



## Abstract-Topic A

Author	Chunbo Cai
Institution	Department of Physical Medicine, Kaiser San, Francisco Medical Center
Email	
Origin	California, USA
Paper NO.	A101

**Title:**

*The health effects of ozone: good up high-bad nearby*

**Abstract:**

Ozone is a highly reactive gaseous molecule consisting of three oxygen atoms. Ozone occurs naturally in the stratosphere (upper atmosphere), where Ozone absorbs ultraviolet (UV) light, reducing exposure to harmful radiation that causes skin cancer and cataracts. In the troposphere (lower atmosphere), ozone is formed primarily from photochemical reaction of man-made air pollutants, also called "ambient" or "ground-level" ozone. Ground level ozone can damage the respiratory tract, leading to a number of adverse health effects including induction of respiratory symptoms decrements in lung function, inflammation of airways, and associated with exacerbation of existing asthma and other chronic lung diseases.



## Abstract-Topic A

<b>Author</b>	<b>Haidong Kan</b>
Institution	Fudan University
Email	haidongkan@gmail.com
Origin	Shanghai, China
Paper NO.	A102

**Title:**

*Air pollution and population health in China*

**Abstract:**

Although China has achieved great progress in ambient pollution reduction in the past two decades, it is still one of the few countries with the worst air pollution levels in the world. Exposure to outdoor air pollution is being considered a major determinant of population health in China. Dozens of epidemiological studies on air pollution and mortality/morbidity have been conducted in China, using time-series, case-crossover, or cross-sectional designs. The increased health risks observed among Chinese population are similar in magnitude, per amount of pollution, to the risks found in other parts of the world. However, the importance of these increased risks is greater than in North America or Europe, because the air pollution in China is at much higher levels in general and Chinese population accounts for more than one fourth of the world's totals. There has been no air pollution cohort study currently available in China examining the long term effects of air pollution; also, no published Chinese data assessed the relation between air pollution and sub-clinical indicators. Future research in China should focus on the prospective analysis of association between air pollution and cardiopulmonary disease and the likely the underlying pathophysiologic link.



## Abstract-Topic A

<b>Author</b>	<b>Shiyong Wu</b>
Institution:	RTI
Email	swu@rti.org
Origin	Research Triangle Park, North Carolina, U.S.A.
Paper NO.	A103

**Title:**

*Using statistical techniques to identify air pollutants associated with asthma attack*

**Abstract:**

A group of important air pollutants are volatile organic compounds (VOCs). The purpose of this study is to use statistical techniques to explore the differences in patterns of VOCs found in breath samples collected from asthma patients at baseline and onset of asthma attacks. Method: Longitudinal breath samples were collected from 24 asthmatic children. Samples were analyzed using gas chromatograph/mass spectrometry and hundreds of VOCs were identified. Several statistical techniques were used to identify multivariate intensity patterns of the VOCs and their correlation with the onset of asthma attacks. Results: Interesting clusters of VOC compounds were discovered as potential triggers of asthma attacks. A group of compounds that might be used for potential biomarkers of the asthma attack were also identified. Significance: Indoor air pollution has been well recognized as an important type of air pollution. Using gas chromatograph, hundreds of potentially harmful VOCs can be measured simultaneously. Our results indicate that the chromatograph analysis combined with advanced statistical techniques have great potential in identifying pollutants and their effects on human health.



## Abstract-Topic A

Author	Zilue Tang
Institution:	Kaiser Permanente Vallejo Hospital
Email	ziluetang@hotmail.com
Origin	Moraga, CA, USA
Paper NO.	A104

### **Title:**

*Legislation of environmental and occupational health in the United States*

### **Abstract:**

There are numerous environmental and occupational laws in the United States. These laws are legislated by congress, enforced by the executive branch, including the White House and a variety of government agencies such as EPA, OSHA, FDA. Disputes and individual violations of the law are judged by the courts. This presentation is going to introduce basic concepts about environmental and occupational laws in 3 categories: 1), pollution control; 2), toxic chemicals, genetically modified organisms, and Hazardous wastes; 3), occupational safety and health standards.



## Abstract-Topic A

<b>Author</b>	<b>Hong Zhang</b>
Institution	Alta Bates Summit Hospital, Oakland,
Email	zhangh1@sutterhealth.org
Origin	CA, USA
Paper NO.	A105

### **Title:**

*Occupational and environmental medicine in US and its implications for China: collaboration opportunities for the dragon and the eagle*

### **Abstract:**

Occupational and Environmental Medicine in US and its Implications for China: Collaboration Opportunities for the Dragon and the Eagle The history of Occupational and Environmental Medicine (OEM) in US began in rural areas and then extended to the urban work place. Although an Italian physician published Disease and Occupations in the 17th century, it was during the 19th century, when substantial industrial work began in mines, on railroads, and at other US construction sites, that physicians started providing care for work-related injuries. By the early 20th century, it was clear that there was an increased need for health care relevant to industrial injuries. A rising number of lawsuits against employers for work-related injuries led to the development of a fault system: workers compensation statutes at national and state levels. Workers Compensation (WC) thus was created. WC includes medical and indemnity benefits to injured employees for all medical care receive wage replacement, either temporarily, permanently or both. Political and marketplace factors have shaped the WC form and function in the 21st century. US OEM provides three levels of medical care: primary (prevention), secondary (diagnosis and treatment) and tertiary (disability/impairment issues). OEM in the US encompasses all health care provided relevant to the work place. The range of OEM practice, unlike most other medical specialties, frequently involves other professionals such as industrial hygienists, epidemiologists, toxicologists, and WC administrators. A board certified OEM physician not only needs a MD license and completion of post MD regular clinical residency training; but he/she also needs to be a MPH. With the advent of the global community and international industry and business relationships, increasing numbers of people are coming in and out of China for business reasons. OEM finds itself no longer dealing only with local health care issues but with worldwide concerns as well. Further, the US has over a century of experience in organized OEM. China is an emerging economic world power. Exciting opportunities for collaboration in clinical health care and research exist. I urge an interface to create an international system of Occupational Medicine and Environmental Health.



## Abstract-Topic A

### Author

Jian Ping Wang<sup>1,2</sup>  
Guang Yu Guan<sup>1,3</sup>  
Jack C.Ng<sup>1,2</sup>

### Institution:

1.National Research Centre for Environmental Toxicology, The University of Queensland, National Research Centre for Environmental Toxicology

2.Cooperative Research Centre for Contamination Assessment and Remediation of the Environment (CRC CARE)

3.National Research Centre for Environmental Toxicology, The University of Queensland, National Research Centre for Environmental Toxicology

### Email

j.ng@uq.edu.au

### Origin

Australia

### Paper NO.

A201

### Title:

Temperature and pH effects on arsenic, selenium and cadmium toxicity to *Euglena Gracilis* Z and SMZ cells

### Abstract:

Adverse health effects by excess intake of metals and metalloids such as arsenic (As), cadmium (Cd) and selenium (Se) have become a significant health concern globally. We investigated the effects of these elements on *Euglena Gracilis* cells with an aim to establish a unicellular model for risk assessment of environmental exposure and effect. *Euglena Gracilis* strain Z (plant model) and its mutant strain SMZ (animal model) are more economical and easier to handle compared to traditional cell line culture and animal experimentation. The toxic effect of As, Cd and Se on cell viability was studied. 3mM As<sup>+3</sup> and As<sup>+5</sup> inhibited the growth rate of Z strain but a little higher concentration was required to exert similar effect on SMZ strain. Both Z and SMZ strains were sensitive to Se<sup>+4</sup> at 0.5 mM and above. Cell growth was significantly reduced by Cd<sup>+2</sup> at higher than 0.25mM. 2 mg/L (25.3 μM) of Se restored the viability of *euglena* cells when exposed to As. However, higher concentration of Se (>3mg/L, 38 μM) together with As or Cd showed enhanced toxicity. *Euglena* cells were cultured in KH medium at pH 3.5 as recommended. We found the cells didn't tolerate pH lower than 2.5. However, good growth rates and increased tolerance to metal toxicity were observed at higher pH of 4.5 and 5.5. *Euglena* survived at ambient temperatures ranged from about 5oC to 35oC, but died



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shortly when temperature reached  $>40^{\circ}\text{C}$ . At low temperatures this unicellular organism would slow down their metabolism and show resistance to metals toxicity comparing at higher temperature. These are important environmental parameters to consider when one attempts to simulate the real environmental exposure settings.  $\text{As}^{+3}$ ,  $\text{As}^{+5}$ ,  $\text{Se}^{+4}$ ,  $\text{Cd}^{+2}$  in toxic concentrations induced morphology changes in Euglena cells with  $\text{Cd}^{+2}$  being the most potent element. Our studies have demonstrated that Euglena can be used as a unicellular tool for environmental toxicology research particularly for risk assessment of metal and metalloid contamination at mine sites where acidic conditions are often present.



## Abstract-Topic A

<b>Author</b>	<b>Dionne Arthur</b>
Institution	The Univeristy of Queensland
Email	d.arthur@uq.edu.au
Origin	Australia
Paper NO.	A202

### **Title:**

*Early adaptive response to arsenic mediated oxidative stress*

### **Abstract:**

Arsenic, an environmental pollutant from both natural and anthropogenic sources, can cause cancer in multiple organs and chronic diseases in humans. Oxidative stress is considered to be a main mechanism of arsenic toxicity. It occurs when the generation of damaging free radicals exceeds that of our body's ability to control their levels. These free radicals can damage DNA, proteins and lipids in our bodies and ultimately cause the cell to either die or become cancerous. The protective mechanisms triggered by our bodies against arsenic toxicity are not fully understood. However, arsenic is known to induce two different enzyme systems: the haem oxygenase-1 (HO-1) and cytochrome P450 2a5 (Cyp2a5). These enzymes are believed to protect against oxidative damage by regulating the antioxidant bilirubin, where Cyp2a5 converts bilirubin to its bilirubin oxidative metabolites (BOMs). This project aims to investigate the basic biology of arsenic-induced Cyp2a5-mediated bilirubin oxidation pathway and identify the BOMs formed in vitro. Alteration of hepatic enzymes HO-1, Cyp2a5, reactive oxygen species (ROS) and malondialdehyde (MDA) were investigated in mice following treatment with saline (control), 20, 40 or 80  $\frac{1}{4}$ mol NaAsO<sub>2</sub>/kg body weight for 6 h. Maximal induction of HO-1 and Cyp2a5 coincided with maximal accumulation of arsenic, a significant increase in oxidised glutathione to reduced glutathione ratio, and a maximal decrease in MDA (product of lipid peroxidation), as well as ROS in the liver compared to control.



