CRI/ICEIT
NEWSLETTER

VOL. 20 NO. 3 – July 2010
ISSN 0858-2793
BANGKOK, THAILAND

Chulabhorn Research Institute

INTERNATIONAL CENTRE FOR ENVIRONMENTAL AND INDUSTRIAL TOXICOLOGY (ICEIT)

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AIR POLLUTION AND THE DEVELOPMENT OF CHILDHOOD ASTHMA

The prevalence of childhood asthma has generally increased worldwide in recent years, and although explanations for relatively rapid changes in prevalence are unknown, environmental factors, independently and jointly with genetic factors are thought to be responsible.

Although air pollution has been consistently shown to exacerbate existing asthma, there are few investigations of asthma onset and air pollution despite the hypothesized link with exposure to outdoor air pollution.

Earlier studies have generally relied on simple measures of traffic proximity and density to estimate exposure and have not found an association between air pollution and asthma incidence. More recent studies have used modeling approaches that provide high-resolution estimates of neighborhood-scale variations in air pollution. Several studies using this approach have observed increases in asthma incidence or asthma symptoms for children exposed to higher levels of traffic-related air pollution. However, not all such studies of this type have reported consistent associations.

Pre- and postbirth exposures to environmental tobacco smoke are independently associated with increased asthma incidence. Although air pollution exposures before 2-3 years of age appear to be most important for asthma development, there have been few studies of the effect of prebirth (or *in utero*) exposure.

Now in the first population-based birth cohort study to explore the relationship between ambient air pollution exposure and the risk of asthma incidence, researchers have examined the effect of *in utero* and first-year exposures to ambient air pollutants, estimated at the individual level, on the risk of asthma diagnosis in children up to 3 and 4 years of age. Pollutant exposures investigated were carbon monoxide (CO), nitrogen oxides [nitric oxide (NO) and nitrogen dioxide (NO_2)], particulate matter [$\leq$ 10 µm and $\leq$ 2.5 µm in aerodynamic diameter (PM_{10} and $PM_{2.5}$)], ozone (O_3), sulfur dioxide (SO_2), black carbon, woodsmoke, and proximity to roads and point sources.

The study cohort comprised all 1999 and 2000 births in southwestern British Columbia (BC) identified by linking administrative data sets from the BC Ministry of Health Services, the BC Vital Statistics Agency, and the BC Perinatal

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Adverse Health Effects of Fine Particulate Matter in Hypertensive and Non-Hypertensive Individuals

The adverse health effects of fine particulate matter, or $PM_{2.5}$ (particulate matter with an aerodynamic mass median diameter £ 2.5 µm), have been widely noted in the epidemiology and toxicology literature. Short- and longterm exposure to $PM_{2.5}$ has been associated with various health effects, including, but not limited to, decreased lung function and increased respiratory symptoms; altered heart rate and heart rate variability; pulmonary and systemic inflammation; cardiopulmonary hospitalizations and mortality; and lung cancer mortality.

Epidemiologic studies have observed associations between personal $PM_{2.5}$ exposure and various biomarkers of oxidative DNA damage in different cohorts with a wide range of exposures, e.g., university students, urban area bus drivers, and boilermakers exposed to high levels of residual oil fly ash. $PM_{2.5}$ is a complex mixture of compounds, including transition metals, which are capable of producing reactive oxygen species (ROS) through the Fenton reaction, and polycyclic aromatic hydrocarbons, which are metabolically activated to o-quinones that can generate ROS through redox cycling. These ROS can cause oxidative damage to DNA, which can further lead to mutations that are associated with the initiation and progression of human cancers. Oxidative stress and associated oxidative damage also have been found to mediate vascular injury and inflammation in many cardiovascular diseases, including hypertension, hyperlipidemia, and diabetes.

Increased susceptibility to various $PM_{2.5}$ health effects has been observed in individuals with preexisting cardiovascular and respiratory diseases. Nevertheless, the susceptibility of these individuals specifically to $PM_{2.5}$-induced oxidative DNA damage has not been examined previously. Given their diseased state, individuals with cardiovascular disease may be more sensitive to oxidative DNA damage associated with $PM_{2.5}$ exposure.

