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# Chulabhorn Research Institute

# INTERNATIONAL CENTRE FOR ENVIRONMENTAL AND INDUSTRIAL TOXICOLOGY (ICEIT)

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

## THE PRINCESS CHULABHORN DISTINGUISHED LECTURE SERIES III

### *Innovative Scientific Paradigms in Cancer Chemotherapy*
### *13 December 2005*


*From left to right:* Prof. J.M. Essigmann, Prof. P.A. Sharp, Prof. Dr. HRH Princess Chulabhorn, Prof. R. Noyori, Prof. R. Sasisekharan, and Prof. N. Rosen

This year's Distinguished Lecture Program was organized to mark the auspicious occasion of Her Royal Highness Princess Chulabhorn's 48th birthday anniversary.

The theme, Innovative Scientific Paradigms in Cancer Chemotherapy, very much reflects Her Royal Highness' special interest in cancer research, evident in the new venture to be added to the Chulabhorn Research Institute's varied activities: the creation of a cancer center that will make available to Thai patients the most up to date cancer treatment.

The five eminent scientists who delivered the lectures are all at the forefront of the most recent developments in cancer research. This years' distinguished lecturers were:

**Professor Phillip A. Sharp** *(Nobel Laureate in Physiology or Medicine, 1993)*, Center for Cancer Research, Massachusetts Institute of Technology, U.S.A.; **Professor Ryoji Noyori** *(Nobel Laureate in Chemistry, 2001),* RIKEN and Department of Chemistry, Nagoya University, Japan; **Professor John M. Essigmann,** Massachusetts Institute of Technology, U.S.A.; **Professor Ram Sasisekharan,** Massachusetts Institute of Technology, U.S.A.; and **Professor Neal Rosen,** Memorial Sloan-Kettering Cancer Center, U.S.A.

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## THE PRINCESS CHULABHORN DISTINGUISHED LECTURE SERIES III

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In her opening address on this landmark occasion, Her Royal Highness expressed her appreciation of the kindness and generosity of the five most distinguished guest lecturers for accepting the invitation to share with the invited audience the knowledge and excitement which is an essential part of being at the forefront of scientific and medical research developments. Over 500 invited guests and participants' attended this year's event.

The lectures presented were on the following topics:

**Professor Phillip A. Sharp**

- The Biology and Therapeutic Potential of Short RNAs

**Professor Ryoji Noyori**

- Pursuing Practical Elegance in Chemical Synthesis

**Professor John M. Essigmann**

- Design of Anticancer Agents that Intentionally Disrupt Multiple Biochemical Pathways

**Professor Ram Sasisekharan**

- Understanding and Exploiting the Roles of Glycans in Cancer

**Professor Neal Rosen**

- Mechanism-Based Cancer Therapy: The Promise and the Challenge

In her closing remarks, Her Royal Highness thanked the lecturers for their outstanding contributions, stating that the presentations of new research and developments in the area of cancer therapy would be a source of inspiration to all who work in the areas of cancer research and treatment in Thailand.

# AIR POLLUTION AND FATAL CORONARY HEART DISEASE IN WOMEN

A growing body of evidence links chronic exposure to air pollution – especially particulate matter (PM) – with mortality resulting from a variety of heart, lung, and respiratory diseases. A new study corroborates this association, and indicates that women may be at greater risk than men of fatal coronary heart disease (CHD) as a result of exposure to airborne PM. When ozone ($O_3$) or sulfur dioxide ($SO_2$) is also present, women's risk appears even greater.

The study, by a team of epidemiologists at Loma Linda University, is part of the 22-year Adventist Health Study on the Health Effects of Smog. It followed 3,239 nonsmoking, non-Hispanic white adults in several mainly urban areas in California from 1976 to 1998. The researchers associated CHD deaths with prior exposure to various levels of several common air pollutants: $PM_{2.5}$, $PM_{10-2.5}$, $PM_{10}$, $O_3$, $SO_2$, and nitrogen dioxide ($NO_2$).

Participants completed a baseline health and lifestyle questionnaire in 1976, and four subsequent questionnaires covering personal sources of air pollution, such as secondhand tobacco smoke and fumes in the workplace. The researchers used airport visibility measurements (for $PM_{2.5}$ only) and data from state-run air pollution monitors (for all other pollutants) to estimate pollutant levels over time for the zip code centroids of participants' work sites and residences. Documented pollutant levels ranged from negligible to above legal limits. California's death certificate files and the National Death Index provided data on numbers and causes of deaths.