## Abstract-Topic A

Author	Qing Li
Institution	Department of Hygiene and Public Health, Nippon Medical School
Email	qing-li@nms.ac.jp
Origin	Japan
Paper NO.	A203

### Title:

*Effect of forest environments on immune function*

### Abstract:

To investigate the effect of forest environments on the human immune system, we studied the effect of phytoncides (wood essential oils) on cell viability, natural killer (NK) activity and the expression of perforin, granzyme A and granulysin in human NK cells in vitro. Phytoncides such as *Chamaecyparis obtusa* (Hinoki) stem oil and alpha-pinene at higher concentrations (>1 ppm) significantly show cytotoxicity on human NK cells, whereas phytoncides at lower concentrations (0.1 ppm) significantly enhance human NK activity in a dose-dependent manner and significantly increase the expression of perforin, granzyme A and granulysin in human NK cells determined by flow cytometry. These findings strongly suggest that forest environments have beneficial effects on human immune function. Thus, we investigated the effects of forest environments on human immune function. Subjects participated in a three-day/two-night trip to forest areas, and blood and urine were sampled on days 2 and 3, and on days 7 and 30 after the trips. NK activity and the numbers of NK, and granulysin-, perforin-, and granzymes A/B-expressing lymphocytes in the blood and the concentration of urinary adrenaline were measured. The same measurements were made before the trips on a normal working day as a control. The NK activity, the numbers of NK, granulysin-, perforin-, and granzymes A/B-expressing cells on forest bathing days were significantly higher than those on the control days, whereas the concentration of urinary adrenaline on forest bathing days were significantly lower than that on the control days in both males and females. The increased NK activity lasted for more than 30 days after the trip, suggesting that a forest bathing trip once a month would enable individuals to maintain a higher level of NK activity. In contrast, a visit to the city as a tourist did not increase NK activity, the numbers of NK cells, or the level of intracellular granulysin, perforin, and granzymes A/B. These findings indicate that forest environments resulted in an increase in NK activity, which was mediated by increases in the number of NK cells and the levels of intracellular granulysin, perforin, and granzymes A/B.



## Abstract-Topic A

<b>Author</b>	<b>Masanori Horie</b>
Institution	National Institute of Advanced Industrial Science and Technology (AIST)
Email	masa-horie@aist.go.jp
Origin	Osaka, Japan
Paper NO.	A204

### **Title:**

*In vitro* evaluation of cytotoxicity induced by ultrafine metal oxide: Particularly, cellular influences induced by ultrafine NiO particles

### **Abstract:**

Metal oxide is one of the important industrial materials. Advancements in industrial technology have enabled the manufacture of ultrafine metal oxide particles. An ultrafine metal oxide particle has higher physical and chemical activities. Therefore biological effect will be stronger than fine particles. The aim of the present study is to understand of potential risk and mechanism of cellular responses by ultrafine metal oxide particles. Particularly, we focused on ultrafine nickel oxide (NiO). It is well known that nickel compounds have exert toxic activity. However, property of cellular response by ultrafine NiO particle is still unclear. In this study, the influence of ultrafine NiO on cellular responses was examined in vitro in order to obtain fundamental data on the biological effects of ultrafine NiO particles. Ultrafine NiO particles showed higher cytotoxicity in cultured cells than fine NiO particles; they also showed higher solubility in the culture medium than fine NiO particles. It is known that the toxicity of nickel compounds is mainly due to the Ni<sup>2+</sup>. Moreover, we prepared a uniform and stable dispersion of NiO in the culture medium, examined its influence on cell viability, and compared it with that of NiCl<sub>2</sub>, which is a soluble nickel compound. If extracellular Ni<sup>2+</sup> concentration was same, the cytotoxic effect of NiO was stronger than NiCl<sub>2</sub>. Transmission electron microscope (TEM) observations showed the uptake of both ultrafine NiO and fine NiO particles into HaCaT cells. The results suggest that the stay of particles in the cells and intracellular Ni<sup>2+</sup> release are an important factor that determines the cytotoxicity of NiO. Additionally, some biomarkers were measured in ultrafine NiO exposure cells. Intracellular reactive oxygen species level and caspase-3 activity was increased in the ultrafine NiO exposure cells. These results indicate uiltrafine NiO particles induce oxidative stress and subsequently apoptosis in the cells.



## Abstract-Topic A

<b>Author</b>	<b>Mohammed Mahabubur Rahman</b>
Institution	Education and Research Center for Subtropical Field Science, Kochi University,
Email	mahabubtarek76@gmail.com
Origin	Japan
Paper NO.	A205

### Title:

*Accumulation, distribution and toxicological effects induced by cadmium on the development of mangrove plant Kandelia candel (L.) Druce*

### Abstract:

A study was performed for investigating accumulation, distribution and toxicological effects induced by cadmium (Cd) on the development of the mangrove seedling *Kandelia candel* (L.) Druce. The five month old seedlings were harvested for the laboratory analysis. Seedlings treated with increasing concentrations of CdCl<sub>2</sub> solution (0, 1, 5, 10, 15, 20, 25 mg L<sup>-1</sup>, respectively) were grown in a basic nutrient solution for three months. This study showed that Cd treatment significantly decreased growth of *K. candel* in terms of seedling height, leaf number and total biomass. At the highest 25 mg L<sup>-1</sup> Cd exposure, there was a 30.54% decrease in final seedling height, 42.68% decrease in leaf number and a 41.57% decrease in total biomass. The present study demonstrates that Cd accumulation ability of *K. candel* seedlings increased with the increase of treatment strength. When comparing Cd concentration in different plant parts with respect to their controls, the results showed that treated plant root bioaccumulated high amounts of Cd. More than 95% of Cd was accumulated mainly in roots. The Cd content in the leaf was only 0.60 % - 8.77% of that in root. The distribution pattern of Cd in *K. candel* was roots > hypocotyls > stems > leaves. Based on the leaf symptoms and morphological change of *K. candel* seedlings under Cd stress, this study indicates that Cd is phytotoxic to *K. candel*.



## Abstract-Topic A

<b>Author</b>	<b>Xiwen Jiang</b>
Institution	The University of Hong Kong
Email	yuanyecat@hotmail.com
Origin	China
Paper NO.	A206

### **Title:**

*CFP algal toxins: development of analytical and bioassay detection methods and assessment of environmental transfer in marine food webs*

### **Abstract:**

Ciguatera is a disease commonly associated with consuming toxic tropical reef fish. These reef fish have accumulated ciguatoxins through what they eat. Ciguatera fish poisoning (CFP) are seafood-toxin illnesses in Hong Kong and Mainland China, and are of growing concern globally. These illnesses occur due to consumption of seafood containing toxins produced by marine dinoflagellates. Incidences of CFP have increased in recent years with increasing international trade in seafood. In this study, several fishing grounds for fishes were collected from the Republic of Kiribati, and some of them are identified to be ciguateric by NBA (Neuroblastoma Bioassay). On the other hand the toxicity of the ciguateric fish is not related with its body size. Toxins is said to be the main contribution to this disease. These dinoflagellates were found to attach themselves to macro algae, which are often, be grazed by herbivorous fish. With 18S rRNA primers and Molecular method, we found the seaweed existing in these herbivorous fishes' digest system. This will provide the sights to study the dynamics and fluxes of CTXs through marine food webs. This research will provide new methods and materials for the study of CTXs, as well as further insights into the patterns and incidences of CFP outbreaks in marine ecosystems.



## Abstract-Topic A

Author	Ling-I Hsu
Institution	Genomics Research Center, Academia Sinica, Nankang,
Email	hsu277@gmail.com
Origin	Taiwan.
Paper NO.	A207

**Title:**

*Arsenic poisoning in Taiwan: more than 50-year experiences*

**Abstract:**

Arsenic exposure is one of the most important public health issues worldwide. Long-term ingestion of arsenic in drinking water had been an environmental disaster in Taiwan. The studies on individual susceptibility to arsenic-induced health hazards have been performed in recent years. Serum  $\beta$ -carotene level, arsenic methylation capability and genetic component such as genetic variants of the enzymes involved in general xenobiotic detoxification, arsenic methylation, oxidative stress detoxification and DNA repair may explain the variations of individual susceptibility to arsenic exposure. This information is helpful for further understanding the molecular mechanisms of arsenic-induced pathogenesis, as well as the identification of subjects at high risk in areas exposed to arsenic for intervention, education and medication concern.



## Abstract-Topic A

**Author****Wenjie Zhang**

Institution:

Chinese Research Academy of Environmental Sciences

Email

flywenzi@126.com

Origin

Beijing, China

Paper NO.

