and anti-apoptotic characteristics, invasion activity, and anchorage-independent growth. Progression is the step to gain further invasive potential for distant metastasis and survival potential of anchorage-independent growth. Colony formation assay is a strong tool for analysis of anchorage-independent growth *in vitro*. Invasion assay is a method to evaluate cellular motility and invasion activity *in vitro*. Both of these assays are useful for evaluating the effect on transformation in untransformed cells and the effect on progression in transformed cells. Activities of c-SRC and ERK have been reported to be closely linked to both transformation and invasion.

It has been reported that well drinking water in cancer-prone areas of Bangladesh contains not only arsenic but also various toxic elements such as iron, manganese, uranium, lead, nickel, and chromium. Particularly, high levels of iron (>1,000 µg/L) have been found in well drinking water in cancer-prone areas. Previous studies showed that iron alone promotes all steps of carcinogenesis including initiation, promotion, transformation, and progression in skin cancer. Moreover, iron from inhaled fibers, such as asbestos, is responsible for their carcinogenicity. Iron also enhances benzo[a]pyrene-mediated carcinogenicity. These studies suggest not only carcinogenicity of iron itself but also enhanced carcinogenicity by coexposure to iron and another carcinogen. However, there have been no studies providing the direct evidence for modulated carcinogenicity by coexposure to arsenic and iron.

In this study, researchers examined the biological risk of coexposure to arsenic and iron after showing contamination of iron in addition to the investigation of arsenic in well drinking water in cancer-prone areas of Bangladesh. A novel method for remediating the elements was also developed.

The study was undertaken to clarify the carcinogenic effects of coexposure to arsenic and iron, anchorage-independent growth and invasion in human untransformed HaCaT and transformed A431 keratinocytes were examined. Since the mean ratio of arsenic and iron in well water was 1:10 in cancer-prone areas of Bangladesh, effects of 1 µM arsenic and 10 µM iron were investigated. Iron synergistically promoted arsenic-mediated anchorage-independent growth in untransformed and transformed keratinocytes. Iron additionally increased invasion in both types of keratinocytes. Activities of c-SRC and ERK that regulate anchorage-independent growth and invasion were synergistically enhanced in both types of keratinocytes. The results suggest that iron promotes arsenic-mediated transformation of untransformed keratinocytes and progression of transformed keratinocytes. A low-cost and high-performance adsorbent composed of a hydrotalcite-like compound for arsenic and iron was then developed. The adsorbent rapidly reduced concentrations of both elements from well drinking water in cancer-prone areas of Bangladesh to levels less than those in WHO health-based guidelines for drinking water. Thus, the study not only demonstrated for the first time increased carcinogenicity by coexposure to arsenic and iron but also proposed a novel remediation system for well drinking water.

Source: Archives of Toxicology, Vol. 87, Issue 3, Pages 439-447, March 2013.

MOLECULAR EFFECTS OF LOW LEVEL ACRYLAMIDE EXPOSURE

In April 2002 the Swedish National Food Agency and Stockholm University presented data demonstrating high concentrations of acrylamide in certain fried, baked and deep-fried foods. Since oral consumption of acrylamide induces tumors in animal experiments, this finding caused worldwide concern regarding human health.

Acrylamide is formed predominantly in carbohydrate-rich food during heat treatment (>120° C) as a result of the Maillard reaction between primarily the amino acid asparagine and a reducing sugar. A fraction of ingested acrylamide is transformed by the monooxygenase CYP2E1 to glycidamide, which is more reactive than acrylamide itself due to its epoxide structure. In the literature several hypothesized modes of action of acrylamide regarding tumor progression are discussed: (1) genotoxicity related to glycidamide formation; (2) endocrine effects and (3) epigenetic effects. It is assumed that at low doses the mutagenic glycidamide is more effective for the formation of tumors than the parent compound acrylamide. Glycidamide forms DNA adducts, induces mutations in *Salmonella*, and displays mutagenic as well as clastogenic properties in human cells.

For detoxification both acrylamide and glycidamide are conjugated with glutathione (GSH) producing water-soluble mercaptates which are excreted via the kidneys, and glycidamide is additionally inactivated by epoxide hydrolases. Several studies have demonstrated that acrylamide and/or glycidamide exposure can change gene expression. In testicular tissue of F344 rats, which were treated for 60 days with 8 mg acrylamide/kg body weight (bw)/day, the expression of several genes involved in oxidative stress and apoptosis were affected. In mice, which were exposed for 3-4 weeks to 500 mg/l acrylamide or 600 mg/l glycidamide dissolved in the drinking water, mitochondria related genes in the liver were influenced. Furthermore, it was shown that preconceptional paternal exposure of glycidamide (61 mg/kg bw/day for 8-12 weeks) to male mice affected embryonic gene expression.

An *in vitro* study demonstrated that acrylamide at a concentration of 1.25 and 2.50 mM can induce the cytochrome P450 enzymes CYP2E1 and CYP1A2 as well as glutathione S-transferase isozymes. However, in all these studies the acrylamide or glycidamide exposure was extremely high and the observed gene expression changes will therefore most probably not reflect the possible effects after low-dose acrylamide exposure by dietary intake. The average daily intake of acrylamide for adults (>18 years) in Europe is estimated to range between 0.3 and 1.1 µg/kg bw. However, one *in vitro* study analyzed gene expression changes after glycidamide exposure also at lower concentrations (0.001-1 mM) using a breast cancer cell line (MCF7).

In this study it is suggested that low concentrations of glycidamide elicit cytoprotective reactions whereas high doses can induce genes involved in tumor progression. So far gene expression data from low-dose exposure experiments with cell lines derived from other tissues are not available.