Now a recent study has investigated the association between personal exposure to $PM_{2.5}$ and oxidative DNA damage and repair, as indicated by urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG), in non-hypertensive and hypertensive individuals. Previous studies have found urinary 8-OHdG to be a useful biomarker in assessing ROS-induced DNA damage in both the clinical and epidemiological setting. The purpose of this study was to examine whether individuals with hypertension were more susceptible to $PM_{2.5}$ effects on oxidative DNA damage.

In this study, the association between personal $PM_{2.5}$ exposure and oxidative DNA damage, as indicated by urinary 8-OHdG concentrations, was examined in a cohort of inner-city adults living in close proximity to a bus terminal. In the analysis including all subjects, $PM_{2.5}$ concentration was associated with a decrease in urinary 8-OHdG after adjusting for age, gender, smoking status, and time of day. However, results from the analysis including an interaction term between $PM_{2.5}$ and hypertension status suggested that the relationship between $PM_{2.5}$ exposure and urinary 8-OHdG concentrations is modified by hypertension status. $PM_{2.5}$ concentration was associated with a decrease in urinary 8-OHdG in individuals with hypertension compared to an increase in those without hypertension after adjusting for age, gender, smoking status, and time of day.

The positive, though not statistically significant, association between $PM_{2.5}$ exposure and urinary 8-OHdG observed in those without hypertension is consistent with results from previous epidemiologic studies. A study carried out in Denmark, observed that the urinary 8-OHdG concentrations in a variety of occupationally and environmentally exposed populations were higher compared with the control population, suggesting that environmental toxins can induce DNA damage.

Oxidative stress may constitute a major pathogenic factor in the development of hypertension. Experimental studies have indicated that ROS, mainly through the production of superoxide anion, could cause important alterations in the cellular signal transduction systems, ultimately leading to vasoconstriction. Further, hypertension is also associated with an impairment of endogenous antioxidant mechanisms. Nevertheless, antihypertensive medications have been shown to have antioxidant activities, including calcium channel blockers (amlodipine), ACE inhibitors (enalapril and lisinopril), and angiotensin II receptor blockers (losartan). In this study, eleven of the 12 hypertensives indicated that they were taking antihypertensive medication and eight of them were on treatments with some antioxidant capability. The antioxidant activity present in some antihypertensive medications may play a role in reducing the effects of $PM_{2.5}$ on oxidative stress; however, it does not fully explain the inverse association observed between $PM_{2.5}$ exposure and urinary 8-OHdG levels among individuals with hypertension. Further studies may consider measuring

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Database Registry. The study region includes the metropolitan centers of Vancouver (population 2,250,000) and Victoria (population 325,000) as well as the surrounding areas within the same airshed. To be eligible, children and their mothers had to be registered for the provincial medical plan (because registration is mandatory for provincial residents under a universal health care system, the entire resident population is effectively included) and reside in the study area for the duration of pregnancy and the first year of life. Children were excluded for low birth weight (< 2,500 g), preterm birth (< 37 weeks of gestation), or multiple births, given that these conditions are known strong risk factors for development of chronic respiratory conditions.

Asthma cases were age- and sex-matched to five randomly chosen controls from the eligible cohort. Each individual's exposure to ambient air exposure was estimated for the gestational period and the first five years of life using high-resolution pollution surfaces derived from regulatory monitoring data as well as land use regression models adjusted for temporal variation. Logistic regression analyses were used to estimate effects of CO, NO, NO_2, particulate matter (PM_{10} and $PM_{2.5}$), O_3, SO_2, black carbon, woodsmoke, and proximity to roads and point sources on asthma diagnosis.

The results of the study revealed that a total of 3,482 children (9%) were classified as asthma cases. Researchers observed a statistically significantly increased risk of asthma diagnosis with increased early life exposure to CO, NO, NO_2, PM_{10}, SO_2, and black carbon and proximity to point sources. Traffic-related pollutants were associated with the highest risks: adjusted odds ratio = 1.08 (95% confidence interval, 1.04-1.12) for a 10-µg/m^3 increase of NO, 1.12 (1.07-1.17) for a 10-µg/m^3 increase in NO_2, and 1.10 (1.06-1.13) for a 100-µg/m^3 increase in CO. These data support the hypothesis that early childhood exposure to air pollutants plays a role in development of asthma.