208

**Title:**

*A pilot study on measurement of ambient aerosols in Beijing by single particle mass spectrometry*

**Abstract:**

An ambient measurement with aerosol time-of-flight mass spectrometry (ATOFMS) was carried out in Beijing between 18-26, June, 2006. The aerodynamic size and chemical composition of individual particles in the fine fraction (0.1-3  $\mu\text{m}$ ) was measured. The inorganic and organic components of the particles were analyzed using laser desorption ionization time-of-flight mass spectrometry, generating positive and/or negative ion mass spectra. Four major representative species were presented, including carbon-containing particles, dust, metal-rich particles, and secondary ions. The representative characteristics of each species were also discussed. As described, carbon-containing particles includes elemental carbon (EC), organic carbon (OC), C<sub>3</sub>H<sub>3</sub> particles, NaK(C<sub>3</sub>H<sub>3</sub>)-EC, and V-containing particles, with the representative m/z of 12nCn<sup>+</sup> and 12nCn<sup>-</sup>, 12nCn<sup>+</sup>, 39K<sup>+</sup> and 12nCn<sup>-</sup>, 23Na+39K<sup>+</sup> and 12nCn<sup>-</sup>, 51V<sup>+</sup> and 67VO<sup>+</sup>, respectively. The dust-containing particles includes NaK-rich, Ca-rich and soil dusts, with the representative +m/z of 23Na<sup>+</sup> and 39K<sup>+</sup>, 40Ca+-56CaO<sup>+</sup> and 57CaOH<sup>+</sup>, 23Na+-27Al+-28Si+-40Ca+-56Fe<sup>+</sup> and 70Ga<sup>+</sup> in positive ions, and with the representative -m/z of nitrate (-46NO<sub>2</sub>, -62NO<sub>3</sub>), phosphate (-79PO<sub>3</sub>)/bromine (-79Br), and sulfate (-97HSO<sub>4</sub>) in negative ions, respectively. Metal-rich particles includes lead and zinc rich particles, with the representative +m/z of +206, +207, +208 for lead and +64, +66, +67, +68 for zinc. This pilot study provides possible insights into the real-time changes in single particle mixing state as a function of size and time for aerosols in Beijing, and may provide a special useful tool for the real time analysis on the experimental simulation research on the formation of secondary ions in smog chamber.



## Abstract-Topic A

Author	Xiaoli Duan Nan Huang Feifei Wang	Zongshuang Wang Qin Li Jinliang Zhang
Institution	Chinese Research Academy of Environmental Sciences	
Email	mepjasmine@gmail.com	
Origin	Beijing, China	
Paper No.	A209	

### Title:

*Health Risk Assessment of Heavy metals in Drinking Water based on Real Measurement of Exposure Factors of Chinese People*

### Abstract:

The purpose of this research is to study the difference of health risks evaluated on the basis of measurement of exposure factors and citation of the recommended levels in EPA exposure factors handbook. Field study was carried out in Miyang county in Henan province, which is located in the junction of Yangtze river and Huai river basin. About 20 drinking water samples in different sites of this county were collected for measuring 14 heavy metals by ICP-MS. Over than 2500 people with different ages and sex were selected as research subjects. Time-activity of drinking water by ingestion and dermal contact of each individual subject during the last three days were kept in dairy in detail by questionnaire. Drinking water volume from direct and indirect consumption of water in each individual subject was measured by measuring cylinder. Time duration of dermal contact to water by washing or showering in each individual subject was measured by measuring watch and kept in record. USEPA health risk assessment models were used to predict health risks of personal exposure to heavy medals in drinking water by ingestion and dermal contact. Health risk results of each individual subject were compared between the methods of using the real measured exposure factors and by using factors recommended in USEPA exposure factors handbook. The results showed that the health risks based on real measurement of exposure factors were about 10%~30% higher than using the recommended factors. This may due to the relatively low body weight in Chinese people and higher volume of drinking water consumption when indirect water consumption was also included. For each heavy medal, health risks of children were higher than adults and women were slightly higher than men. This may result from the low body weight of children and more frequent water contact to water by women. This research indicated that exposure factors are very important in health risk assessment. Factors in USA may not be suitable for Chinese people when predicting health risks. To explore special exposure factors for Chinese people are in urgent need.



## Abstract-Topic A

**Author****Jun-Yan Hong**

## Institution

School of Public Health/Environmental and Occupational Health Sciences Institute, University of Medicine and Dentistry of New Jersey

## Email

jyhong@eohsi.rutgers.edu

## Origin

New Jersey, USA

## Paper NO.

A210

**Title:***Role of CYP2A13 in Smoking-related Human Breast Cancer***Abstract:**

Although exposure to tobacco smoke, including active and passive smoking, has been demonstrated to be an important cause of many types of human cancers, it is not clear if it plays the same etiological role in the development of human breast cancer. Cytochrome P450 (CYP) enzyme-catalyzed metabolic activation of chemical carcinogens is a critical step in environmental carcinogenesis and human CYP2A13 has been demonstrated to be the most efficient enzyme, among all the human CYPs, in the metabolic activation of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a major carcinogen in cigarette smoke. CYP2A13 also metabolically activates 4-aminobiphenyl (ABP), another major carcinogen in tobacco smoke. Recently, we demonstrated that CYP2A13 protein is selectively expressed in human breast ductal cells. We hypothesize that CYP2A13-mediated metabolic activation of NNK in situ plays an important role in the development of breast cancer. To test this hypothesis, we have established human mammary epithelial cell lines with stable expression of CYP2A13 (MCF-10A/2A13). NNK-induced toxicity was significantly increased in these cells. We are currently in the process to determine if these CYP2A13 are also more susceptible to NNK-induced malignant transformation. In addition, we plan to establish a transgenic mouse model with mammary epithelial cell-specific expression of human CYP2A13 to determine the in vivo role of CYP2A13 by induction of mammary cancer in NNK-treated humanized mice. Results from these studies will help to establish the role of tobacco smoke in breast cancer etiology/pathogenesis and provide a novel animal model for relevant mechanistic and prevention studies (supported by Flight Attendant Medical Research Institute).



## Abstract-Topic A

Author	Louming Wang
Institution:	Shenzhen Entry-Exit Inspection and Quarantine Bureau, Shekou
Email	ciqlm@126.com
Origin	Shenzhen, China
Paper NO.	A211

### Title:

*Determination of Perchlorate in Import Fertilizer*

### Abstract:

Perchlorate is a water soluble, mobile, and persistent environmental contamination something linked with the use of some kinds of fertilizer. Perchlorate may cause hypothyroidism by interfering with the uptake of iodide needed by the thyroid to produce thyroid. Generally the EPA method (EPA/600/R-01/026) is used for the determination of perchlorate in fertilizer. But the sample treatment procedure is complex as well as time-consuming and the used column have not got enough efficiency to separate perchlorate anion from others. A new determination method is developed in our laboratory by using The IonPac AS21 + AG21 column and supersonic extraction technique. The perchlorate separation efficiency of this new method achieved a better result than the EPA method. And the treatment procedure is simpler and quicker. The spike recovery reached above 90% and relative standard deviation was 1.07~3.09%. The examination of above 200 potassium fertilizer and compound fertilizer samples from 6 countries showed that perchlorate is present at levels lower than the test limit of 200 mg/kg. These preliminary results suggest that the import potassium fertilizer and compound fertilizer could not be the source for perchlorate accumulation in the food chain.



## Abstract-Topic A

### Author

Jiayin Dai

Institution:

Institute of Zoology, Chinese Academy of Sciences

Email

daijy@ioz.ac.cn

Origin

Beijing, China

Paper NO.

A301

### Title:

Proteomic analysis for testis of rats chronically exposed to perfluorododecanonic acid

### Abstract:

Perfluorododecanonic acid (PFDoA), a ubiquitous contaminant detected in environmental matrices, wildlife, and human blood, has been shown to produce adverse effects on male reproduction in rats. The mechanism of action of PFDoA in testis, however, is not well understood. In the present study, male rats were orally exposed to PFDoA (0.02, 0.2, and 0.5 mg/kg/d for 110 days), and a 2-DE gel-based proteomic approach was employed to investigate the alteration of protein expression in the testes. Matrix-assisted laser desorption/ionization (MALDI) tandem time of flight (TOF/TOF) mass spectrometry analysis allowed the unambiguous identification of 40 differentially expressed protein spots. These proteins are mainly involved in sperm activity, mitochondrial respiration, oxidative stress, cytoskeleton, and intracellular signal transduction. Furthermore, PFDoA led to decreases in activities of superoxide dismutase (SOD), mitochondrial H-ATPase, and cytochrome c oxidase as well as to an increase in lipid peroxidation in testes. Decreased serum progesterone levels and disordered mitochondria ultrastructures of testicular cells were also observed. Our results indicated that these proteins, which are involved in mitochondrial respiratory and antioxidative responses, play important roles in the inhibition of testicular steroidogenesis in response to PFDoA. Our data demonstrate that alterations of multiple pathways are associated with the toxic effects of PFDoA on testes. SOD and H-ATPase subunit d represent potential candidate biomarkers for PFDoA toxic action in testes.



## Abstract-Topic A

### Oral Presenter

Hitoshi Iwahashi

Institution:

HTRC AIST, Ikeda

Email

hitoshi.iwahashi@aist.go.jp

Origin

Osaka, Japan

Paper NO.

A302

### Title:

Evaluation of the physiology of medaka as a model animal for standardized toxicity tests of chemicals using mRNA expression profiling

### Abstract:

The Fish Acute Toxicity Test in "OECD Guideline for Testing of Chemicals" is an essential test for environmental toxicity. Here we have tried to evaluate the physiology of medaka during this test procedure by using genomics. Genomics technology can provide genome-wide expression profiles of mRNA, and these profiles correspond to the physiology of organisms. Thus, a comparison of mRNA expression profiles gives information on the reproducibility of experimental conditions. Expression profiles of mRNA were measured for medakas maintained within the allowable range of the test conditions and also under extreme conditions beyond the guidelines limits. We confirmed the high physiological reproducibility of medaka kept in the recommended conditions of the Fish Acute Toxicity Test in the "OECD Guideline for Testing of Chemicals" from the expression profiles obtained under all experimental conditions except for the type of feeding.



