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CRI's ICEIT has been designated as a
"UNEP Centre of Excellence for Environmental and Industrial Toxicology".

ENGINEERED NANOPARTICLES AND CONSUMER PROTECTION

The International Organization for Standardization (ISO) defines a nanomaterial as a material with any external dimension between 1 and 100 nm. (By comparison, a double strand of DNA is about 2 nm thick).

Nanoparticles, which have been the focus of most nanotoxicology studies to date, are one subset of nanomaterials. Nanoparticles include structures of various shapes, such as nanotubes, nanowires, quantum dots, and fullerenes. They also occur naturally in substances like air, smoke, and sea spray, and "incidental" nanoparticles are created during processes such as combustion and food milling, churning, freezing, and homogenization. Naturally occurring and incidental nanoparticles were not included in the National Organic Standards Board's recommendation to ban engineered nanomaterials (ENMs).

Nanotechnology – the deliberate synthesis and manipulation of nanomaterials – began in the 1980s. Today thousands of ENMs are manufactured in a kaleidoscope of substances, shapes, and sizes for use in a wide range of products and industrial processes that take advantage of their novel physical, thermal, optical, and biological properties. These properties may be determined by the ENM's chemical composition, size or shape, crystal structure, solubility, adhesion (the force that holds the nanoparticle components together), or surface chemistry, charge, or area.

Industry analysts have been forecasting "game-changing" advances as a result of nanotechnology in renewable energy, computers, communications, pollution cleanup, agriculture, medicine, and more. Clothing, sunscreens, cosmetics, sporting equipment, batteries, food packaging, dietary supplements, and electronics are just a few of the types of nanotechnology-enabled goods in use by U.S. consumers. But safety questions arise around the nanoparticles in some of these products. The novel biological and physical properties of some ENMs pose unique challenges to comprehensive safety research, and investigators are working to figure out just how hazardous they might be to people, wildlife, and the environment. Compared with larger particles, nanoparticles' tiny size means tissues may take them up more readily. It also can give them an unusual ability to travel throughout the body, including into cells and cell nuclei, and across the placenta and the blood-brain barrier, as demonstrated in rodent studies.

No cases of human illness or death have been definitively attributed to ENMs. However, a number of researchers and consumer and environmental advocates have warned that the abundant unknowns make it necessary to proceed with caution lest there is a repeat of the history of asbestos, polychlorinated biphenyls, the insecticide DDT, and other innovations that seemed valuable when they were introduced, proceeded with little oversight, and ultimately caused major health or environmental problems.

Many researchers point to the emerging field known as green nanotechnology that is attempting to make

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ENMs and their production processes safer for people and the environment. They also look ahead to applications like the targeted delivery of chemotherapy drugs, tiny foodborne contaminant sensors, and advanced air- and water-filtration systems as plausible advances that could truly benefit society.

But while many critics say they are enthusiastic about some of those positive applications, they remain adamant that safety research and regulation must catch up and keep up with the technology's proliferation.

Source: Environmental Health Perspectives, Vol. 119, No. 3, Pages A120-A125, March 2011.

The Contribution of Dermal Exposure to the Internal Exposure of Bisphenol A in Man

Bisphenol A (BPA) is an industrial chemical which in its monomeric form is widely used in the production of epoxy resins and polycarbonate plastics.

Human exposure is via food and beverages which have been in contact with polycarbonate plastic materials, via polycarbonate tableware and by indirect exposure via the environment from emissions of BPA production plants.

New findings on BPA contents in thermal printing papers, and receipts, in g/kg concentrations and on its dermal uptake (up to 60%) prompted researchers to assess the risk arising from dermal exposure. In a new study using physiologically based toxicokinetic modelling, researchers simulated concentrations in blood, in liver and kidney, the target organs exhibiting the lowest no observed adverse effect levels (NOAEL). By comparing organ concentrations at the dose level of the NOAEL divided by a safety factor of 100 (liver: 50 µg/kg/day; kidney: 500 µg/kg/day), with concentrations arising from the dermal dose of 0.97 µg/kg/day this dermal exposure can be assumed safe.

The study simulated the concentration time profile not only in blood but also in the liver and in the kidney as the liver is the target organ with the lowest NOAEL from which the tolerable daily intake (TDI) is derived and kidney is the organ with the next lowest NOAEL.