The researchers found that CHD caused 23.7% of all the deaths in the study cohort (155 women and 95 men). Adjusting for past smoking, body mass index, education level, frequency of eating meat, and calendar year (as PM levels declined over the study period), the researchers conducted statistical analyses to determine whether fatal CHD was associated with long-term exposure to the pollutants, either singly or in combinations of single gases and PM.

Women showed a relative risk for fatal CHD of 1.42, 1.38, and 1.22 with each increase of 10 micrograms per cubic meter (□g/m$^3$) of airborne $PM_{2.5}$, $PM_{10-2.5}$, and $PM_{10}$, respectively, in the air pollution they encountered during the four years preceding death. Postmenopausal women showed higher relative risks of 1.49, 1.61, and 1.30 for each 10 □g/m$^3$ increase in $PM_{2.5}$, $PM_{10-2.5}$, and $PM_{10}$, respectively. Neither $O_3$, $SO_2$, nor $NO_2$ was associated with fatal CHD on its own. $O_3$ and to a lesser degree $SO_2$ (but not $NO_2$) increased the effect of all sizes of PM. $O_3$ in conjunction with $PM_{2.5}$ yielded the most striking results: a relative risk 2.0 in all women. Contrary to findings from several other studies that found increased risk of cardiopulmonary deaths due to PM in both genders, men showed no response to any of the pollutants.

The researchers highlight several physiological mechanisms that may explain their findings. Short-term exposure to PM is known to increase arrhythmia, inflammation, and blood viscosity, and to decrease heart rate variability, among other adverse effects that could lead to fatal CHD. Other findings show that $O_3$ exposure increases lung permeability, perhaps easing PM's entry into the bloodstream.

Further studies are needed from larger cohorts and/or with longer follow-up to support the findings of a sex-differential effect of PM on risk of fatal CHD. Developing more accurate ways to assess an individual's exposure to ambient levels of PM will improve precision of risk estimates. It is important to study whether the effects of air pollution are reversible in a manner similar to that found when smokers stop smoking. The effect of different exceedance frequencies should also be explored as well as the effect of different chemical compositions of PM.

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***Source:*** Environmental Health Perspectives, Vol. 113, No. 12, December 2005.

# EFFECTS OF LOW LEVEL ENVIRONMENTAL CADMIUM EXPOSURE IN WOMEN

Identification of risk factors for chronic renal failure is essential in order to prevent reduction of life quality and life expectancy and to minimize the high costs of treatment. Cadmium is a widespread environmental pollutant known to cause renal damage. Apart from smoking, the major sources of cadmium exposure in the general population are cereals, vegetables, and shellfish. There is increasing evidence that toxic effects may occur at much lower exposure levels than those observed in occupational settings or in severely polluted environments. Still, the attempts to estimate the level of critical exposure for kidney effects have so far displayed large variations. Furthermore, possible effects in populations residing in areas with no particular industrial cadmium emission are undetermined.

Cadmium accumulates in the renal cortex and induces tubular toxicity, which is first detected as increased urinary excretion of low-molecular-weight proteins and tubular enzymes. Glomerular dysfunction may also emerge, as demonstrated in heavily exposed subjects. It is not known, however, whether the glomerulus is affected by long-term low-level environmental exposure. Diabetes, an increasing health problem in many areas and one of the leading causes of incident end-stage renal disease, has been suggested to augment the risk of cadmium-induced kidney damage.

Now a new study assesses the association between cadmium concentrations in blood and urine and a series of markers of tubular and glomerular function focusing on women at the age when the accumulation of cadmium in the kidney is at its maximum. Within a population-based women's health survey in southern Sweden, researchers investigated cadmium exposure in relation to tubular and glomerular function, from 1999 through early 2000 in 820 women in the age range of 53 to 64 years.