## Abstract-Topic A

Author	Yue Ge, Julian Preston,	Maribel Bruno Jeffrey A. Ross
Institution:	National Health and Environmental Effects Research Laboratory, United States Environmental Protection Agency, Research Triangle Park	
Email	ge.yue@epa.gov	
Origin	North Carolina, U.S.A.	
Paper NO.	A303	

### Title:

Application of OMICS data to human health risk assessment of environmental chemicals

### Abstract:

More than 30,000 new chemicals are produced yearly. Environmental exposure is world wide and so there is a great need for toxicological evaluations. The methods currently used to study the toxic effects of environmental chemicals rely mainly on histopathological or morphological studies. These are time-consuming, costly and require the use of many experimental animals. Therefore, there is an urgent demand for alternative methods and safety testing strategies which can improve the prediction of the long-term toxic potential of chemicals in short to medium term studies. Previous studies have demonstrated the potential of OMICS technologies to predict specific endpoints of toxicity after short-term in vivo exposure in animals because these methods permit the simultaneous analysis of thousands of genes, proteins or metabolites before the morphological changes occur. To apply quantitative toxicoproteomic analysis to the evaluation of toxicity of environmental chemicals for human health risk assessment, we have developed an integrated toxicoproteomic platform. This platform has been applied to the analysis of the effects of several environmental tumorigens, including arsenic, bromate, benzo[a]pyrene, and conazoles. The endpoints studied include protein expression, phosphorylation, and oxidation in mouse and rat liver, lung, thyroid, and kidney and human cells. My presentation will focus on the development of proteomics technologies and applications, to the identification of mechanisms of toxic action or modes of action which are required and routinely used for human health risk assessment of environmental chemicals.

This abstract does not necessarily reflect EPA policy.



## Abstract-Topic A

Author	Huaqin He
Institution:	College of Life Science, Fujian Agriculture and Forestry University
Email	hehq3@yahoo.com.cn
Origin	Fuzhou, China
Paper NO.	A304

### Title:

Differential regulation of proteins and phosphoproteins in rice under drought stress

### Abstract:

As economic development and urbanization proceed in many parts of Asia, drought has become the largest constraint to rice production, with over 25 million ha affected. Considerable work has recently been undertaken to understand the genetic basis of putative drought-adaptive traits in rice, but it has been difficult to identify genetic segments with clear and repeatable effects on yield under stress. Proteomics is a recent addition to the molecular tools used to analyze drought affected plants, and protein phosphorylation has been recognized as an important mechanism for environmental stress signaling. However, the differential expressing proteins and phosphoproteins induced by drought in rice are still largely unknown. In this paper, we report the identification of differential expressing proteins and phosphoproteins induced by drought stress in rice using proteomic approaches. Three of drought responsive proteins were identified, including up-regulation of late embryogenesis abundant (LEA) like protein and Abscisic acid (ABA) and stress inducible protein, down-regulation of Rieske Fe-S precursor protein. Totally ten phosphoproteins were identified. Three of these proteins, NAD malate dehydrogenase, ribosomal protein and Guanine nucleotide-binding protein beta subunit-like protein were already known to be phosphorylated under various conditions of drought and/or by exogenous ABA in different species. The functions of three other phosphorylated proteins, Abscisic acid- and stress-inducible protein, Ethylene-inducible protein and Drought-induced S-like ribonuclease could be related to stress, although not exclusively to drought stress. The decreased of serine phosphorylation of Putative r40c1 protein and OSJNBb0039L24.13 protein, the increase of serine phosphorylation of OSJNBa0084K20.14 protein were also observed in this research. However, to date, there is little direct evidence for how these three proteins phosphorylated or dephosphorylated function in vivo. In the future, it will be of interest to experimentally determine the kinases and phosphatases that act on the ten drought-regulated phosphoproteins.



## Abstract-Topic A

<b>Author</b>	<b>Hui Li</b>
Institution	Proteome Center, Sun Yat-Sen University
Email	lihui32@sysu.edu.cn
Origin	Guangzhou, China
Paper NO.	A305

### **Title:**

Network regulating of streptomycin-resistant outer membrane proteins in *Escherichia coli*

### **Abstract:**

Altered outer membrane (OM) proteins in response to streptomycin (SM) resistance have been reported, but little is known about the OM proteome and their interaction in the SM resistance. In the present study, sub-proteomic approach was utilized to characterize OM proteins of *E. coli* with SM resistance. The OM proteins TolC, OmpT and LamB were showed to be up-regulated, and FadL, OmpW and an unknown location protein Dps were down-regulated in the SM resistant *E. coli* strains. These changes at the level of protein expression were validated by 1-DE and 2-DE Western blotting. Then, genetic modified strains with the gene deletion of these altered proteins were used to investigate the possible roles of these proteins in response to SM resistance. The resulting changes in functional characterization suggest that TolC and OmpT, and Dps, respectively may play a key role in response to SM resistance directly, and negatively regulate SM resistance in *E. coli*. At last, possible interaction among these altered OM proteins in the regulation of SM resistance was characterized by comparison of these gene deletion mutants with their corresponding SM-resistant strains in changes of MIC, survival capability and protein expression with respect to the difference of those between SM-R-O and SM-R. Our results suggest that a network among these altered OM proteins.



## Abstract-Topic A

Author	Ming-Hua Wang
Institution:	Xiamen University
Email	wmhyao2007@xmu.edu.cn
Origin	Xiamen, China
Paper NO.	A306

### Title:

Proteomic response in hepatic tissue of zebrafish (*Danio rerio*) experimentally exposed to microcystin-LR

### Abstract:

MC-LR (Microcystin Leucine Arginine) is the most toxic and most frequently encountered hepatotoxin in aquatic environment, and the toxic effects of which have been examined based on conventional toxicological indices and transcriptional data in a number of previous studies. To further understand the mechanisms of action and identify the potential protein biomarkers for MC-LR exposure, two-dimensional electrophoresis (2D-electrophoresis) coupled with mass spectrometry has been used to identify protein differentially expressed in the livers of zebrafish (*Danio rerio*) following the 30 d exposure to MC-LR. Meanwhile, the ultrastructural study of hepatocyte was undertaken in the zebrafish liver, as well as the analysis of PPase activity in the hepatic tissue. In the comparison of 2D-electrophoresis gel protein profile from the control and exposed groups, 29 protein spots were found to remarkably alter in abundance (>2-fold). Matrix-assisted laser desorption/ionization (MALDI) tandem time-of-flight mass spectrometry (TOF/TOF) analysis allowed the unambiguous identity of 26 spots, corresponding to 25 different proteins. The identified proteins were involved in cytoskeleton assembly, oxidative stress, macromolecule catabolism, cell signaling and apoptosis, which confirms that proteomics approach may become a valuable tool to identify signaling pathway implicated in MC effects. In addition, microcystin-LR treatment engendered a significant damage in liver ultrastructure. However, the toxin treatment remarkably induced the PPase activity.



## Abstract-Topic A

<b>Author</b>	<b>Chan-Lai Leo</b>
Institution	State Key Laboratory of Marine Environmental Science, Xiamen University
Email	llchan@hkucc.hku.hk
Origin	China
Paper NO.	A307

**Title:** Ciguatera: Development of Analytical, Bioassay and Immunological Detection Methods and Assessment of Environmental Transfer in Marine Food Webs

**Abstract:** The occurrence of Ciguatera fish poisoning (CFP) in Hong Kong has increased in recent years with increasing international trade in seafood. The major risk from CFP at present is due to the importation of live reef fish caught from regions of high ciguatera risk. There is no system in place in Hong Kong that identifies the source of imported reef fish such that all imports are potentially contaminated. A preliminary fish sampling study in the Republic of Kiribati, a global hotspot of CFP occurrence, found that 22 of 27 of the collected reef fishes were strongly ciguatoxic as determined by an optimized mouse neuroblastoma (MNB) assay for ciguatoxin (CTX) detection, but that toxicity varied among species: the highest toxicity was found in blue-spotted grouper (*Cephalopholis argus*; 12.88ppb Pacific Ciguatoxin 1 (P-CTX1) equivalents), while the lowest toxicity was measured in brown-marbled and camouflage groupers (*Epinephelus fuscoguttatus* and *E. polyphemus*, respectively). These results suggest that some species have a higher ability to accumulate CTXs. Further analysis showed that CTX accumulation in the sampled coral reef fishes was size-independent, as *C. argus* contained the greatest toxin concentration, but was of the smallest size (length=24cm), while *E. fuscoguttatus* was of the largest size (length=90cm) but had the lowest toxicity. It is unknown however, whether there is an inter-specific and intra-specific age-dependence of CTXs in groupers. Therefore, the carnivorous fish *C. argus* has been targeted for subsequent study. The absence of signs of intoxication and overt pathology in ciguatoxic fishes suggests that the carrier species are immune to the effects of CTXs. Protein extracts of blood sera, livers and tissues of contaminated and non-contaminated reef fishes have been analyzed by 2-DE and 2-DIGE for the presence of CTX-binding proteins; the identified proteins have the potential to be useful components of receptor-binding assays for routine monitoring of CTXs in fish. In addition, a molecular technique has been used to trace the species composition in the gut of the herbivorous fishes that graze on coral rubble or macroalgae. Identification of the organism(s) responsible for the production of CTXs and their derivatives in toxic reef fishes is of critical importance for the future regulation and management of fisheries resources to ensure safe harvest and consumption of these species.



## Abstract-Topic A

### Author

Xuan-Xian Peng

Institution:

Proteome Center, Sun Yat-Sen University

Email

wangpeng@xmu.edu.cn

Origin

Research Triangle Park Guangzhou, China

Paper NO.