In this population-based study, children with higher early life air pollution exposures, particularly to traffic-derived pollutants, were observed to have an increased risk of asthma diagnosis in the preschool years. This adds to evidence that outdoor air pollution not only exacerbates asthma but also may be associated with development of new disease. The risk increase is small at an individual level but presents a significant increase in burden of disease on a population level because in most urban and suburban settings, traffic-derived air pollution exposure is ubiquitous.

Source: Environmental Health Perspectives, Vol. 118, No. 2, Pages 284-290, February 2010.

Adverse Health Effects of Fine Particulate Matter in Hypertensive and Non-Hypertensive Individuals

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antioxidant activity to examine the effects of hypertensive medication use on the relationship between $PM_{2.5}$ and 8-OHdG levels.

Another possible hypothesis for the observed inverse association in hypertensive individuals may be that $PM_{2.5}$ exposure does not decrease oxidative damage, but rather reduces capacity to repair DNA damage. DNA damage that is not repaired tends to promote mutagenesis. Urinary 8-OHdG is a specific DNA repair product in the urine and although it is often considered a marker of oxidative damage, perhaps it also reflects repair of that damage.

Other study examined 8-OHdG levels in leukocytes and urine in patients with lung cancer and two control groups. The level of 8-OHdG in DNA isolated from leukocytes of cancer patients was significantly higher than that in DNA from the two control groups. Nevertheless, urinary 8-OHdG levels were similar in the cancer patients and control group. It was concluded that the higher rate of oxidative damage in the cellular DNA of lung cancer patients was a result of a deficiency of repair mechanisms in this group. Similarly, the inverse association between $PM_{2.5}$ concentrations and urinary 8-OHdG levels observed in the hypertensive individuals in this study may suggest a reduced capacity for DNA repair with increased $PM_{2.5}$ exposure in this potentially susceptible population.

In conclusion, this study shows that the association between personal exposure to $PM_{2.5}$ and urinary 8-OHdG, a biomarker of oxidative DNA damage and repair, was modified by hypertension status. A positive, but not statistically significant, exposure-response relationship was observed between urinary 8-OHdG concentrations and $PM_{2.5}$ exposure in individuals without hypertension. In contrast, a statistically significant decrease in urinary 8-OHdG levels in relation to $PM_{2.5}$ exposure was observed in those with hypertension. Because it is highly unlikely that $PM_{2.5}$ has healthful effects on hypertensive individuals, these counterintuitive results require confirmation in further studies and exploration of possible mechanisms.

Source: Journal of Occupational and Environmental Medicine, Vol. 51, Issue 10, Pages 1158-1166, October 2009.

Ambient Air Pollution and the Progression of Atherosclerosis in Adults

Cardiovascular disease (CVD) is the most important cause of morbidity and mortality in the developed world, and atherosclerosis is the central underlying pathology. Atherogenesis is a lifelong process involving a range of mechanisms including lipid peroxidation and inflammation affecting the vascular wall. The clinically most relevant results of this pathology are myocardial infarction and stroke. Evidence for acute cardiovascular effects of air pollution has substantially increased in recent years; most experts agree that ambient particulate matter (PM) plays a role in triggering cardiovascular events among those with predisposing cardiovascular pathologies. Experimental studies indicate a mechanistic role of air pollution in various acute cardiovascular processes including ischemia, endothelial dysfunction, activation of the fibrinolytic system and possibly plaque destabilization.

Far less research has tested the question whether ambient air pollution also contributes to the development of chronic pathologies, such as atherosclerosis, that predispose to acute cardiovascular disease. Animal studies conducted in rabbits, rats or mice with urban PM instillation and inhalation experiments, indicate more rapid progression of atherosclerosis among animals exposed to urban PM compared to filtered air. A few cross-sectional studies observed significant associations between ambient PM or other markers of air pollution and the degree of atherosclerosis, measured with carotid artery intima-media thickness (CIMT), and both coronary and aortic calcifications.