From the simulated concentration-time profiles researchers derived peak blood concentrations (C_{max}) and the area under the curve (AUC) over 24 h. In comparing the results which are obtained with identical doses by dermal exposure with those after oral exposure it is obvious that the concentration and also AUC in blood are in the same range whereas in the liver exposure on the oral route results in 10 fold higher concentrations and AUC is twofold higher than after dermal exposure. The finding can be explained by the physiology of dermal versus oral absorption. When absorbed through the skin, BPA first enters the venous blood. The venous blood is drained into the upper main vein, passing the right ventricle and the lungs where the blood is oxygenized, and then from the left ventricle distributed via arterial blood throughout the body by systemic circulation. The blood entering the liver is mixed arterial (hepatic artery 7% of the cardiac output) and venous blood drained from the gastrointestinal tract into the portal vein (16.9% of the cardiac output). After BPA absorption through the skin the blood in the portal vein has a concentration lower than after absorption of the same BPA dose by the intestinal tract. This is because after dermal absorption BPA is distributed into the whole blood volume whereas after absorption in the gastrointestinal tract BPA is distributed in the blood of the portal vein which contains only 16.9% of the cardiac output. A second factor influencing C_{max} in the liver is the rate of absorption. Dermal absorption of BPA is 8 h as opposed to 15 min for the oral absorption. Thus, C_{max} in the liver is several fold lower after dermal as compared to the oral administration. Concerning the endpoint hepatic toxicity it is not known whether it is related to AUC or to C_{max}. Nevertheless, with respect to liver toxicity, the dermal dose of 0.97 µg/kg/day which is the worst case estimate would be safe as AUC is 96 fold and C_{max} even 700 fold lower than the values for 50 µg/kg/day by the oral route which is the TDI.

The results of the study allow the following conclusions. First, dermal exposure may contribute to a relevant extent to the overall internal BPA-exposure. Second, concentrations in blood and in kidney on the one hand and in the liver on the other differ remarkably for BPA if given by the dermal as compared to the oral route due to the high first pass in the liver. Third, even if higher blood concentrations of a dose given by the dermal route are taken into consideration, the doses to reach the concentrations reported by most of the authors in the literature are orders of magnitude higher than estimated, based on measurements. Hence, the measured unexpectedly high blood concentrations are thought to be erroneous. Fourth, more data should be made available on the external exposure with BPA by the dermal route. In order to reduce the uncertainty on the extent of absorption, which however does not greatly influence the findings, dermal absorption of BPA should be measured in an *in vivo* human study using specific analytical methods.

Source: Toxicology Letters, Vol. 204, Issue 2, Pages 190-198, July 2011.

RELATIONSHIP BETWEEN OUTDOOR TEMPERATURE AND BLOOD PRESSURE

Numerous study results have shown a link between high ambient temperatures and increased mortality, especially for cardiovascular diseases, and exposure to cold temperature has also been shown to increase mortality.

Recently, associations between ambient temperature and morbidity have also been reported, although these associations have not always been similar in magnitude to mortality, and null findings have also been reported. Also, while the association between temperature and cardiovascular mortality has been reported to be U-shaped in many studies, the association with cardiovascular hospitalisation was reported to be linear in the USA. As climate change has been predicted to increase not only ambient mean temperature by 1.4°C to 5.8°C by the end of this century, but also the variability of temperature, the occurrence of extreme weather conditions such as heat waves and sudden weather pattern changes may also increase. Therefore, the effects of ambient temperature on human health have recently become a target of vigorous research.

Increased blood pressure is a risk factor for cardiovascular mortality and for coronary heart disease and stroke morbidity. Therefore, changes in blood pressure might also play a part in the development of cardiovascular events associated with changes in temperature. The effects of mild exposure to cold have been tested under controlled conditions, and the results have shown that short-term exposure to cold causes subcutaneous vasoconstriction that increases central blood volume, which further increases blood pressure. However, the effects of temperature on blood pressure under ambient conditions with changing air pressure and humidity, which may also include intermittent exposures as people enter and exit buildings, may differ substantially from those in chamber studies, and have not been thoroughly studied. Two epidemiological studies from Europe have reported that systolic blood pressure (SBP), or both SBP and diastolic blood pressure (DBP) decrease in association with increasing outdoor temperature. Another study has found that increases in outdoor and indoor temperatures may have independent, although similar, negative effects on SBP. However, more studies also from North America are needed to assess the validity of these conclusions.

The mechanisms behind temperature-related cardiovascular mortality and morbidity are not fully established. As elevated blood pressure is a known risk factor for cardiovascular disease and stroke events, blood pressure can also be part of the mechanism leading to temperature-related deaths. The researchers studied the effect of outdoor temperature on DBP and SBP among elderly men using three different temperature variables (ambient, apparent and dew point temperature (DPT)). In this study, researchers controlled for confounding by black carbon, a marker of combustion particles that has been shown to have an effect on blood pressure in the cohort and elsewhere. Possible confounding by ozone was also studied as a suggestion of an association between ozone and blood pressure has been reported.