A308

### Title:

Characterization of outer membrane proteins and EnvZ/OmpR two-component signal transduction system of *Escherichia coli* in response to a phenol

### Abstract:

Gram-negative bacteria are generally more tolerant to disinfectants than Gram-positive bacteria due to outer membrane (OM) barrier, but the tolerant mechanism is ill-defined. We utilized comparative proteomic methodologies to characterize the OM proteins of *E. coli* K-12 in response to phenol stress and found ten proteins were altered significantly. They were OM proteins OmpA, FadL, LamB, OmpT and OmpF, cytoplasmic-associated proteins AceA and EftU, inner membrane protein AtpB, putative capsid protein Q8FewO and unknown location protein Dps. The alteration and functional characterization of the four OM proteins were further investigated, respectively by Western blotting and genetically modified strains with gene deletion, complementation and overexpression of these altered proteins. Our results indicate that of the four OM proteins except for OmpF, OmpA and OmpT played a more important role than the other two. Furthermore, EnvZ/OmpR two component signal transduction system, being responsible for the regulation of OmpC and OmpF expression, was also studied using the genetically modified strains of their gene deletion. Survival capability and Western blotting results indicated that EnvZ/OmpR played an important role in the regulation of *E. coli* to phenol tolerance by regulating OmpC and OmpF expression. These findings contribute to an understanding of bacterial disinfectant-tolerance mechanism (s).



## Abstract-Topic A

<b>Author</b>	<b>Shunqing Xu</b>
Institution	School of Public Health, Tongji Medical College, Huazhong University of Science and Technology
Email	shunqing@mails.tjmu.edu.cn
Origin	Wuhan, China
Paper NO.	A309

### **Title:**

Differential expression of miRNAs in response to PFCs in zebrafish

### **Abstract:**

Biological effects of perfluorochemicals (PFCs) have generated a considerable interest in recent years. Although much work has been done, the epigenetic effect of PFCs remains largely unknown. MicroRNAs (miRNAs), a class of small RNA species are recognized as important regulators in post-transcription gene expression. To explore the role of miRNAs in zebrafish's response to PFCs, a custom  $\mu$ paraflo<sup>TM</sup> microfluidic array containing release version 12.0 zebrafish miRNA probes (<http://microrna.sanger.ac.uk/sequences/>) was used to discover PFCs -responsive miRNAs with the differences in miRNA expression between zebrafish exposure with or without PFCs. miRNA microarray hybridization revealed that miR-19b and miR-181b families had significantly altered expression after exposure to PFCs for 120 hrs. The results were validated by SYBR green real-time qRT-PCR. miR-181b are strongly associated with tumorigenesis in multi-cancers and as a significant factor in the dysregulation of cortical gene expression in schizophrenia in human, while the expression level of miR-19b, a member of mir17-92 cluster, is detected in leukemias. The mRNA targets (e.g., p55, rag1, bax, Oct 4, MMP2/TIMP2, Cdk5, smad1, Sgk and gp96) regulated by the two miRNAs in zebrafish have been shown to play critical roles in cell cycle check point control and apoptosis, thus we assumed that the change of key miRNAs in response to PFCs may influence embry development by a large impact on cell cycle control and chemosensitivity.



## Abstract-Topic A

<b>Author</b>	<b>Qiang He</b>
Institution	Department of Civil & Environmental Engineering, University of Tennessee
Email	qianghe@utk.edu
Origin	USA
Paper NO.	A310

### **Title:**

Functional genomics analysis of *Desulfovibrio vulgaris*

### **Abstract:**

To exploit SRB effectively for the remediation of heavy metal and radionuclide contaminated sites, it is important to understand the microbial responses to adverse environmental factors commonly encountered in these subsurface environments. One such factor is the high nitrate concentration of many contaminated sites due to mining operations, industrial processing, weapons production. The presence of nitrate may pose a specific stress to SRB as nitrate has been observed to suppress sulfate reduction activity in situ. Thus, it is important to examine the responses of sulfate-reducing microorganisms in metabolic and regulatory pathways following nitrate exposure to understand their defense mechanisms. Such knowledge would facilitate the development of strategies to monitor and predict the performance of these microorganisms in bioremediation. Using *Desulfovibrio vulgaris* as a model sulfate-reducing bacterium, functional genomics studies found that significant growth inhibition was effected by 70 mM NaNO<sub>3</sub> but not 70 mM NaCl, indicating the presence of inhibitory mechanisms in addition to osmotic stress. While the differential expression of a small number of genes in response to nitrate suggested the potential involvement of osmotic and nitrite stress responses, the roles of these two stress responses appear minor given the lack of similarity in the overall transcriptional profiles between nitrate, nitrite, and NaCl stress responses. The presence of unique stress response pathways in nitrate stress is further suggested by the lack of extensive similarities in the response profiles between nitrate stress and various other stress conditions. In addition, the importance of genes with functions in the metabolism of S-adenosylmethionine in the shift of energy flow was implicated in nitrate stress response.



## Abstract-Topic A

<b>Author</b>	<b>Xifei Yang</b>
Institution	Department of Civil & Environmental Engineering, University of Tennessee
Email	bio-research@hotmail.com
Origin	USA
Paper NO.	A311

### **Title:**

Nanometer SiO<sub>2</sub> induces toxicological effects and protein expression alteration in HaCaT cells

### **Abstract:**

Nanometer silicon dioxide (nm-SiO<sub>2</sub>) has widespread applications in modern biomedical industry; however, the potential toxicity of nm-SiO<sub>2</sub> on cells remains unclear. Methods: We use toxicological methods and proteomic techniques to analyze the cytotoxicities and the differentially expressed proteins caused by nm-SiO<sub>2</sub> with different particle diameters in HaCaT cells (15nm, 30nm and 100nm). Results: The survival rates of the cells were significantly decreased in a concentration-dependent manner after the treatment of nm-SiO<sub>2</sub>. The IC<sub>50</sub> was positively correlated with the particle diameters of nm-SiO<sub>2</sub>. All the doses of nm-SiO<sub>2</sub> could induce apoptosis in HaCaT cells in a concentration-dependent manner. Furthermore, the smaller nm-SiO<sub>2</sub> particles are, the higher apoptosis rate occurred. The proteomic analysis showed that 155 different protein spots were found in nm-SiO<sub>2</sub>-treated HaCaT cells compared with the control. Among these proteins spots, 40 were identified by MALDI-TOF-TOF-MS. These proteins belong to 34 different types of proteins and can be generally classified into 5 categories: 1. oxidative stress-associated proteins; 2. cytoskeleton-associated proteins; 3. signal transduction-associated proteins; 4. substance and energy metabolism-associated proteins; 5. apoptosis and tumor-associated proteins. Conclusions: These results show that nm-SiO<sub>2</sub> exerted toxicological effects and altered protein expression in HaCaT cells. The data indicate the altered expression of proteins such as oxidative stress-related proteins could underlie the toxicological effects of nm-SiO<sub>2</sub>.



## Abstract-Topic A

<b>Author</b>	<b>Liu Jianjun, He Haowei, Gong Chunmei, Zhang Bing, Jiang Yingzhi, Huang Haiyan</b>
Institution	Shenzhen Center for Disease Control and Prevention
Origin	Shenzhen, China
Paper NO.	A312

### Title:

The DIGE Proteomic Study on the Cytotoxicity Caused by nm-SiO<sub>2</sub> with Different Particle Diameters in HaCaT Cells

### Abstract:

Nanomaterials have been shown to have higher biological activities and be able to cause negative biological effects more easily due to the unique physical-chemical properties relative to the homogeneous micro-sized materials. Previous studies demonstrated that nanomaterials could exert toxic effects on biological organisms at different levels. However, the proteomic study on the cytotoxicity induced by nanomaterials was not performed so far. Methods Here, we compared the cytotoxicities and screened the differentially expressed proteins caused by nm-SiO<sub>2</sub> with different particle diameters in HaCaT cells by choosing three kinds of nm-SiO<sub>2</sub> with different particle diameters (15nm, 30nm and 100nm) as the research materials and using in vitro toxicology methods combined with proteomics techniques. We detected the effects of nm-SiO<sub>2</sub> on proliferation and apoptosis of HaCaT. We also did the analysis of protein expression by 2D DIGE in HaCaT cells treated with nm-SiO<sub>2</sub>. Results The survival rates of the cells were significantly decreased in a concentration-dependent manner after the treatment of nm-SiO<sub>2</sub> with particle diameters. The IC<sub>50</sub> was positively correlated with the particle diameters of nm-SiO<sub>2</sub>. All the doses of nm-SiO<sub>2</sub> induced apoptosis of HaCaT cells in a concentration-dependent manner. The smaller nm-SiO<sub>2</sub> particles are, the higher apoptosis rate occurred. The data from the proteomic study showed that 155 differentially expressed protein spots were found in nm-SiO<sub>2</sub>-treated HaCaT cells compared with the control. 40 of them were identified by MALDI-TOF-TOF-MS. These proteins belong to 34 different kinds of proteins and can be generally classified into 5 categories: 1. oxidative stress-associated proteins; 2. cytoskeleton-associated proteins; 3. signal transduction-associated proteins; 4. substance and energy metabolism-associated proteins; 5. apoptosis and tumor-associated proteins. Conclusions: our data confirm that nm-SiO<sub>2</sub> with different diameters can affect exerts cytotoxic effects on HaCaT cells. The function and the changes of expression level of the proteins are important for elucidating the molecular mechanisms underlying the effects of nm-SiO<sub>2</sub> on cell growth, apoptosis induction and the anti-oxidative damage ability. The findings provide clues to explain the relationship between the biological effects of nm-SiO<sub>2</sub> and the nanoparticle size at the protein level.