Multiple linear regression showed cadmium in blood (median, 0.38 □g/L) and urine (0.52 □g/L; density adjusted = 0.67 □g/g creatinine) to be significantly associated with effects on renal tubules (as indicated by increased levels of human complex-forming protein and *N*-acetyl-β-D-glucosaminidase in urine), after adjusting for age, body mass index, blood lead, diabetes, hypertension, and regular use of nephrotoxic drugs. The associations remained significant even at the low exposure in women who had never smoked. Associations with markers of glomerular effects were also found: glomerular filtration rate and creatinine clearance. Significant effects were seen already at a mean urinary cadmium level of 0.6 □g/L (0.8 □g/g creatinine). Cadmium potentiated diabetes-induced effects on kidney. In conclusion, the study found that tubular renal effects occurred at lower cadmium levels than previously demonstrated, and more important, glomerular effects were also observed. Although the effects were small, they may represent early signs of adverse effects, affecting large segments of the population. Subjects with diabetes seem to be at increased risk.

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***Source:*** Environmental Health Perspectives, Vol. 113, No. 11, November 2005.

# Impacts of Strong Aerosol Cooling on Climate Change

Researchers investigating the effect of fine particles known as aerosols on climate change have warned that reducing air pollution could trigger a surge in global warming causing future rises in sea level and other environmental consequences.

Because the particles are so light, they remain in the atmosphere for long periods, where they cool the Earth by reflecting radiation from the sun back out to space. However, in the future, aerosol cooling is expected to decline relative to greenhouse gas (GHG) forcing, because of the aerosols' much shorter lifetime and the pursuit of a cleaner atmosphere.

Future changes in the balance of climate forcing factors – such as increasing GHGs but decreasing aerosol burdens – mean that historical changes are not sufficient to constrain future projections. The climate will become more dependent on climate sensitivity as the aerosol burden is reduced. Furthermore, the response of the natural carbon cycle to future climate is also dependent on the climate sensitivity, implying large uncertainties in future $CO_2$ concentrations.

In the first report of the Intergovernmental Panel on Climate Change (IPCC) climate change was considered to be driven by anthropogenic GHG emissions. Our knowledge of aerosol effects were considered inadequate to estimate their magnitude. Since then, however, the number of aerosol-caused climate effects considered have steadily grown, as have the estimates of their cumulative magnitude.

All aerosol types (sulphates, organics, mineral dust, sea salt, and so on) intercept incoming sunlight, and reduce the energy flux arriving at the Earth's surface, thus producing a cooling. Some aerosols (for example, soot) absorb light and thereby warm the atmosphere, but also cool the surface. This warming of atmospheric layers may also reduce cloudiness, yielding another warming effect. In addition to these "direct" radiative effects, there are several "indirect", cloud-mediated effects of aerosols, which all result in cooling: more aerosols produce more, but smaller, droplets in a given cloud, making it more reflective. Smaller droplets are less likely to coalesce into raindrops, and thus the lifetime of clouds is extended, again increasing the Earth's albedo. Finally, modifications in rainfall generation change the thermodynamic processes in clouds, and consequently the dynamics of the atmospheric "heat engine" that drives all of weather and

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# SCIENTIFIC CONFERENCE ON ASIA PACIFIC ENVIRONMENTAL HEALTH

## *– Significant, Emerging and Current Challenges, Research and Capacity Building Opportunities, Collaborative Response Needs –*

This international Scientific Conference was held at the Convention Center, Chulabhorn Research Institute, Bangkok from 8-11 December 2005. It was jointly organized by the Chulabhorn Research Institute, the Ministry of Natural Resources and Environment and the Ministry of Public Health and was supported by World Health Organization, United Nations Environment Programme, Asian Development Bank and United Nations Development Programme.

The conference was attended by 28 designated high-level officials from Ministries of Environment and of Health from ASEAN countries, China, Japan, Mongolia and Republic of Korea and 309 invited participants.

Professor Dr. Her Royal Highness Princess Chulabhorn Mahidol who delivered the keynote lecture at the opening of the conference set the context for the Scientific Conference thus:

"The environment in which we live greatly affects our health. The World Health Report 2002, released by the World Health Organization, identified the three main environmental risks in the Asia Pacific region to be unsafe water, sanitation and hygiene; urban air pollution; and indoor smoke from solid fuels. Issues that deserve increased attention include climate and ecosystem changes, as well as transboundary air pollution.

Clean water is essential to good health yet it is a commodity that is lacking for a significant number of people, particularly in developing countries. It is estimated that 99.8% of deaths associated with unsafe water, sanitation and hygiene occur in developing countries. Clearly, this is an issue that needs to be addressed.