This is the first study in humans to investigate the association between markers of exposure to ambient air pollution and the progression of CIMT, an accepted measure of the progression of atherosclerosis. CIMT results from the cumulative atherogenic processes that occur in the artery wall. As such, CIMT progression is associated with future clinical cardiovascular events. The data indicate that the progression of subclinical atherosclerosis correlates with home outdoor air quality, with particularly strong associations among those living along highways. Southern California highways have exceptionally high traffic density (i.e. several hundred-thousand vehicles per day) – several fold higher then on main surface roads – and most highways are designated truck routes. Moreover, trucks are the key source of diesel particles while passenger cars operate primarily with gasoline in North America. These features may explain the extreme gradients in ultrafine particles and other primary pollutants observed along Southern California highways with some ten-fold concentrations reported within the first 30 meters as compared to the background levels measured at > 150-200 meters. In line with the difference in traffic density – thus lower pollution – the finding of smaller effect estimates if the 'exposed' included 215 subjects living within 50 meters of a main road is plausible.

While the progression findings in this study have not been previously reported, the results agree with cross-sectional observations in humans and with several prospective animal experiments where rats, mice, and rabbits exposed to ambient PM developed atherosclerotic plaques and calcification. These animal studies – one placing mice adjacent to a Southern California highway – reported a range of effects relevant to atherogenesis and significant progression of atherosclerosis, which was possibly modified by endogenous or exogenous factors such as genetics and diet.

Despite pooling five trials, the major weakness of the study remains the limited sample size. The percent of people living very close to highways is small, in general, and was only 1.6% in the more affluent population. Thus, the strongest results relied on only 23 'exposed' subjects (i.e. within 100 meters of a highway). In contrast, results of the $PM_{2.5}$ analyses were not affected by this limitation as this exposure metric is defined on a continuous scale. The $PM_{2.5}$ estimates did not reach statistical significance in the full data, but were clearly significant among the pool of four instead of five studies (excluding the B-Vitamin Atherosclerosis Intervention Trial) as well as among the on-trial treatment group. In fact, the most intriguing and challenging aspect of the results is the sub-group findings. All subgroups tested were identified *a priori,* based on prior studies and hypotheses, and the confirmation of modifiers of effects underscores the plausible notion that there exist groups who are more susceptible to oxidative and inflammatory air pollutants. In line with other U.S.-based air pollution studies, the effects were stronger among the socioeconomically disadvantaged, a possible marker for concomitant adverse environmental exposures, poor diet, and a more stressful life.

This study indicates an association between exposure to traffic-related air pollution and the progression of atherosclerosis in humans. While in agreement with cross-sectional findings and animal studies, these results need to be corroborated with longitudinal studies particularly designed to evaluate this hypothesis, and to investigate the role of endogenous and exogenous cofactors that may interact with the vascular toxicity of ambient pollutants. Future studies should investigate whether atherogenic effects of air pollution may be larger in women, among the socially deprived or poorly educated, and possibly among those under treatments that interact with atherogenic pathways. The issue is of substantial public health relevance due to the high burden of morbidity and mortality related to atherosclerosis, and the very high number of people exposed to ambient air pollutants through the entire lifecourse.

Source: PLoS ONE, Vol. 5, Issue 2, e9096, February 2010.

Associations between Exposure to Particulate Air Pollution and Changes in Cardiovascular Function and Plasma Mediators in Older Adults

In many industrialized countries, the economic and societal costs of caring for older people who are suffering from health conditions are significant. In Canada, for example, older adults account for more than one half of all hospital admissions and 44% of health care expenditures.

Epidemiological studies using administrative databases have suggested that older adults may be more susceptible to particulate and gaseous air pollution-related cardiovascular and respiratory morbidity and mortality than the general population. The underlying biological mechanisms have not been firmly established. Although several panel studies using elderly subjects have reported that daily concentrations of particulate air pollution are associated with adverse changes in heart rate variability, electrocardiographic repolarization, vascular function, blood C-reactive protein (CRP), and von Willebrand factor, other studies did not find significant associations between exposure to particulate pollutants and changes in vascular function or systemic inflammation and thrombosis in older subjects. Little is known about the adverse effects of exposure to indoor particulate pollutants on the health of seniors. Since seniors spend most of their time indoors, information on whether acute exposures to increased particulate air pollution monitored indoors and at a personal level can adversely affect the health of seniors would be useful in enabling policy makers to develop scientifically sound air pollution control policies.