The study found that DBP among elderly men increases in association with decreasing ambient and apparent temperature. These increases were not due to particulate pollution, ozone or extreme temperatures. Weaker associations between temperature and SBP, were found, as was increase in DBP in association with cumulative exposure to decreasing outdoor temperature.

Black carbon was a significant confounder for the associations between temperature and blood pressure, and inability to control for black carbon would have resulted in biased effect estimates. This finding is not surprising as an association between black carbon and blood pressure has already been seen in the study cohort. In general, traffic-related air pollution and particles from combustion sources may have even greater adverse effects on cardiovascular health than PM_{10} or $PM_{2.5}$ (particles with diameter <10 and <2.5 µm, respectively). Therefore, the possible confounding by particles specifically from these sources should be controlled for, but several studies assessing the health effects of temperature have failed to do this. Even though confounding by particles has not been observed in all studies of the health effects of temperature, the evidence that PM_{10} may act as a confounder in temperature-related cardiovascular mortality and the current finding for black carbon underline the importance of considering ambient particles as confounders when the effects of temperature on blood pressure and other cardiovascular outcomes are evaluated.

Of the three temperature variables, the study found the strongest associations for apparent temperature, but the effect of ambient temperature was very similar and the effect lag structures of these variables were consistent. Apparent temperature is an exposure variable that is used to describe how people perceive the combination of temperature and humidity. At warm temperatures, high humidity increases the feeling of discomfort and heat stress, and therefore apparent temperature may be more a sensitive exposure variable for physiological effects than ambient temperature. However, based on these findings, both of these exposure variables are useful when estimating the health effects of outdoor temperature. DPT had slightly different effect estimates from ambient and apparent temperatures, especially with the cumulative exposures, which may be due to the close relationship between DPT and relative humidity. DPT reflects temperature well on days when humidity is high, but if humidity is low it may be a worse proxy of temperature than humidity.

In conclusion, the study found that a decrease in outdoor temperature can cause an increase in DBP among elderly men. These results suggest that blood pressure may increase with decreasing temperature, therefore possibly playing a part in cold-related, but not heat-related, mortality. However, more research on the effects of outdoor temperature on blood pressure is needed using diverse study cohorts and personal measurements to confirm the findings. Ambient and apparent temperature can be used as exposure variables when investigating the health effects of temperature.

Source: Occupational and Environmental Medicine, Vol. 68, No. 4, Pages 296-301, April 2011.

National Survey of the Level of Persistent Organochlorine Pesticides in the Breast Milk of Mothers in China

Organochlorine pesticides (OCPs) are widely used for agriculture, forestry, building protection, and insect control. Most OCPs are lipophilic, very persistent, and highly stable. They can accumulate in ecosystems.

Many toxic effects on the reproduction, development and immunological function of animals from the use of OCPs have been reported. Several OCPs have weakly estrogenic or anti-estrogenic effects and also harm the nervous system. OCPs such as aldrin, chlordane (CHL), dichlorodiphenyltrichloroethane (DDT), dieldrin, endrin, heptachlor, hexachlorobenzene (HCB), mirex and toxaphene were listed in the initial "dirty dozen" agents in the Stockholm Convention in 2001. In 2009, hexachlorocyclohexane (HCH) isomers such as α-HCH, β-HCH and γ-HCH were added to the list of persistent organic pollutants (POPs) of the Stockholm Convention for their potential adverse effects on humans and ecosystems. Now, most nations and regions have restricted or banned the use of persistent OCPs.

Compared with blood or adipose tissue, breast milk is a unique biological matrix for investigating certain environmental contaminants because it can provide exposure information about the mother and breastfed infant. In addition, breast milk offers a convenient sampling specimen for monitoring the residues of OCPs in human tissues through a non-invasive method of collection. The levels of OCPs in breast milk have been used to assess the trend of pollution by OCPs in the environment since the early 1970s and to evaluate the effect of banning OCPs in many countries. A general declining trend of concentrations of OCPs in breast milk after the limited use or banning of OCPs has been reported. Similarly, a downward trend in the concentrations of HCHs and DDTs was observed in the breast milk from mothers in some regions of China. However, the surveys focused only on DDTs, HCHs and HCB in smaller districts. The background exposure to OCPs across the country and regional differences such as north-south or urban-rural gradients was not investigated.

Now researchers have completed a national project for biomonitoring the background level of persistent OCPs in the breast milk of Chinese mothers based on the WHO-coordinated Fourth Survey of Breast Milk for Persistent Organic Pollutants in cooperation with the United Nations Environment Programme. The present survey included eight OCPs (DDTs, HCHs, HCB, drins, CHLs and mirex) except toxaphene. All breast milk samples were collected in 2007 according to the fourth WHO survey protocol, in which a Chinese total diet study (TDS) was carried out simultaneously.