The challenges in urban settings revolve around air pollution as well as impacts of waste management on human health. The major source of urban air pollution is the combustion of fossil fuels, used for transportation, power production, or other human activities. Specific pollutants include particulate matter, polycyclic aromatic hydrocarbons, metals and volatile organic chemicals which can lead to both acute and chronic disease outcomes. In order to be able to reduce the risks associated with exposures to such pollutants, it is necessary to use science as the basis for policy actions that will reduce exposures to acceptable levels.

In many parts of the world people are exposing themselves to high levels of air pollution from indoor activities such as heating and cooking through the use of solid fuels. The types of pollutants emitted from such activities include respirable particles, carbon monoxide, sulfur oxides and benzene. Many studies have strongly linked these pollutants with disease outcomes such as lower respiratory infections, chronic obstructive pulmonary diseases and cancer.

It is increasingly the case that environmental policies and practices of one country do not only affect the people within that country. There must be a concerted effort to tackle many of the environmental issues facing the world today.

It is crucial that our attempts to tackle these aforementioned issues are based on research and collaboration. Promoting research that will form the fundamental basis for taking preventive or corrective action is of the utmost importance. Policy actions require sound scientific evidence."

The program of the Scientific Conference was organized under two main headings: Emerging Environmental Health Challenges and Significant Environmental Health Challenges, each with four main sessions comprising a number of presentations and roundtable and panel discussions.

The eight main sessions of the conference were as follows:

- Climate Impacts on Environmental Health
- Transboundary Air Pollution and Environmental Health
- Ecosystem Change and Human Health
- International Risk Assessment and Management of Chemicals with Focus on Persistent Organic Pollutants

- Challenges in Rural and Peri-Urban Settings
- Challenges in Urban Settings
- Research, Education, Training and Financing for Significant and Emerging Environmental Health Challenges
- Opportunities and Modalities for Increasing Regional Cooperation in Environmental Health

The presentations and discussions in these eight main sessions focused on ASEAN and East Asia and took into account the economic dynamism; quest for state of the art science and technology; the priority accorded to learning and knowledge; the diverse and long cultural traditions and practices which respect the old and incorporate the new; and the increasing trend in cooperation between and amongst the countries in the Asia Pacific region. As outcomes to the deliberations, the conference identified the following main areas for action and elaboration:

- Significant, emerging and priority areas for research at the interface of environment, health and development.
- The major thematic areas, from the structure of the Scientific Conference programme of an evolving framework for increasing understanding and improving management of the expanding area of environmental health.
- The differentiated needs for capacity building and training to support the Millennium Development Goals.
- The need to promote and facilitate the introduction of pedagogically unique education that will fuse research and teaching, enhancing enquiry and the search for knowledge and innovations.
- Information and data dissemination and exchange systems on environmental health, drawing upon the advances in information and communication technologies and systems.
- Mechanisms and means to foster and support collaboration amongst disciplines, countries, and major stake holders.
- New and innovative funding modalities for addressing environmental health.
- The need for a Network of public and private sectors scientific institutions for collaborative research, education, training and capacity building, to support regional initiatives and the envisaged Regional Ministerial Forum.

# The Second High-Level Meeting on Health and Environment in ASEAN and East Asian Countries

## 12-13 December 2005, Bangkok, Thailand


The highlights of issues raised by the Scientific Conference on Asia Pacific Environmental Health and the response measures needed were presented at the Second High-Level Meeting that was held on 12 December 2005, immediately following the Scientific Conference. At the end of 2006, the First Joint Ministers of Environment and of Health Forum of ASEAN countries, China, Japan, Mongolia and Republic of Korea will be held in Thailand, underscoring recognition and importance of the emerging and expanding area of environmental health. The goal of accelerated and sustained human and economic development would be difficult to attain if the health of the people and the environment which they depend upon for life support and sustenance are impaired. The interconnectedness of health and environment was clearly presented and articulated at the Scientific Conference.

The presentations by renowned scientists and practitioners and the highlights of issues and response measures needed that emerged from the conference, will be considered by ministers in this year's Ministerial Forum.

These issues could also help catalyze institutions in Asia Pacific to increase research, education and training in the emerging area of environmental health.