## Abstract-Topic A

<b>Author</b>	<b>Panlada Tittabutr</b>
Institution	School of Biotechnology, Suranaree University of Technology
Email	bio-research@hotmail.com
Origin	Nakhon Ratchasima, Thailand
Paper NO.	A313

### Title:

Cloning, expression and proteomic studies of two different dioxygenase systems responsible for initial degradation of phenanthrene in *Burkholderia* sp. C3

### Abstract

*Burkholderia* sp. C3 isolated from petroleum-contaminated soil can rapidly degrade many polycyclic aromatic hydrocarbons (PAHs) including phenanthrene. Two catabolic pathways, 1,2- and 3,4-dioxygenation have been previously proposed for initial degradation of phenanthrene in this specie. The objective of this study was to elucidate enzymes responsible for the degradation and identify gene(s) involved in the phenanthrene initial dioxygenation in C3. Both of nah- and phn-like genes were identified in this specie. The nah-like gene cluster of C3 is more than 90% homolog to nag genes of *Ralstonia* sp. U2, while phn-like gene cluster is almost identical to phn genes of *Burkholderia* sp. RP007. The *E. coli* clone containing ferredoxin-, large- and small-subunits of dioxygenase from nah-like gene cluster and the clone of large- and small-subunits of phn-like gene cluster, could degrade naphthalene, phenanthrene and dibenzothiophene but in different substrate preference. The clone from phn-like gene cluster degraded phenanthrene better than the nah-like gene cluster. The expression of phnAc-like gene was higher than nagAc-like gene during first 16 h, while nagAc-like gene was highly expressed after 16 h in the presence of phenanthrene. These results indicated both genes are responsible for initial phenanthrene degradation. The metabolite analysis showed both 1-hydroxy-2-naphthanoic acid and 2-hydroxy-1-naphthanoic acid present in the culture of the *E. coli* clone derived from phn-like gene cluster; however, with a high concentration of 1-hydroxy-2-naphthanoic acid. These results revealed the function of phn-like gene responsible for both 1,2- and 3,4-dioxygenation, and 3,4-dioxygenation is the major pathway of phenanthrene degradation in *Burkholderia* sp. C3. The protein analysis showed that proteins associated with multiple pathways of PAHs-degradation were induced in response to phenanthrene, including enzymes from phn-like gene cluster.



## Abstract-Topic A

Author	Robert Laumbach
Institution:	UMDNJ-Robert Wood Johnson Medical School, Piscataway
Email	laumbach@eohsi.rutgers.edu
Origin	New Jersey, USA
Paper No	A501

### Title:

Inter-individual variability in urinary 1-aminopyrene following a controlled exposure to diesel exhaust

### Abstract:

Emissions from diesel engines are a major source of urban particulate matter air pollution, which has been linked to cardiovascular and respiratory morbidity and mortality. Assessment of diesel exhaust (DE) exposure has been a challenge due to lack of a valid, specific marker for this complex and variable mixture. Urinary metabolites of 1-nitropyrene (1-NP), a relatively specific component of DE particles (DEP), may be useful markers for DE exposure. We sought to develop and evaluate a feasible method to measure 1-aminopyrene (1-AP), a metabolite of 1-nitropyrene, in urine of volunteers undergoing a brief controlled exposure to DE. Fifty-five healthy nonsmoking adults (33 female, 22 male, mean age 24.8 yr) underwent one 60 min exposure to clean air (CA) control condition and one 60 min exposure to diluted DE (~300 g m<sup>-3</sup> as DEP) in random order, at least 1 week apart. Spot urine samples were collected immediately prior to exposure, and then at each spontaneous void up to 24 hours after the exposure. The acetylated 1-AP conjugate was acid hydrolyzed and the extract was analyzed by HPLC with fluorescence detection. Time-weighted average concentrations of urinary 1-AP were significantly greater following the DE exposure compared to the control exposure (median 138.7 ng g<sup>-1</sup> creatinine vs. 21.7 ng g<sup>-1</sup>).



## Abstract-Topic A

**Author****Akira Toriba**

Institution:

Kanazawa University

Email

toriba@p.kanazawa-u.ac.jp

Origin

Kakuma-machi, Kanazawa, Japan

Paper NO.

A502

**Title:**

Urinary 1-nitropyrene metabolites as a biomarker for exposure to nitropolycyclic aromatic hydrocarbons

**Abstract:**

Nitropolycyclic aromatic hydrocarbons (NPAHs) are formed through the incomplete combustion of fossil fuels. They are widespread environmental contaminants observed in the extracts of diesel exhaust particulate matter (DEP) and airborne particulate matter (AP). Many NPAHs are carcinogenic/mutagenic compounds, and among these compounds, 1-nitropyrene (1-NP) and dinitropyrenes have been previously reported as the main contributors of direct-acting mutagenicity of DEP. 1-NP is one of the most abundant NPAHs in AP and DEP, and the metabolites of 1-NP are expected to be a biomarker for assessment of exposure to NPAHs and/or DEP. We have developed a highly specific and sensitive analytical method using liquid chromatography with tandem mass spectrometry (LC-MS/MS) for determining urinary the 1-NP metabolites. Hydroxy-N-acetyl-1-aminopyrenes (6- and 8-OHNAAP) and hydroxy-1-nitropyrenes (3-, 6-, and 8-OHNP) in human urine have been identified and quantified for the first time, in agreement with previous *in vivo* and *in vitro* studies that predicted that these metabolites should be excreted into human urine. In this study, we investigated exposure to airborne fine particulate matter (PM<sub>2.5</sub>) and 1-NP and the levels of urinary 1-NP metabolites in groups of schoolchildren in China. The study group consisted of 200 children in four schools in Shengyang and Shanghai, China. First morning void urine samples were collected for 3 days in winter and summer seasons (March and September, 2007). To monitor the exposure to PM<sub>2.5</sub> and 1-NP, personal samplers were placed inside and outside classrooms and subjects houses. The results showed higher concentrations of urinary 1-NP metabolites and ambient PM<sub>2.5</sub> and 1-NP in Shengyang, suggesting the higher respiratory exposure to NPAHs of residents in Shengyang. This study also suggested that urinary 1-NP metabolites increased with increasing 1-NP concentrations in ambient air and may be useful for the surveillance of exposure to NPAHs and/or DEP. This study was supported, in part, by the Industrial Technology Research Grant Program in 2005 from New Energy and Industrial Technology Development Organization (NEDO) of Japan (ID: 05A21705a).



## Abstract-Topic A

Author	Yang Xia
Institution:	Centers for Disease Control and Prevention
Email	yxia@cdc.gov
Origin	Georgia, USA
Paper NO.	A503

### Title:

Tobacco exposure biomarkers in the National Health and Nutrition Examination Survey (NHANES)

### Abstract:

The National Health and Nutrition Examination Survey (NHANES) is a unique study addressing the health and nutritional status of adults and children in the United States. It is the only survey that combines both health interview and examination data to produce an in-depth view of the health of the entire, noninstitutionalized U.S. population. Findings from this survey are used to determine the prevalence of major diseases and risk factors for diseases, current nutritional status, and for a variety of other purposes. As part of NHANES, the Division of Laboratory Sciences at CDC measures biomarkers including cotinine (a nicotine metabolite), and 4-Methylnitrosamino-1-(3-pyridyl)-1-butanol (NNAL), a tobacco-specific nitrosamine and probable carcinogen in all participants to assess tobacco smoke exposure levels in smokers and especially to identify nonsmokers exposed to secondhand smoke (SHS). Cotinine has been measured in NHANES since 1988 and the data from 1988 through 2002 have confirmed that a substantial decrease (approximately 70%) in the exposure of nonsmokers in the U.S. population to SHS occurred during that time. More recently, we have developed an accurate and sensitive LC/MS/MS method to measure NNAL and now also include that assay among the current NHANES analyses. NNAL concentrations can be readily measured in urine from active users of tobacco. In addition, although the concentrations among nonsmokers are typically quite low, we have found significant increases in NNAL among nonsmokers following exposure to SHS. Our method for NNAL measurements provides a sensitive approach with excellent sample throughput suitable for application to high volume epidemiologic investigations such as NHANES. The addition of NNAL analyses in the future to the cotinine assays that we have been measuring in past surveys is expected to provide important new information concerning the exposure of both smokers and nonsmokers to tobacco smoke.



## Abstract-Topic A

**Author****Shu-Li Wang**

Institution:

Divi. of Environ. Health &amp; Occup. Med, National Health Research Institutes

Email

slwang@nhri.org.tw

Origin

Taiwan

Paper NO.

A504

**Title:**

Prenatal and postnatal exposure to phthalates and the relation to steroid hormone alterations in children from central Taiwan

**Abstract:**

We study phthalate ester metabolites in pregnant women and their newborns in a perspective cohort during 2001-2006. We collected urine, cord serum, and human milk in 451 health pregnant women and their children aged 2 and 5 years from central Taiwan. Eleven phthalate metabolites representing the exposure to five commonly used phthalates (DEHP, DiBP, DnBP, BP, DiNP) were measured by fully automated LC-LC/MS-MS-system. Urinary total phthalate metabolite concentration was found to be higher in 2-years-old children and 5-years-old than the pregnant women. The concentration of urinary phthalate metabolite was higher for DEHP metabolites (2yr children: 200.3; 5yr children: 152.3; pregnant women: 102.2), followed by MnBP (2yr: 100.4; 5yr: 75.1; p.w.: 72.3), MiBP (2yr: 17.2; 5yr: 25.2; p.w.: 12.5), and MBzP (2yr: 3.40; 5yr: 3.61; p.w.: 0.96). The proportion of DiNP metabolites was higher in children urine samples than in adult samples (2y: 17.5; 5y: 27.7; p.w.: 1.71). The concentrations of phthalate metabolites are much lower in cord blood samples (GM =37.5, 95% C.I.: 33.8-41.5) and milk (14.9, 11.0-20.2) compared to urinary samples. DEHP metabolite levels in pregnant women urine samples and their corresponding cord blood samples are significantly correlated. Maternal urinary metabolite levels may be useful for studies of prenatal exposure and related effects.