The present comprehensive study on OCPs residues in breast milk showed that DDTs were the most abundant pesticides, followed by HCHs and HCB. These concentrations of DDTs and HCHs dramatically declined with time compared with data from regional breast milk surveys in China in the past 20 years. Even so, the level of DDTs, HCHs and HCB was mid-range compared with data from other countries. The relatively low DDE/DDT ratio in the Fujian rural area suggested more recent exposure to DDT than in other areas. Mean levels of DDTs in breast milk from southern areas were higher than those from the northern part of China if these regions were divided between the Yangtze River (Changjiang), and may be attributed to increased consumption of fish. The large variation in levels of HCHs in breast milk also revealed that animal-derived foodstuffs (especially intake of seafood) could be a significant source of exposure to HCHs. The concentration of HCHs from urban areas was higher than from rural areas in China. The mean estimated daily intakes (EDIs) of DDTs, HCHs (total), heptachlor (total), aldrin/dieldrin, endrin, lindane and mirex by infants were lower than the tolerable daily intake (TDI) guidelines recommended by the Ministry of Health of China. The mean EDIs of HCB and chlordane in infants did not exceed the corresponding guidelines from Canada. However, the EDI of DDTs, HCHs, HCB in infants from some provinces were close to, or even higher than, the TDI guidelines.

Source: Environmental Pollution, Vol. 159, Issue 2, Pages 524-531, February 2011.

Effects of Maternal Exposure to PAHs

Polycyclic aromatic hydrocarbons (PAHs) are a large family of toxic compounds generated from the combustion of organic materials, diesel exhaust, and industrial waste by-products, and they are widely spread pollutants present in the atmosphere, water and soil.

Humans and wild animals are exposed to a diverse array of PAHs, and the primary source of PAH exposure in the general population is through dietary intake of contaminated food. Some PAHs are classified as human carcinogens and also elicit a broad spectrum of toxic responses in human and animals. Exposure to a highly toxic PAH, benzo[a]pryene (B[a]P), caused infertility in mice and subcutaneous administration of B[a]P, benzo[a]anthracene, or fluoranthene in immature rats produced estrogenic responses. Benzo[b]fluoranthene (B[b]F), a non-alternant PAH congener, is a common constituent of PAH complexes produced from the incomplete combustion or pyrolysis of organic materials and is designated as a probable human carcinogen based on IRIS (Integrated Risk Information System). Despite the prevalent presence of B[b]F in foods, such as meat, fish, shellfish, vegetables, fruits, eggs, dairy products, cereals, and oils, most studies have focused on its carcinogenic activity at higher doses, and scarce data are available concerning its reproductive toxicities.

The testis is the central organ in the male reproductive system and is composed of the seminiferous tubules and the interstitial space between the tubules. Spermatogenesis is a dynamic and complex process leading to testicular germ cell development in

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THE EFFECT OF INORGANIC ARSENIC AND ITS METABOLITES ON THE VIABILITY OF THE NEURAL PROGENITOR CELLS

The aim of this study is to determine the effect of inorganic arsenic (As) and its metabolites on the viability of the neural progenitor cell (NPC) line C17.2, in order to evaluate cellular mechanisms involved in As developmental neurotoxicity.

As is an element that is present in nature in a great number of chemical forms of varying toxicity. Inorganic arsenic [As(III) + As(V)] is considered a human carcinogen by the International Agency for Research on Cancer. Moreover, chronic exposure to inorganic As is associated with an increase in type 2 diabetes, cardiovascular and cerebrovascular problems, chronic obstructive respiratory diseases, and non-carcinogenic skin disorders.

Intake of As through water and food is the main way of exposure for humans. A large part of the world's population consumes drinking water with an As concentration below 10 µg/l, the limit recommended by the World Health Organization (WHO), however, in some areas the concentration may exceed 100 µg/l. The predominant form of As in drinking water is arsenate [As(V)]. Its metabolism in the organism gives rise to other chemical species [arsenite, As(III), monomethylarsonic acid, MMA(V), dimethylarsinic acid, DMA(V), monomethylarsonous acid, MMA(III), and dimethylarsinous acid, DMA(III)], some of which, especially the trivalent forms, have greater toxicity than the initial compound.

Prenatal exposure to inorganic As could have a considerable effect on the health of the child population. Exposures to inorganic As since the moment of the child gestation have been associated with neurobehavioral disorders. Some studies also describe the toxic effect of As during development of the nervous system. As(III) affects neurite growth and complexity during development. Other studies showed that exposure to As(III) in the stage of rapid brain growth in rats (postnatal days 4-10) was associated with defects in migration, delayed maturation, and alteration in the nuclear area of the Purkinje cells of the cerebellum. Researchers using primary cultures of neonatal rat neural cells, showed a reduction of neuronal viability and morphological changes.