The finding that acrylamide is generated in a large number of commonly consumed food products has raised considerable concern about the possible health effects for the general public and several epidemiological studies have been undertaken to investigate the link between dietary acrylamide intake and the risk of several cancer types.

Among these analyses, some studies demonstrated a weak positive correlation between increased dietary acrylamide intake and an increased risk for postmenopausal endometrial and ovarian cancer. However, other studies could not find such an association. Therefore, in regard to the generally low-dose acrylamide exposure by dietary intake, the aim of this study was to analyze if treatment of ovary and endometrial cell lines and primary hepatocytes with glycidamide/acrylamide at low concentrations, could induce genes potentially responsible for the development or progression of ovary, endometrial and hepatocellular tumors. Moreover, molecular detoxification mechanisms should be identified.

The *in vitro* data from the present study suggest that low-dose glycidamide exposure promotes the elimination of the toxicant. Only exposure to high concentrations of glycidamide – exceeding the dietary exposure of the general population by far – is able to up-regulate genes with carcinogenic potential.

Source: Toxicology Letters, Vol. 217, Issue 2, Pages 111-120, February 2013.

ROAD TRAFFIC NOISE AND DIABETES

Noise is an environmental stressor that stimulates the body's sympathetic nervous system and the hypothalamus-pituitary-adrenal axis, leading to increased blood pressure, heart rate, and levels of the "stress hormone" cortisol.

Until now research on traffic noise has focused on cardiovascular effects, although given the putative mechanisms of action, traffic noise might also contribute to type 2 diabetes. First, excess of glucocorticoids, as seen in Cushing syndrome, have been found to inhibit insulin secretion by pancreatic β cells and reduce insulin sensitivity in liver, skeletal muscle, and adipose tissue, as well as increase the risk of diabetes. Second, experimental reduction in the duration or quality of sleep in human volunteers has been associated with alterations in glucose regulation including a drop in glucose tolerance, increased morning levels of glucose, and decreased levels of insulin and reduced insulin sensitivity. Slow-wave sleep, which is associated with inhibition of cortisol secretion, decreased sympathetic nervous system activity, increased vagal tone, and stimulation of growth hormone release, is especially important for glucose regulation. A 90% reduction in slow-wave sleep caused by acoustic stimuli has been associated with decreased glucose tolerance and reduced insulin sensitivity. Third, hormones responsible for appetite regulation have been found to be affected by sleep reduction, with decreased leptin levels and elevated ghrelin levels resulting in up-regulation of appetite, which in turn may result in higher body mass index (BMI) and an increased risk of diabetes.

The aim of the present study was to investigate the hypothesis that exposure to residential road traffic noise increases the risk of incident diabetes.

In the population-based Danish Diet, Cancer and Health cohort of 57,053 people 50-64 years of age at enrollment in 1993-1997, researchers identified 3,869 cases of incident diabetes in a national diabetes registry between enrollment and 2006. The mean follow-up time was 9.6 years. Present and historical residential addresses from 1988 through 2006 were identified using a national register, and exposure to road traffic noise was estimated for all addresses. Associations between exposure to road traffic noise and incident diabetes were analyzed in a Cox regression model.

The results revealed that a 10-dB higher level of average road traffic noise at diagnosis and during the 5 years preceding diagnosis was associated with an increased risk of incident diabetes, with incidence rate ratios (IRR) of 1.08 and 1.11, respectively, after adjusting for potential confounders including age, body mass index, waist circumference, education, air pollution (nitrogen oxides), and lifestyle characteristics. After applying a stricter definition of diabetes (2,752 cases), it was found IRRs of 1.11 and 1.14 per 10-dB increase in road traffic noise at diagnosis and during the 5 years preceding diagnosis, respectively.

The results also suggest that there was no association between road traffic noise and diabetes among participants with > 10 years of education, in contrast with participants who had less education. A possible explanation is that more educated participants may live in larger houses or flats than less educated participants, and therefore may be more likely to have the option to chose a bedroom oriented away from a busy street, resulting in lower exposure to road traffic noise during sleep and differential misclassification of exposure according to education. Another possible explanation is that the observed association between road traffic noise and diabetes among less-educated participants could reflect residual confounding by socioeconomic factors that were not accounted for in the analyses. The assumption that the highest educated were exposed to lower levels of traffic noise than the less-educated participants, combined with residual confounding by socioeconomic factors such as physical activity, could result in false positive associations between noise and diabetes among the lowest educated. On the other hand, differences in exposure to traffic noise according to socioeconomic status might not be pronounced because many highly educated people in Denmark live in central urban areas, evidenced by very high property prices in the inner cities of Copenhagen and Aarhus, with relatively high traffic noise.

In the present study it was estimated that there were only small differences in road traffic noise exposure according to education, which suggests that residual socioeconomic confounding is not a major problem in the present study. Residual confounding by dietary factors not accounted for might also be an issue, though adjusting for potential confounders related to socioeconomic status and diet, such as years of school attendance, BMI, physical activity, occupational status, and intake of fruit, vegetables, and saturated fat had little effect on estimated associations.

No association was found between exposure to railway noise and diabetes, consistent with previous studies reporting that road traffic noise is associated with more sleep disturbance than railway noise. However, exposure estimates for railway noise, which was classified in 5 dB categories for levels ≥ 60 dB only, were less accurate than estimates of road traffic noise exposure. Furthermore, in contrast to the road traffic noise model, the railway noise estimation included no information on screening by buildings.

This study provides further evidence that urban noise may adversely influence population health. A statistically significant positive association was found between long-term exposure to road traffic noise at the residence and the risk of incident diabetes. The results suggest that reducing population exposure to road traffic noise may improve health, and specifically reduce the risk of diabetes.

Source: Environmental Health Perspectives, Vol. 121, No. 2, Pages 217-222, February 2013.

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