## Abstract-Topic A

<b>Author</b>	<b>Kerstin Becker, Margarete Seiwert André Conrad, Helga Pick-Fuss Christine Schulz, Marike Kolossa-Gehring</b>
Institution	Federal Environment Agency
Email	marike.kolossa@uba.de
Origin	Berlin, Germany
Paper NO.	A505

### Title:

Use and benefit of biomarkers of exposure – the example of the German Environmental Survey

### Abstract:

The German Environmental Survey (GerES) is a representative population study and has been repeatedly carried out since the mid-1980s. GerES is part of the German health-related environmental surveillance system and GerES IV which was conducted between 2002 and 2006 was the first survey focussing solely on children. The main objective of GerES has been to evaluate the body burden of pollutants in the general population and thus to identify especially exposed subgroups. However, GerES also gives insights into major exposure pathways. This is possible by taking into account pollutants in the indoor environment (indoor air, drinking water and house dust) and by using information on potential exposure pathways from questionnaires. Analyses of appropriate biomarkers in German children revealed that exposure to lead, cadmium and mercury as well as PCP and PAH has decreased in the last decades especially in East Germany after reunification; exposure to organochlorine compounds (DDE, PCB) is still a matter of concern. Although they were banned in the 80s children are still exposed by breast feeding; exposure to pyrethroids is low in all, while exposure to organophosphates might be too high in some children. High exposure to more than one phthalate occurs in some children which raises the question of synergistic effects; ETS exposure is a relevant matter of concern for around 50% of the children. Data on the concentrations of the biomarkers of exposure from GerES are a sound basis for defining reference values for the German population. They are extremely valuable to assess individual and hot spot results. Comparing individual exposures and derived daily intakes with HBM- and TDI-values allows the assessment of the population proportion of individuals at risk. GerES data provide the basis for identifying health risks in the general population and for environmental and public health policy decisions. They might help to develop preventive measures and enhance further research. GerES will support the implementation of an EU-wide human biomonitoring programme.



## Abstract-Topic A

<b>Author</b>	<b>Pao-Chi Liao</b>
Institution	Department of Environmental & Occupational Health, National Cheng Kung University
Email	liaopc@mail.ncku.edu.tw
Origin	Tainan, Taiwan
Paper NO.	A506

**Title:**An overview to human dioxin exposure in Taiwan

**Abstract:** Polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/Fs) are unintentional by-products in various thermal and industrial processes and ubiquitous environmental pollutants in most industrialized countries. Exposure to PCDD/Fs can result in a broad spectrum of health effects. In Taiwan, about 90% of the population resides on the urbanized and industrialized western plain of the island where there are twenty municipal waste incinerators and many factories with combusive processes. A series of studies has been conducted to assess the PCDD/F exposure in Taiwan residents, including background and accidental dioxin exposure. For the background dioxin exposure, adult and infant exposures were evaluated. Two hundred fifty one adult subjects from the general population were recruited from 2001 to 2006 for surveying the background dioxin exposure of adults. The PCDD/Fs levels in the 251 human serum samples ranged from 4.92 to 26.7 pg WHO1998-TEQ/g lipid (median: 11.5). Five factors, age, gender, residential region, dietary status, and smoking status, show statistically significant association with the PCDD/F levels in serum. The infant dioxin exposure was evaluated indirectly by the PCDD/F levels in breast and formula milk. At 12th month of age for infants, the average daily intake of PCDD/Fs for breast-feeding infants was 13 pg WHO1998-TEQ/kg/day and 6.2 times higher than those for formula-feeding infants. For accidental dioxin exposure, two accidents were investigated, including the Yucheng incident and the episodes related to a contaminated site caused by a pentachlorophenol (PCP) plant in Tainan. The Yucheng incident is a mass poisoning from rice-bran oil contaminated by heat-degraded PCBs in 1978~1979. The polychlorinated biphenyl (PCBs) and PCDD/F levels 15 years after the incident in the Yucheng victims are still 9 and 50 times respectively higher than those in the general population of Taiwan. For the investigation of dioxin contaminated site in Tainan, our finding revealed that the PCDD/F levels in the residents living in the vicinity of PCP plant were much higher than those in the general population of Taiwan. In addition, the PCDD/F congener patterns in serum, fish, and soil samples collected near the PCP plant were different from those from other areas in Taiwan without known PCDD/F pollution. Based on those data, our investigation may have discovered a hot spot in Taiwan.



## Abstract-Topic A

<b>Author</b>	<b>Hiroshi Ide</b>
Institution	Department of Mathematical and Life Sciences, Hiroshima University, Graduate School of Science
Email	ideh@hiroshima-u.ac.jp
Origin	Higashi-Hiroshima, Japan
Paper NO.	A601

### **Title:**

Repair of reactive nitrogen species-mediated DNA damage

### **Abstract:**

Living organisms are exposed to highly reactive nitrogen species (RNS) in the environment as collectively defined as nitrogen oxides (NO<sub>x</sub>) by the US Environmental Protection Agency and the World Health Organization. Nitrosative stress imposed by exposure to RNS is a subclass of oxidative stress that leads to oxidative deamination in DNA. Adenosine is converted to inosine in DNA when it is exposed to nitrosating agents such as nitric oxide or nitrous acid. Endonuclease V (endo V) mediates an evolutionarily well-conserved pathway to repair adenosine deamination in both prokaryotic and eukaryotic organisms. Endo V is an enzyme that initiates repair of deaminated DNA bases by making an endonucleolytic incision at the 3' side one nucleotide from a base lesion. The biochemical mechanism of endo V-mediated lesion recognition, repair pathway will be presented in light of recent biochemical, genetic studies, as well as structural biology and single-molecule investigations. Endo V-mediated repair appears to be important mechanism in maintaining genome integrity and reducing genotoxicity.



## Abstract-Topic A

<b>Author</b>	<b>Weiguo Chao</b>
Institution	Department of Genetics and Biochemistry, Clemson University
Email	wgc@clemson.edu
Origin	South Carolina, USA
Paper NO.	A602

### **Title:**

Genotoxic effects and repair of DNA-protein crosslink lesions

### **Abstract:**

DNA-protein crosslinks (DPCs) are ubiquitous genomic lesions and produced by environmental agents such as aldehydes, heavy metal ions, ultraviolet light, and ionizing radiation, and also by a certain class of chemotherapeutic agents such as 5-azacytidine and platinum compounds. DPCs are unique in that they are extremely bulky as compared to conventional DNA lesions. Consequently it is very likely that DPCs sterically hinder access by proteins involved in replication, transcription, and repair, impairing the faithful propagation of genetic information. However, it remains largely elusive how cells mitigate the genotoxic effects of DPCs and maintain genetic integrity in the face of this type of genomic insults. We have used genetic and biochemical approaches to elucidate how DPCs are processed in *Escherichia coli* and mammalian cells. In *E. coli* cells, the damage tolerance mechanism involving homologous recombination (HR) and subsequent replication restart provides the most effective means of cell survival against DPCs. Elimination of DPCs from the genome primarily relies on nucleotide excision repair (NER), which provides a second and moderately effective means of cell survival against DPCs. The upper size limit of crosslinked proteins amenable to bacterial NER is 12-14 kDa, and DPCs with oversized proteins are processed by HR. Collectively, HR and NER cooperate closely to mitigate the genotoxic effect of DPCs in *E. coli*. In mammalian cells, the genotoxic effect of DPCs is mitigated by HR exclusively. Cells deficient in HR are hypersensitive to DPC-inducing agents, and treatment of cells with DPC-inducing agents leads to the formation of RAD51 and gamma-H2AX nuclear foci. Unlike *E. coli*, NER is unable to participate in the removal of DPCs from the genome, since the size limit of crosslinked proteins amenable to mammalian NER is lower than that of bacterial NER. The present results highlight the differential involvement of NER in the repair of DPCs in bacterial and mammalian cells, and demonstrate the versatile and conserved role of HR in tolerance to DPCs among species.



## Abstract-Topic A

<b>Author</b>	<b>Ke Jian Liu, Laurie G. Hudson, Xujun Qin Wei Ding, Wenlan Liu, Karen L. Cooper</b>
Institution	Department of Pharmaceutical Sciences, College of Pharmacy, University of New Mexico
Email	kliu@salud.unm.edu
Origin	Japan, New Mexico, USA
Paper NO.	A603

### Title:

Inhibition of DNA damage repair as a mechanism of arsenic carcinogenesis

### Abstract:

Inorganic arsenic is a complete carcinogen and enhances tumor development when combined with other carcinogens including ultraviolet radiation (UVR). Arsenite stimulates reactive oxygen species (ROS) in keratinocytes leading to DNA damage. We have observed that low arsenite concentrations enhance UVR-induced 8-hydroxyl-2'-deoxyguanine (8-OHdG) formation, DNA strand break, and cyclobutane pyrimidine dimers (CPDs). Biochemical studies suggest that disruption of zinc finger DNA repair protein function may represent an underlying mechanism for arsenic carcinogenicity. We find that i) activity of the zinc finger protein poly(ADP ribose) polymerase-1 (PARP-1) is impaired at 200 nM arsenite concentration, ii) oxidative DNA damage is enhanced in the presence of a PARP-1 inhibitor, and iii) inclusion of zinc counteracts arsenite-enhancement of UVR-induced 8-OHdG lesions on DNA. Mass spectrometry analysis provides evidence that arsenite displaces or ejects zinc from the zinc finger domain of a PARP-1 zinc finger peptide. Collectively our studies demonstrate that two properties of arsenite, namely binding of trivalent arsenicals to sulfhydryls and ROS/RNS formed by arsenic exposure, can modify PARP-1 protein and function leading to elevated oxidative DNA damage.



## Abstract-Topic A

**Author****Nan Mei**

Institution:

National Center for Toxicological Research, US  
Food and Drug Administration

Email

Nan.Mei@fda.hhs.gov

Origin

Arkansas USA

Paper NO.