In some parts of the world, the presence of high concentrations of As in drinking water is combined with concentrations of fluoride (F) that exceed the maximum recommended by the WHO (1.5 mg/l). Fluoride is considered an essential trace element and its use is recommended to prevent dental caries and for bone development. However, studies conducted in China showed effects on neonatal neurobehavioral development after a high intake of F during pregnancy.

The present study thus aims to make an *in vitro* evaluation of the effects of inorganic As and its metabolites, and the coexposure to F on the viability of neural progenitor cells, in order to evaluate cellular mechanisms involved in As or As/F developmental neurotoxicity. For this purpose, it has used C17.2 cell line, originally derived from the developing mouse cerebellum. This cell line has the ability to differentiate into neurons, astrocytes or oligodendrocytes and was employed as a model to evaluate the toxic effect on neural development of other elements, such as methylmercury and manganese.

The results show that NPCs are not susceptible to pentavalent As species [As(V), MMA(V), and DMA(V)] and F alone. However, the trivalent metabolites of As(V) [As(III), MMA(III), and DMA(III)] are toxic at concentrations below 1 mg/l, and this susceptibility increases when there is coexposure with F. Arsenite triggers apoptosis after 24 h of exposure, whereas DMA(V) produces necrosis at very short times (2 h). As(III) leads to an increase in intracellular calcium levels and decrease in mitochondrial trans-membrane potential, release of cytochrome c, and consequent activation of caspases. A slight activation of calpain also takes place, which might favor activation of the mitochondrial pathway or might activate other pathways. The treatment with some antioxidants such as quercetin and α-tocopherol shows only a partial reduction of the cytotoxicity.

This might be one of the causes of the effects on cognitive capabilities observed in child populations exposed to As from the moment of their conception. As(III) and other metabolites, especially MMA(III), might also affect other critical processes in neural development, such as migration, differentiation, and synaptogenesis. Moreover, coexposure to As and F, which is very common in areas with endemic chronic arsenicism, increases the reduction of cell viability. These results show the need to evaluate the toxic effects of combinations of trace elements, which often coexist in water and food and are usually studied individually. There is also a need for studies to evaluate chronic exposure to these trace elements and their combinations, since the exposures used in the present study are acute and therefore do not entirely reflect what happens in chronically exposed populations.

Source: Toxicology Letters, Vol. 203, Issue 3, Pages 237-244, June 2011.

Effects of Maternal Exposure to PAHs

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which the total balance of estrogen and androgen is required. The quality of human semen over a 50-year period has declined, and epidemiology studies suggest that environmental exposures are associated with the decline in sperm quality. B[b]F has been detected in the milk of healthy, nonsmoking, lactating women at 0.560 ± 1.39 µg/kg milk as wet weight, raising the demand for the need for risk assessment of offspring after maternal exposure to B[b]F. In the present study, pregnant mice were orally exposed to low doses of B[b]F, at which no signs of obvious maternal toxicity were observed, during gestational and lactational periods, and their male offspring were assessed.

Maternal B[b]F exposure disturbed normal sperm function in F1 offspring. To understand the molecular and cellular mechanisms by which the perinatal exposure to B[b]F decreased sperm quality, the testes of young adult F1 mice were examined for changes in expression of steroidogenesis-related and testicular apoptosis mediators and found that aryl hydrocarbon receptor, estrogen receptor α, and a set of proapoptotic proteins including Bax, Noxa, Bad, and Bim were significantly upregulated. Therefore, the current trans-generational animal study implies that consumption of PAH-contaminated diets by mothers may possibly influence their offspring to cause dysfunctional male reproductive function in humans.

Source: Toxicology Letters, Vol. 203, Issue 1, Pages 54-61, May 2011.

ACUTE TOXIC EFFECTS OF PARTICULATE MATTER IN MOUSE LUNG

Particulate matter (PM) is a mixture of airborne particles derived from the combustion of fossil fuels or from the breakdown of crustal components.

Currently, PM standards are based on total mass and size, which can range from few nanometers to tens of micrometers.

Particles below 10 µm in diameter have the potential to reach and be deposited in the alveoli, while those greater than 10 µm are likely to land in proximal airways and be removed by the ciliary activity. Particles smaller than 2 µm in diameter show a clear tendency to achieve greater peripheral deposition than those greater than 2 µm. Numerous epidemiological studies presented convincing evidence of the association between increase in respiratory disease morbidity and increased levels of coarse PM, especially among susceptible populations. Some research suggests that this fraction may contribute predominantly to possible toxic and pro-inflammatory effects by its constituents, which include biological agents, metals and organic compounds.