# RESEARCH AT CRI

## GENOTOXIC AIR POLLUTANTS: A STUDY OF TRAFFIC-CONGESTED AREAS OF BANGKOK

***With the seemingly ever increasing number of vehicles and traffic congestion in our cities and urban areas, atmospheric pollution from incomplete fossil fuel combustion has become a major health hazard in many countries.***

In order to gauge the seriousness of this problem, a study has been carried out in various susceptible groups of the population in 5 traffic-congested areas in Bangkok, Thailand.

Two of the main genotoxic substances found in urban atmospheric pollution are polycyclic aromatic hydrocarbons (PAHs) and benzene. Exposures to these compounds are a concern, especially in occupational exposures, where levels tend to be higher, and in children, where there is a potentially greater susceptibility to their toxic effects.

PAHs constitute a large class of compounds that are generated through the incomplete burning of fossil fuels, tobacco, and meat, as well as natural-occurring processes such as volcanic eruptions and forest fires. Less than 20 of these compounds, out of more than a hundred, have been well-studied and characterized, and many of those, including benzo[a]pyrene (BaP), have been classified as probable human carcinogens. Exposures to PAHs can occur in the home, or occupationally, and may be through the inhalation of contaminated air or the consumption of contaminated food and water. Biomarkers have been developed to assess human exposure to PAHs. Urinary 1-hydroxypyrene (1-OHP) has served as a marker of occupational exposure to volatile PAHs where levels are generally low in people exposed only to ambient air pollution.

Benzene is also found in the environment from both natural and anthropogenic sources. It is found in crude oil and is released during volcanic eruptions and forest fires. Significantly, benzene is also released into the atmosphere from burning of coal, tobacco smoke, and gasoline. The primary route of exposure to benzene is through inhalation of contaminated air. Benzene is classified as a known human carcinogen, with the main target tissue being the hematopoietic system. Apart from measuring ambient and blood levels of the parent compound, urinary *trans,trans*-muconic acid *(t,t*-MA*)* is a good indicator for assessing exposure to low levels of benzene.

Environmental monitoring of air pollutants such as benzene and PAHs is important because the information obtained can help to ascertain if there is a potential health problem and who the high-risk groups are.

In the present study, 5 heavily congested areas of Bangkok were chosen as study locations for roadside levels of PAHs and benzene, namely the Pratunam, Banglampu, Chakrawad, Pratumwan, and Anusawaree areas. One temple from each of 3 of these areas (Pratunam, Banglampu, and Anusawaree), located approximately 500 m from the main roads, was chosen in which to study ambient air levels, personal exposure levels, as well as biomarkers of exposure for all test subjects. Three schools were chosen in which to study exposures of school children to PAHs and benzene. Two of these schools are situated in Bangkok (Chakrawad and Pratumwan) and the other is situated in Bangphra district, Chonburi province.

All test subjects were non-smoking, healthy volunteers between the ages of 18 and 40. School

children were healthy 10 to 12 year-old boys. Street vendors set up their stalls directly at the roadside. The 2 control groups were monks/nuns who spent most of their time in the temples, and primary school children who attended a rural school outside Bangkok.

Air particulates for PAH analysis were collected on glass fiber filters (37 mm) using personal air samplers pump (2 L/min). Benzene was sampled by attaching diffusive badges (3M organic vapor monitor 3500). Air samples were collected from both ambient air and in the breathing zone of study subjects for 8 h. Urine samples were collected in the morning (prior to the start of the work or school day) and afternoon (at the end of the work or school day), and stored frozen until analysis.

In a previous study carried out in Bangkok, it was found that traffic policemen were exposed to PAHs in the range of 46.60-96.95 ng/m$^3$. Those levels are very similar to levels from samples collected directly on the roads in this study (32.18-83.88 ng/m$^3$). Compared to levels measured directly on the road, levels measured at roadside in the present study were

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relatively lower (7.10-83.04 ng/m$^3$). Levels measured in temples, 500 m away from main roads, ranged from 1.67 to 3.04 ng/m$^3$. It may be concluded from this observation that occupational exposure groups at greatest risk are those who have to work directly on the roads, such as traffic policemen or street vendors who set up their stalls at roadsides and are exposed to pollution from traffic for significant portions of their day.