Sources of fine particulate matter (particles ≤ 2.5 µm in aerodynamic diameter, $PM_{2.5}$) and black carbon (BC) are typically from the combustion of fossil fuels in urban locations, most commonly associated with vehicular emissions. Several studies have found BC concentrations to be higher in close proximity to roadways that have diesel vehicles than $PM_{2.5}$, with some literature also finding exacerbations in respiratory illness, and, thus, hypothesizing that diesel emissions are responsible for these effects on health. A study conducted in Amsterdam, the Netherlands, demonstrated that in homes located near busy roadways both $PM_{2.5}$ and BC concentrations were elevated in the outdoor and indoor environments, the BC concentrations being about a factor of 2 higher compared with homes located in low traffic area.

Now researchers in Ontario, Canada, have designed a longitudinal study to test the hypothesis that an acute increase in exposure to particulate air pollution monitored indoors, outdoors, and at a personal level is associated with impairment in cardiovascular function and increases in mediators of vascular function, inflammation, and oxidative stress in seniors.

Subjects were recruited from three nursing homes located in Windsor, Ontario, Canada, one located next to the Ambassador Bridge, the Canada-U.S.A. border-crossing bridge, one located on a major roadway that feeds into the Ambassador Bridge, and one in a residential area. Eligibility criteria were nonsmokers, man or woman, 65 years of age or older, no obvious heart and lung conditions, and able to give informed consent. Indoor smoking of tobacco products was prohibited in these nursing homes during the study. The study was conducted between February 11, 2007, and March 31, 2007, in the three nursing homes simultaneously.

A questionnaire on age, gender, medical history, and medication use was administered during the first visit to the clinic. Weight and height were determined, and body mass index calculated using standard procedures.

Daily indoor and outdoor BC and $PM_{2.5}$ and personal $PM_{2.5}$ were monitored daily for 28 nonsmoking subjects. Their blood pressure, heart rate, and brachial artery function were then measured and plasma mediators of inflammation, vascular function, and oxidative stress marker thiobarbituric acid reactive substances (TBARS) were determined. Associations were tested using mixed-effects models.

The results of this study showed that increases in BC and $PM_{2.5}$ were associated with increases in blood pressure, heart rate, endothelin-1, vascular endothelial growth factor, TBARS and a decrease in brachial artery diameter.

The study therefore concluded that daily exposure to particulate exposure, likely traffic-related, may result in adverse effects on cardiovascular function and blood mediators that modulate vascular system in older adults.

Source: Journal of Occupational and Environmental Medicine, Vol. 51, Issue 9, Pages 1088-1098, September 2009.

ASSOCIATION OF URINARY BISPHENOL A CONCENTRATION WITH HEART DISEASE

Bisphenol A (BPA) is a man-made compound that is suspected to act as an endocrine disruptor capable of causing dysfunction to hormonally regulated body systems. It is used extensively in drinks containers and food packaging. Widespread and continuous human exposure to BPA is believed to be mainly through dietary intake, with additional exposure through drinking water, dental sealants, dermal exposure and inhalation of household dusts.

The potential for BPA to cause adverse human health effects is believed to be a consequence of its well-documented estrogenic activity, with reports of both estrogen agonist and androgen antagonist activity. Reported additional modes of action include liver damage, disrupted pancreatic Beta-cell function, thyroid hormone disruption and obesity promoting effects. Many of these effects have been reported to occur at concentrations below recommended safe daily exposure levels, prompting much recent debate on the requirement for revision of current legislation.