Recently, attention has been focused on the fine fraction, constituted of particles with an aerodynamic diameter below 2.5 µm ($PM_{2.5}$). These particles, which are usually present in high number in PM samples, may be more harmful than larger ones, as they are more efficiently retained in the alveolar lung portion. As a general rule, the primary biological targets of inhaled particles are cells of the pulmonary epithelium as well as resident macrophages. Among these cells, alveolar epithelial cells are affected in a number of respiratory PM induced diseases. The fine fraction is frequently suggested to be responsible of cardiac disorders and acute cardiovascular events, such as myocardial infarction, as well as inflammatory pathologies. Increased plasma viscosity and other changes in blood-related parameters have been detected after inhalation of fine PM. However, the biological mechanisms of such events are still unclear; even the pulmonary endothelium appears to be the initial target site for ultrafine particles, which can translocate into the blood vessels, and reach other organs.

Lipopolysaccharide, a constituent of the outer membrane of gram-negative bacteria associated with PM, and polycyclic aromatic hydrocarbons (PAHs), an organic class of PM components, differ in PM concentration between summer and winter seasons. PM composition seasonal variation has been related to the different biological responses, and cytokine release is one of the parameters affected.

Thus in a new study, the toxicity of size-fractionated particulate matter (PM_{10} and $PM_{2.5}$) collected in Milano during two different seasons (summer and winter) has been evaluated *in vivo*. The focus is on time related (3 h, 24 h and 1 week) lung response following a single intratracheal aerosolization in BALB/c mice. The bronchoalveolar lavage fluid (BALf) and the lung parenchyma were screened for different markers of inflammation and cytotoxicity. Histology and immunohistochemistry were performed on excised fixed lungs to assess the effects produced by the different PM fractions. All the analyzed inflammatory markers (PMNs percentage, TNF-α, Hsp70 in the BALf, HO-1 in lung parenchyma), increased after summer PM_{10} administration; on the contrary winter PM_{10} and $PM_{2.5}$ specifically increased the amount of the Cyp1B1, a protein putatively involved in the induction of pro-carcinogenic effect. Moreover, researchers detected an intensification of lactate dehydrogenase activity in the BALf after the administration of winter PM_{10} and $PM_{2.5}$, potentially related to an in progress necrotic process while after summer PM_{10} and $PM_{2.5}$ administration, the initiation of the caspase cascade suggested a cytotoxic effect sustained by apoptosis. The results evidenced the toxicity mechanisms elicited by size fractionated PM samples, collected in winter and summer seasons, which differs for dimensions, chemical and microbiological composition. PM_{10} has been indicated to elicit above all a pro-inflammatory response, linked to its specific biological components, while $PM_{2.5}$ is supposed to be more harmful due to its smaller dimension and the ability to distribute into the lung alveolar districts. The researchers hypothesized that adverse health effects observed after a single dose of winter $PM_{2.5}$ is at least partly caused by specific winter PM components, i.e. PAH and transitional metals.

Source: Toxicology Letters, Vol. 202, Issue 3, Pages 209-207, May 2011.

Effects of Centella asiatica on Lead-induced Oxidative Stress and Suppressed Reproductive Performance in Male Rats

Use of herbal extracts has been practiced for centuries in all parts of the world in various systems of medicine like Ayurveda, Siddha, Unani, and Naturopathy.

The success of herbal extracts is chiefly because they comprise many positive factors but the factor 'no toxic effects of its own' being important. The use of traditional herbal extracts to combat chemical toxicity has been greatly acknowledged in recent years. *Centella asiatica* (CA) is a member of Umbelliferae family and popularly known as 'Saraswataku' in southern parts of India, particularly Andhra Pradesh. The medical applications of CA comprise wound healing property, improvement of memory, treatment of asthma, renal failures, respiratory problems and other medical uses being treatment of headache and leprosy. Some studies also suggest that CA has ability to counteract arsenic-induced oxidative stress with its antioxidative properties. Protective effect of CA on antioxidant tissue defense system against adriamycin-induced cardiomyopathy and age-related neurological disorders are also well-known. Even though several studies suggest the beneficial role of CA, its effects against lead-induced reproductive toxicity is not yet reported. The present study was undertaken to investigate if the oral intake of aqueous plant extract of CA could modify the oxidative stress and, suppressed reproduction induced by lead (Pb) in male rats.