Differences in occupational exposure levels to PAHs were as expected. Clothes vendors had higher PAH exposure levels than the control population (monks and nuns), while grilled-meat vendors had the highest exposure levels, most probably due to the additional source of PAHs from the grilling of meat. Of particular interest in the study was that the exposure levels in monks and nuns were greater than the ambient temple levels. It is possible that monks and nuns were exposed to PAHs from other temple-related sources, for example, incense and candle burning. Additionally, exposure through passive smoking cannot be ruled out.

Urinary 1-OHP has been reported in units of □mol 1-OHP/mol creatinine. Normalization of urinary 1-OHP levels to creatinine clearance factors out effects of urine concentration on 1-OHP levels. Urinary 1-OHP levels were generally higher in the street vendor groups compared to controls, except for the urine samples collected in the morning for clothes vendors. Apart from being a baseline measure to which afternoon levels can be compared to determine changes in urinary 1-OHP levels that result from exposures during the working day, morning levels may also be indicative of exposures outside of work (i.e., at home). Morning levels in grilled-meat vendors were statistically significantly higher than in controls and this may be due to some pre-working day activity, e.g., traveling in or near traffic from home to the work site, or preparation of the work stall, particularly the starting of the fire grill or the pre-grilling of some meat. Another possible reason is the incomplete clearance of 1-OHP within the previous 12-h period. As expected, afternoon levels were significantly higher than morning levels in clothes vendors, but surprisingly, this was not the case with the grilled-meat vendors. One of the disadvantages to using creatinine-normalized data is that creatinine levels can be affected by factors such as physical exertion. It is quite possible that this is the reason for afternoon levels not being significantly higher than morning levels in grilled-meat vendors. When they were expressed as ng 1-OHP/L urine, afternoon levels were clearly higher than morning levels, even though not statistically significantly so.

Primary school children in the Bangkok schools chosen for this study were exposed to significantly greater levels (5-fold; $P < 0.001$) of total PAHs than children in the rural school and this was reflected in the urinary 1-OHP levels, which were significantly higher in urine samples collected from the Bangkok school children at all 3 time points of sample collection.

Compared with results seen in adults (i.e., monks and nuns), who were exposed to similar levels of total PAHs, the finding that urinary 1-OHP levels in the afternoon were not significantly higher than those in the morning would seem to suggest that these exposure levels (5.34-6.70 ng/m$^3$) over the associated exposure period, were not enough to cause significantly elevated levels in either children or adults. Another interesting observation was that levels in urine samples collected the morning of the following day were significantly higher than in samples collected the previous morning. This would seem to imply an increased exposure after the end of the school day.

Ambient air levels of benzene at various sites ranged from 16.35-49.25 ppb at roadsides and 10.16-16.25 ppb at 500 m from the roads. Mean exposure level of benzene in street vendors was approximately 2-fold higher than monks and nuns ($P < 0.001$). Also, afternoon levels of urinary *t,t*-MA were statistically significantly higher in street vendors than in monks and nuns ($P < 0.05$).

The Bangkok school children were exposed to 2-fold more benzene than school children from the rural school and this difference is statistically significant ($P < 0.001$). This was reflected in blood benzene levels, which were also significantly higher in the Bangkok school children than the school children from the rural school ($P < 0.01$). As far as urinary *t,t*-MA levels were concerned, there was an increasing, yet not statistically significant, trend with respect to afternoon levels compared to morning levels in Bangkok school children.

In terms of the increasing trend observed in afternoon *t,t*-MA levels with respect to the morning, levels decreased the following morning, signaling a lack of significant benzene exposure outside of school, which contrasts with the present findings with PAHs.

It is a concern that levels of exposure to genotoxic compounds such as benzene and certain PAHs are relatively high in certain populations, due in part to the increased use of automobiles and other modes of transportation powered by fossil fuels, yet it is fortunate that there is also an increased awareness as to the potential health impacts of this exposure and that much effort is currently being expended to determine exposure levels and to identify people who are at risk. With a clearer understanding as to the patterns of exposure to these genotoxic compounds and who are at risk, it may be possible to initiate preventive or corrective measures so that the health risks from exposure to traffic related pollution can be reduced.

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***Source:*** Toxicology and Applied Pharmacology, Vol. 206, No. 2, August 2005.