Once ingested, BPA is metabolised to form the highly water soluble major metabolite, bisphenol A-glucuronide. Researchers have reported that the half life for renal clearance of this metabolite from blood following oral administration was 5.3 hours in adult male and female subjects. Exposure studies in humans are restricted due to ethical reasons and by the difficulties in finding individuals completely unexposed to BPA from the environment. As such, there are no *in vivo* data on the rate at which unconjugated BPA is converted to bisphenol A-glucuronide in humans, and only predictions have been made. Given the urinary route of clearance of the major metabolite, urine is considered to be the most appropriate body fluid for BPA exposure assessment. Based on the animal and laboratory evidence, the researchers of the present study previously hypothesised that higher urinary BPA concentrations would be associated with adverse human health effects, especially in the liver and in relation to insulin, cardiovascular disease and obesity. In 2008 data were released from the US National Health and Nutrition Survey (NHANES) 2003/04 providing the first large-scale population-representative epidemiological data on urinary BPA concentrations with sufficient statistical power to detect low-dose effects. Higher BPA concentrations in NHANES respondents were found to be associated with cardiovascular disease diagnoses (Odds Ratio (OR) per 1 standard deviation (SD) increase in BPA concentration = 1.39; 95%CI: 1.18-1.63; p = 0.001 in fully adjusted regression models). Higher BPA concentrations were also associated with diagnosed diabetes (OR per 1SD increase in BPA concentration = 1.39; 95%CI 1.21-1.60; p<0.001) but not with other common diseases, suggesting specificity of the reported findings.

These first reports clearly need to be replicated in independent studies, to ensure that the findings are robust and to refine estimates of effect sizes. Thus, a new report presents an epidemiological analysis of the NHANES 2005/06 BPA biomonitoring results, which measured BPA levels on a new independent cross-sectional sample of the US non-institutionalized population. Researchers re-tested the originally identified associations of higher urinary BPA concentrations associated with reported heart disease, diabetes and liver enzymes. They also estimated the strength of these associations in all the available data.

Data were from the US NHANES study 2003/04 and 2005/06. The study assesses health and diet, and the samples are representative of the non-institutionalized population of the United States. NHANES surveys are cross-sectional, recruiting new samples for each wave.

Subjects were n = 1455 (2003/04) and n = 1493 (2005/06) adults aged 18-74 years, representative of the general adult population of the United States. Regression models were adjusted for age, sex, race/ethnicity, education, income, smoking, body mass index, waist circumference, and urinary creatinine concentration. Main outcomes were reported diagnoses of heart attack, coronary heart disease, angina and diabetes and serum liver enzyme levels. Urinary concentrations of (free and conjugated) BPA in 2005/06 (geometric mean 1.79 ng/ml, 95%CI: 1.64 to 1.96) were lower than in 2003/04 (2.49 ng/ml, CI: 2.20 to 2.83, difference p-value = 0.00002). Higher BPA concentrations were associated with coronary heart disease in 2005/06 (OR per z-score increase in BPA = 1.33, 95%CI: 1.01 to 1.75, p = 0.043) and in pooled data (OR = 1.42, CI: 1.17 to 1.72, p = 0.001). Associations with diabetes did not reach significance in 2005/06, but pooled estimates remained significant (OR = 1.24, CI: 1.10 to 1.40, p = 0.001). There was no overall association with gamma-glutamyl transferase concentrations, but pooled associations with alkaline phosphatase and lactate dehydrogenase remained significant.

The report concluded that higher BPA exposure, reflected in higher urinary concentrations of BPA, is consistently associated with reported heart disease in the general adult population of the USA. Studies to clarify the mechanisms of these associations are urgently needed.

Source: PLoS ONE, Vol. 5, Issue 1, e8673, January 2010.

EXPOSURE TO PHTHALATES AND BREAST CANCER RISK IN MEXICAN WOMEN

Phthalates are endocrine disruptors that have shown effects on reproductive health and development. Infertility, decreased sperm counts, cryptorchidism, reproductive tract malformations, hypospadias, and testicular tumors, as well as reduction on testosterone levels, anogenital distance, and reproductive organ weights and nipple retention, have been described both in animal and human studies. Exposure to various phthalates in adult men has been associated with altered semen quality, reduced concentration of certain sexual and thyroid hormones, reduced pulmonary function, and increases in certain metabolic syndrome markers. In boys, prenatal exposure to some phthalates has been associated with a reduced anogenital distance. Exposure to phthalates before birth has been related to gestational age, and exposure during childhood has been associated with respiratory problems, asthma, and allergies.