The study revealed significant decrease in the weights of testes and epididymis in lead treated animals. Exposure to lead acetate significantly increased malondialdehyde levels with a marked decrease in the superoxide dismutase (SOD) and catalase activities in the liver, brain, kidneys and testes of rats.

Epididymal sperm count, viable sperms, motile sperms and hypo-osmotic-tail coiled sperms as well as testicular steroidogenic enzyme activities also decreased significantly in Pb-exposed rats.

The deterioration in the selected sperm parameters might be due to increased oxidative stress during Pb intoxication. Sperm plasma membrane, being rich in polyunsaturated fatty acids (PUFA), is highly susceptible to reactive oxygen species (ROS) attack. Poor sperm quality caused by oxidative stress due to generation of ROS has been reported to result in infertility. Several studies suggest the correlation between increased ROS production and decreased sperm motility. The mechanism of ROS induced altered sperm motility is still unclear. However, it is hypothesized that hydrogen peroxide (H_2O_2), one of the lipid peroxidation products, might diffuse across the membrane and affect the vital enzymes in the sperms thereby results in decreased sperm motility.

It is evident that Pb crosses blood-testis barrier and alters testicular functions like production of sperms and testosterone. In the present study, Pb toxicity caused testicular oxidative stress by increasing the levels of lipid peroxidation and decreasing the activities of SOD and catalase in testes. In general, SOD is the first line of defense against oxidative stress and plays a pivotal role in dismutation of superoxide anions to H_2O_2 and catalase neutralizes H_2O_2 to molecular oxygen and water. The decrease in these enzymes in Pb treated rats clearly postulates improper dismutation of superoxides and improper decomposition of H_2O_2. Other studies reported increased lipid peroxidation products in the testes and epididymis of rats after exposure to lead.

In the present study, CA treatment was found to significantly decrease the levels of lipid peroxidation and increase the activities of SOD and catalase in the testes as compared to control rats. Epididymal sperm count, sperm viability and motility were also significantly increased in the rats subjected to co-administration of CA extract as compared to Pb-exposed rats. These findings indicate the possible role of CA, characterized by increased level of antioxidant enzymes and decreased lipid peroxidation in testis, in combating the testicular toxicity of Pb. The antioxidant potential of CA has been reported earlier by several workers. CA contains high amounts of potent antioxidant compounds, viz. madecasic acid, asiatic acid and asiaticoside. Besides, the concentrations of phenolic compounds are more in CA and these compounds are the major contributors to antioxidant activities of CA. Researchers also identified a strong correlation between antioxidant activities and phenolic levels, suggesting that phenolic compounds are probably responsible for the antioxidative activities of CA. A similar finding was reported in a study that suggested that phenolic compounds are the major contributors to the antioxidative activity in CA, pineapple and vegetable juices. Although phenolic compounds are found to be the major contributors to the antioxidative activity in CA, the identity of these compounds still remains unknown.

It could be concluded from the present results that coadministration of aqueous extract of CA offers significant protection to Pb-induced oxidative stress by decreasing lipid peroxidation and activating antioxidant enzymes in the testes, thereby ameliorating Pb-induced suppressed reproduction in male rats. From the study, however, it is not clear whether CA has ability to chelate Pb and thereby reduce oxidative injury. It will be interesting to evaluate the reproductive performance of rats exposed to Pb and Pb + CA.

Source: Environmental Toxicology and Pharmacology, Vol. 32, Issue 1, Pages 146-154, September 2011.

CONGRESS ANNOUNCEMENT

The 7th Princess Chulabhorn International Science Congress (PC VII)
CANCER: FROM BASIC RESEARCH TO CURE

November 29 – December 3, 2012, Shangri-La Hotel, Bangkok, Thailand

Chairperson of Organizing Committee: **Professor Dr. HRH Princess Chulabhorn**

Keynote Speaker: ***J. Michael Bishop (Nobel Laureate, U.S.A.), Cancer: The Genomic Era Arrives***

ANNOUNCEMENT AND CALL FOR ABSTRACTS

The Congress will be held to commemorate the seventh cycle (84 years) of the birth of His Majesty King Bhumibol Adulyadej and also the eightieth birthday of Queen Sirikit. The program will feature a Keynote Lecture, Plenary Lectures, Symposia, Roundtable Discussion and Poster Presentations. Concurrent workshops on issues relating to the focus of the Congress are also organized.