# ARSENIC INDUCED APOPTOSIS IN RAT LIVER

Under normal circumstances apoptosis is a naturally occurring process by which organisms intentionally eliminate damaged cells. The cell population control system can be disrupted by toxicant exposure, including exposure to metallic compounds. *In vitro* arsenic exposure leads to cell death through apoptosis. Now a new study attempts to elucidate the role of free radicals in arsenic toxicity and to investigate the nature of *in vivo* sodium arsenite induced cell death. The results of biochemical assays show a significant elevation in hepatic cytochrome-P450 and lipid peroxidation. It is suggested that arsenic-induced lipid peroxidation in liver could possibly result from an enhanced microsomal oxidative capacity induced by arsenic. Thus, elevated levels of cytochrome-P450 would lead to high rates of free radical production, which, in turn, would favour increased rate of lipid peroxidation. The study also shows significant decrease in GSH level along with significant fall in GSH generating enzymes (G6PD and GR) and scavenging enzyme (GST, GPx, SOD, CAT). Such alteration of oxidative stress markers is suggested to be due to overuse failure of the antioxidant defense system secondary to reactive oxygen species production as evidenced by earlier studies.

Cell death is thought to take place by at least two ways: apoptosis and necrosis. Apoptosis, frequently referred to as "programmed cell death", is an active and physiological mode of cell death, in which the unneeded or diseased cell die through a controlled process. It was formally labeled apoptosis. In contrast, necrosis is an uncontrolled cell death. In the present study, the cellular morphology showed cells with apoptotic features as well as cells with combination of necrotic and apoptotic features. The latter is suggested to be an expression of a specific pattern of apoptosis called delayed-apoptosis or post-mitotic apoptosis. Cells undergoing post-mitotic apoptosis are said to either show morphological features of both, necrosis as well as apoptosis, or show atypical changes which lack the key morphological and biochemical features of apoptosis. Apoptosis was further verified by carrying out Terminal deoxynucleotidyl transferase mediated dUTP Nick end-labeling (TUNEL) assay of liver cells. An increase in the TUNEL positive cells in the study groups as compared to the controls was found, thereby suggesting arsenic induced apoptosis. Increased arsenic doses led to an increase in the TUNEL positive cells, indicating that apoptosis was dose dependent. But certain necrotic cells of liver have also been shown to demonstrate TUNEL positivity. To determine if the TUNEL positive cells are really apoptotic, DNA gel electrophoresis was carried out. A ladder pattern was obtained which is said to be highly specific for apoptotic mode of cell death, thereby confirming arsenic induced cellular apoptosis. It is suggested that, while classical apoptosis is seen in the heavily damaged cells, the less damaged cells undergo replication on a damaged DNA template. During the future replications of these surviving cells, their DNA damage gets amplified and the cells finally die by the post-mitotic apoptosis and thus manifest as cells with atypical morphological features. Although any linkage to carcinogenic effect is tenuous in the present study, enhanced apoptosis is thought to be associated with carcinogenesis, at least in part, through a selection process pertaining to subpopulation of cells that are damaged but yet survive. It is suggested from this study that following chronic arsenic exposure, the cells in this sub-population might be identified by their combined apoptotic and necrotic morphological features. The detection of such cells may thus help in estimating risk of arsenic induced carcinogenesis, which warrants further research.

***Source:*** Toxicology, Vol. 217, January 2006.

## Impacts of Strong Aerosol Cooling on Climate Change

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climate. The recent tremendous growth in knowledge of the climatic effects of aerosols, along with the emergence of the likelihood of positive feedbacks between climate and the carbon cycle, have transformed the orderly picture of climate change of the early 1990s, dominated by GHG warming, into a complex mix of opposing effects.

Incomplete consideration of aerosols in current climate models may well have led to an underestimation of the true climate sensitivity. Recent analysis suggests the possibility that climate change in the twenty first century will exceed current estimates with unpredictable consequences for the Earth system.

To reduce these uncertainties a multi-pronged approach is needed. First, there is a great need for *in situ* studies that investigate the response of cloud microphysics and dynamics to enhanced aerosol concentrations. Second, at the regional and global scale, the effects of aerosols on cloud properties and abundance must be studied using remote-sensing data from the newly available and upcoming satellite sensors. Third, parameterizations of cloud processes and feedbacks in General Circulation Models (GCMs) must be improved. Finally, uncertainties in feedbacks that are strongly dependent on climate sensitivity, such as the carbon cycle feedback, must also be reduced, through process studies and model improvements.

***Source:*** Nature, Vol. 435, June 2005 and Vol. 438, December 2005.




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