Several phthalates, such as diethyl phthalate (DEP) and dibutyl phthalate (DBP), are widely used, especially in cosmetic and personal care products for infants, children, and adults. Other phthalates, including diisobutyl phthalate (DiBP), butylbenzyl phthalate (BBzP), di(2-ethylhexyl) phthalate (DEHP), and di-*n*-octyl phthalate (DOP), can be used as plasticizers in the manufacture of flexible vinyl plastic in consumer products, flooring and wall coverings, food contact applications, and medical devices. Phthalates can also be used as solvents in combination with other plasticizers in floor coverings as well as in some cosmetics and pharmaceutical products.

Some phthalates can be absorbed through the skin; in addition, they can be ingested, because they can migrate from wrappers and containers to foods. The metabolism of most phthalates in humans occurs first by hydrolysis of one ester bond to form the hydrolytic phthalate monoesters. Some phthalates may undergo a phase I biotransformation in which oxidative metabolites are formed. Both monoester and oxidative metabolites may react with glucuronic acid in a phase II biotransformation to form their respective glucuronide conjugates. The phase II conjugation facilitates urinary excretion of the phthalate metabolites. The urinary concentrations of phthalate metabolites have been used extensively to assess exposure to phthalates in epidemiologic studies.

Women may be at a higher risk than men for potential adverse health effects of phthalates due to phthalate exposure through cosmetics use. However, potential effects of phthalate exposure have been documented primarily in males. Health effects in women have been scarcely characterized, and studies have been limited to endometriosis and thyroid hormone changes.

Breast cancer (BC) is hormone dependent. Less than 25% of patients have a history of early menarche, later age at first childbirth, nulliparity, family history of BC, or history of benign breast biopsy; however, in most cases the causes of breast tumors are unknown, and environmental and genetic factors may play a role.

Now a new study examines the association between exposure to six phthalates, estimated from urinary concentrations of nine selected phthalate metabolites, and the risk of BC among a group of northern Mexican women. Researchers age-matched 233 BC cases to 221 women residing in northern Mexico. Sociodemographic and reproductive characteristics were obtained by direct interviews. Phthalates were determined in urine samples by isotope dilution/high performance liquid chromatography coupled to tandem mass spectometry.

Phthalate metabolites were detected in at least 82% of women. The geometric mean concentrations of monoethyl phthalate (MEP) were higher in cases than in controls (169.58 vs. 106.78 µg/g creatinine). Controls showed significantly higher concentrations of mono-*n*-butyl phthalate, mono(2-ethyl-5-oxohexyl) phthalate, and mono(3-carboxypropyl) phthalate (MCPP) than did the cases. After adjusting for risk factors and other phthalates, MEP urinary concentrations were positively associated with BC [odds ratio (OR), highest vs. lowest tertile = 2.20; 95% confidence interval (CI), 1.33-3.63; p for trend < 0.01]. This association became stronger when estimated for premenopausal women (OR, highest vs. lowest tertile = 4.13; 95% CI, 1.60-10.70; p for trend < 0.01). In contrast, researchers observed significant negative associations for monobenzyl phthalate (MBzP) and MCPP.

The results show for the first time that exposure to DEP, as assessed by urinary MEP concentrations, may be associated with an increase in BC risk, whereas the exposure to other phthalates, measured by the urinary concentrations of MBzP (BBzP) and MCPP (DOP and other phthalates), were negatively associated with BC. The findings require confirmation to exclude the possibility that these parent/metabolite phthalates are surrogates of unrecognized lifestyle or dietary BC risk factors.

The various sources and levels of exposure to relevant phthalates present in cosmetics and other personal care products deserve further assessment, particularly at critical windows of exposure, such as adolescence. Also, the biological mechanisms warrant clarification.

Source: Environmental Health Perspectives, Vol. 118, No. 4, Pages 539-544, April 2010.