Plenary Lectures (partial list)

- Future practice of Medicine, ***Ausiello, D.A.*** *(U.S.A.)*
- Inflammation and cancer: Interweaving microRNA, free radicals, cytokine and p53 pathways, ***Harris, C.C.*** *(U.S.A.)*
- Environmental and occupational determinants of cancer: Interventions for primary prevention, ***Neira, M.P.*** *(WHO, GENEVA)*
- Using omics to find the causes of complex diseases, ***Smith, M.T.*** *(U.S.A.)*
- Molecular targets for cancer chemoprevention, ***Steele, V.E.*** *(U.S.A.)*
- Understanding early life exposures in childhood and adult cancers, ***Suk, W.A.*** *(U.S.A.)*
- Molecular epidemiology: Cancer etiology and prevention, ***Wild, C.P.*** *(IARC, FRANCE)*
- Recognition of 'foreign' antigens by the immune system, ***Wilson, I.A.*** *(U.S.A.)*

Symposia (partial list)

Cancer Etiology, Mechanisms and Epigenetics: ***Trumpp, A.*** *(GERMANY);* ***Trosko, J.E.*** *(U.S.A.);* ***Herceg, Z.*** *(IARC, FRANCE);* ***Mutirangura, A.*** *(THAILAND);* ***Sicinski, P.*** *(U.S.A.)*

Carcinogenesis: Environment and Emerging Exposures: ***Autrup, H.*** *(DENMARK);* ***Collman, G.*** *(U.S.A.);* ***Thiantanawat, A.*** *(THAILAND);* ***Schrenk, D.*** *(GERMANY);* ***Kanno, J.*** *(JAPAN)*

Molecular Approaches and Targets for Cancer Therapy and Prevention: ***Chakrabarty, A.M.*** *(U.S.A.);* ***Wogan, G.N.*** *(U.S.A.);* ***Kaina, B.*** *(GERMANY);* ***Surh, Y-J.*** *(SOUTH KOREA);* ***Au, W.W.*** *(P.R. CHINA)*

Drug Discoveries: ***Newman, D.J.*** *(U.S.A.);* ***Nifantiev, N.E.*** *(RUSSIA);* ***Burgess, K.*** *(U.S.A.);* ***Chen, D.*** *(SOUTH KOREA);* ***Shriver, Z.H.*** *(U.S.A.)*

New Approaches Towards Individualized Cancer Therapeutics: ***Rossbach, M.*** *(SINGAPORE);* ***Novina, C.D.*** *(U.S.A.);* ***Banerji, U.*** *(U.K.);* ***Hokland, P.*** *(DENMARK); Zänker, K.S. (GERMANY)*

Recent Advances in Liver Cancer Research: ***Wiltrout, R.H.*** *(U.S.A.);* ***Wang, X.W.*** *(U.S.A.);* ***Ng, I.O.L.*** *(HONG KONG);* ***Groopman, J.*** *(U.S.A.);* ***Loffredo, C.A.*** *(U.S.A.)*

Collegium Ramazzini's Symposium on Hot Topics on Environmental and Occupational Origins of Cancer: ***Straif, K.*** *(IARC, FRANCE);* ***Landrigan, P.J.*** *(U.S.A.);* ***Soffritti, M.*** *(ITALY);* ***McDiarmid, M.*** *(U.S.A.);* ***Koh, D.S.Q.*** *(SINGAPORE);* ***Xia, Z-L.*** *(P.R. CHINA)*

Arsenic: Complex Environmental Contaminant Linked to Cancer and Other Chronic Diseases: ***Fry, R.C.*** *(U.S.A.);* ***Ruchirawat, M. and Navasumrit, P.*** *(THAILAND);* ***Tokar, E.J.*** *(U.S.A.);* ***Smith, A.*** *(U.S.A.);* ***Kim, K.W.*** *(KOREA)*

Approaches to Early Detection and Diagnosis: ***Gascoyne, P.R.C.*** *(U.S.A.);* ***Frei, E.*** *(GERMANY);* ***Engelward, B.P.*** *(U.S.A.);* ***Strauss, L.G.*** *(GERMANY);* ***Svasti, J.*** *(THAILAND)*

Towards the Cure: Targets for Therapeutic Intervention: ***Gant, T.W.*** *(U.K.);* ***Savaraj, N.*** *(U.S.A.);* ***Wangpaichitr, M.*** *(U.S.A.);* ***Isidoro, C.*** *(ITALY);* ***Fetzer, O.*** *(U.S.A.)*

CALL FOR ABSTRACTS:

All congress participants are invited to submit abstracts for poster presentations. The final selection will be made by the Scientific Committee based on significance and quality of work.

Deadline for abstract submission is on **September 1, 2012.**

LIST OF TOPICS FOR POSTER PRESENTATIONS:

1. Cancer Etiology and Mechanisms
2. Early Detection, Diagnosis and Prognosis
3. Cancer Prevention
4. Towards the Cure
5. New Approaches Towards Cancer Therapeutics
6. Molecular Targets for Therapeutic Intervention
7. Drug Design, Discovery and Development

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