Health Effects from Exposure to Benzene with Co-exposure to 1,3-butadiene and PAHs in Various Susceptible Populations

Exposure to benzene in human populations can occur in various work-related settings in which benzene is used or produced, or from traffic emissions or other combustion processes, such as coal and incense burning, as well as cigarette smoke. Combustion-derived emissions contain a mixture of volatile compounds and particles that varies in composition depending on the source, weather, topography and other factors. Other carcinogenic compounds, such as 1,3-butadiene and certain polycyclic aromatic hydrocarbons (PAHs), are also found in combustion-derived emissions, and thus could potentially result in interactive effects with benzene. Since in real world situations people are exposed to varying concentrations of these mixtures of carcinogens, it is of great interest to assess the potential effects of this exposure in susceptible populations.

Benzene, 1,3-butadiene and certain PAHs are carcinogens that can cause DNA damage. These compounds require metabolic activation to exert their carcinogenic activities. Their reactive metabolites, which are electrophilic, can bind to DNA and cause damage, e.g. DNA adducts. Additionally, certain pathways in their metabolism lead to the generation of reactive oxygen species (ROS), which can interact with DNA and induce oxidative DNA damage, such as 8-hydroxy-2'-deoxyguanosine (8-OHdG) and DNA strand breaks. Oxidative damage has been linked to the development of cancer.

In the present studies, 2 scenarios of benzene exposure were assessed in 4 susceptible groups in Thailand. The first scenario is work-related exposures primarily to benzene, with the study subjects consisting of petrochemical laboratory workers and gasoline service station attendants exposed to benzene at levels of 78.32 and 360.84 μg/m^3, respectively. The second scenario is traffic-related exposure and exposure to incense smoke, where co-exposures to other pollutants (i.e. 1,3-butadiene and PAHs) occur, with the study groups consisting of school children, who attend schools in the Bangkok city center and are exposed to traffic emissions, and temple workers exposed to incense smoke. The individual benzene exposure levels were approximately 19.38 μg/m^3 in city school children and 45.90 μg/m^3 in temple workers. Measured levels of 8-OHdG, DNA strand breaks and DNA repair capacity in the study subjects were used as biomarkers of early effects from exposure to these compounds.

In terms of effects of work-related exposures to benzene, petrochemical laboratory workers and gasoline service station attendants had significantly higher levels of DNA strand breaks and significantly lower DNA repair capacity compared to controls, while gasoline service station attendants also had significantly higher levels of 8-OHdG than controls. As for effects of environmental co-exposures to benzene and other carcinogens, city school children had significantly higher levels of PAH-DNA adducts, 8-OHdG, and DNA strand breaks, and significantly lower levels of DNA repair capacity compared to rural children. Temple workers also had significantly higher levels of 8-OHdG and DNA strand breaks and significantly lower levels of DNA repair capacity compared to controls. Results of correlation analysis between exposure and effects were indicative of relationships between levels of exposure to benzene, PAHs and 1,3-butadiene, individually, and resultant early biological effects, with implications for health risks. Results from a multivariate regression analysis were indicative of a major influence of PAHs concentrations over benzene and 1,3-butadiene for certain endpoints.

In conclusion, the researchers observed that: (1) 8-OHdG is a biomarker of DNA damage that responds to increasing levels of exposure to benzene, (2) total PAHs concentrations converted to B[a]P equivalents was identified as the factor significantly influencing both 8-OHdG levels and DNA repair capacity in school children, while 1,3-butadiene significantly influenced DNA repair capacity, (3) PAHs concentrations significantly influenced both DNA strand breaks and DNA repair capacity in temple workers, while benzene significantly influenced DNA strand breaks, and (4) children may be physiologically more susceptible to carcinogen exposures, as observed from higher levels of biomarkers of early effects compared to those in the adult study groups despite the lower exposure levels.

It is clear from these studies that relatively low levels of benzene exposure, alone or concurrently with other carcinogens, result in early biological effects in the study populations that have implications for the risk of cancer development. It is important to be aware of these real world exposures and possible resultant effects such that life-style decisions can be made to minimize/prevent them.

Source: Chemico-Biological Interactions, Vol. 184, Issues 1-2, Pages 67-76, March 2010.

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The ICEIT NEWSLETTER is published quarterly by the International Centre for Environmental and Industrial Toxicology of the Chulabhorn Research Institute. It is intended to be a source of information to create awareness of the problems caused by chemicals. However, the contents and views expressed in this newsletter do not necessarily represent the policies of ICEIT.

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