A604

**Title:**

Genome-wide analysis of genotoxicity induced by carcinogenic pyrrolizidine alkaloid in Big Blue rats

**Abstract:**

Riddelliine is isolated from plants grown in the western United States and is a prototype of genotoxic pyrrolizidine alkaloids (PAs), which are probably the most common plant constituents that poison livestock, wildlife, and humans worldwide. In this study, we investigated riddelliine-induced genotoxic effects and gene expression changes in the target tissue. The female Big Blue transgenic rats were gavaged with riddelliine 5 days a week for 12 weeks with 0.1-1 mg/kg body weight, the doses were demonstrated to induce liver tumour in a previous carcinogenesis bioassay. A significant dose-dependent increase in mutant frequency (MF) was found, and the MF in the high-dose group was 3-fold higher than that in the control group. Molecular analysis of the mutants indicated that there was a significant difference between the mutational spectra from riddelliine-treated and control rats. We also performed rat whole genome gene expression microarray to determine riddelliine-induced gene expression profiles in livers. By analysis with the Ingenuity Pathway Analysis software, we found that the differentially expressed genes were mainly involved in cancer, cell death, tissue development, cellular movement, tissue morphology, cell-to-cell signalling and interaction, and cellular growth and proliferation. We further analyzed the genes involved in metabolism, injury of endothelial cells, liver abnormalities, and cancer development in detail. These results provided further insight into the mechanisms involved in genotoxicity and carcinogenesis after exposure to riddelliine.



## Abstract-Topic A

Author	Martha M. Moore
Institution:	National Center for Toxicological Research, US Food and Drug Administration
Email	Martha.Moore@fda.hhs.gov
Origin	Arkansas, USA
Paper No	A605

### Title:

A new strategy to inform the mode-of action (MOA) assessment of carcinogens that are mutagens but not necessarily mutagenic carcinogens

### Abstract:

Currently mutagenic chemicals are identified using a number of well-validated mutation or genetic toxicology tests. The routine test battery was selected to be a sensitive indicator of mutagenic potential and to have the ability to detect chemicals inducing point mutation and/or chromosomal alterations. The ability to detect the full spectrum of genetic damage is important for hazard identification. The routine battery is heavily focused on in vitro assays. It is widely recognized that, while these in vitro assays are very sensitive to genetic damage, they may not always reflect the ability of the test chemical to cause genetic damage in vivo. The in vivo component of the routine battery is generally conducted in bone marrow and is restricted to the measurement of chromosomal damage. When one moves past hazard identification to assess the mode of action (MOA) for carcinogens, it is important to determine whether the chemical can, in fact, cause mutation in the cancer target tissue. We propose a new strategy to help determine whether carcinogenic chemicals assessed to be mutagens or genotoxins in the routine battery are, in fact, causing cancer via a mutagenic or non-mutagenic MOA. The approach involves using transgenic rodent mutation models, chronic treatment, assessing time to mutation, and performing a quantitative comparison between the mutation and tumor dose response curves in the target tissue.



## Abstract-Topic A

**Author****Jack Ng**

Institution:

The University of Queensland, National  
Research Centre for Environmental Toxicology

Email

j.ng@uq.edu.au

Origin

Queensland, Australia

Paper NO.

606

**Title:**

Toxicity and carcinogenicity of arsenic

**Abstract:**

Globally, up to 100 million people are at risk being exposed to excessive levels of arsenic. Chronic exposure to arsenic could lead to cancers of the skin, lung and bladder and other non-cancer endpoints in humans. The generally lack of a suitable animal carcinogenesis model has been a challenge for scientists to unravel the mechanism of arsenicosis. It has been suggested that arsenic exerts its adverse effect via several modes of action including oxidative damage. Our studies showed that arsenic and its methylated pentavalent metabolites MMAV and DMAV do not form DNA-adducts in-vitro or in-vivo. However, inorganic arsenic inhibits the repairs of DNA-adducts induced by benz(a)pyrene (Bp) in-vivo. This inhibitory effect of arsenic can be prevented by selenium, a well-known antioxidant. It is plausible to conclude that a potential way for inorganic arsenic to cause carcinogenicity is via the inhibition of DNA repair mechanism(s). We induced tumours in C57Bl/6J mice exposed to environmentally relevant inorganic arsenic concentrations in drinking water for over two years. We also demonstrated arsenic-induced point mutations in the p53 gene. These results demonstrated for the first time the carcinogenic and mutagenic effects of arsenic in-vivo. Although the genotoxicity of arsenic is well-known this is the first in-vivo evidence suggesting the mutagenic potential of inorganic arsenic. More recently we have shown that monomethylarsonous acid (MMAIII), a methylated trivalent metabolite of inorganic arsenic, is also carcinogenic to C57Bl/6J mice. Our studies demonstrated that tumour incidences induced by arsenic were in a dose response fashion at 0, 100, 250 and 500  $\mu\text{g As/L}$  for both sodium arsenate and MMAIII respectively. Microarray was performed in selected tumour and non-tumour liver tissues. Signaling pathways in relation to NF $\kappa$ B and CD40 are thought to be important in arsenic carcinogenesis. Since we have demonstrated that MMAIII is carcinogenic to mice, it suggests that the arsenic methylation pathway is not necessarily a detoxification pathway but may in fact in some circumstances enhance the toxicity of the element, and that MMAIII might play a significant role in mammalian arsenic carcinogenicity.



## Abstract-Topic A

Author	Cheng Peng
Institution	The University of Queensland, National Research Centre for Environmental Toxicology
Email	cpeng@uq.edu.au
Origin	Queensland, Australia
Paper No	A607

### Title:

Genotoxicity induced by the benzene metabolite, hydroquinone in A549 cell

### Abstract:

Benzene is a potent organic environmental and industrial pollutant and has been classified as group A carcinogen. Its effects on health have been studied extensively, but the mechanisms behind has not been fully understood because of complexities of its effects. Although benzene is mainly metabolized in liver and proven to be leukemogenic, the association with the lung cancer by long exposure has also been reported. Lung is not only the primary target for the toxicity of inhaled compound but also capable of transforming many organic toxicants. Lung cytochrome P450 enzymes are responsible for metabolism of many organic compounds including benzene. It has been known that benzene exert its effects via its active metabolites such as hydroquinone (HQ), benzoquinone (BQ) etc. The aim of this study is to investigate the genotoxicity of HQ in human alveolar epithelial cells (A549). The cytotoxicity of HQ was evaluated in time course of 1, 6, 12 and 24 hours using the 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt (MTS) assay with the LC50 of 59.3, 36.3, 37.7 and 32.6  $\mu\text{M}$  respectively. DNA damage induced by HQ was measured by alkaline single cell gel electrophoresis assay (Comet assay) and immunocytochemistry of gamma H2AX phosphorylation. The genotoxic effects of HQ on A549 cell was further investigated by chromosome aberration (CA) testing. The genotoxicity of HQ showed a dose response manner in a range between 2.5 and 40 M in above assays. ROS induced by HQ was monitored using the immunostaining of the hydroxydeoxyguanosine (8-OHdG) formation and GSH depletion assay. Based on the results from the present study we concluded that the HQ exerts its genotoxicity in A549 cell and the effect is via the ROS formation. Our results also suggest that A549 is sensitive to HQ and suitable for toxicological study of benzene metabolites.



## Abstract-Topic A

**Author****Qien Wang**

Institution

The Ohio State University, Columbus

Email

wang.771@osu.edu

Origin

Ohio, USA

Paper No

A608

**Title:**

NA repair protein modification and degradation in response to UV irradiation

**Abstract:**

UV exposed cells, and bulky adducts induced by exposure to numerous chemical compounds. It is hypothesized that many DNA repair proteins are regulated by post-translational modifications and degradation to modulate the DNA repair efficiency. Recently, we have found that the xeroderma pigmentosum group C (XPC), a DNA damage recognition protein in NER, is modified by both ubiquitylation and sumoylation in response to UV irradiation. By using several NER deficient cell lines, we found that DDB2 and XPA are required for UV-induced XPC modifications. Furthermore, XPC protein is degraded significantly upon UV irradiation, this is independent of protein ubiquitylation. The subunits of DDB-Cul4A E3 ubiquitin ligase differentially regulate UV-induced XPC degradation, e.g DDB2 is required and promotes, whereas DDB1 and Cul4A protect the protein degradation. Mutation of XPC K655 to alanine abolishes both UV-induced XPC modification and degradation. Regarding the function of XPC degradation, we found that XPC degradation is necessary for recruiting XPG and efficient NER. The overall results provide crucial insights regarding the regulation, fate and role of XPC protein in the initiation of excision repair.



## Abstract-Topic A

<b>Author</b>	<b>Altaf A. Wani</b>
Institution	Department of Radiology, The Ohio State University
Email	wani.2@osu.edu
Origin	Columbus, Ohio, USA
Paper NO.	A609

### **Title:**

Cellular responses to genotoxic damage induced by exposure to environmental agents

### **Abstract:**

Genome of living organisms is prone to incessant damage by a variety of endogenous as well as ubiquitous environmental agents. The lesions introduced within the chromatin provoke rapid and dramatic responses to help cells overcome the biological consequences, ranging from recruitment of specific repair machineries for reversing the structural alterations to transduction of damage signal culminating in cell cycle arrest or even outright elimination of severely damaged cells by apoptosis. The coordinated response to genotoxic damage begins by recruitment of specific protein factors exhibiting a high degree of cross-talk to orchestrate individual pathway events. The common initial step, i.e., accessing DNA damage embedded within chromatin, is a key factor in determining the course of DNA damage response and efficiency of damage processing. In this context, studies in yeast have indicated that SWI-SNF, an ATP-dependent chromatin remodeling complex, is required for efficient nucleotide excision repair (NER), by influencing chromatin accessibility of NER factors. However, the role of the SWI-SNF complex in DNA damage repair in mammalian cells remains to be established. Our recent studies sought to understand the roles for the mammalian SWI-SNF components in NER and checkpoint activation. We have knocked down Brg1, the catalytic component and SNF5, the core component, of the SWI-SNF complex, and assessed the impact of these knockdowns on NER and checkpoint activation. Using a micrococcal nuclease based genomic DNA digestion assay, we showed that Brg1 mediates UV-induced chromatin relaxation. Furthermore, cells transfected with Brg1 siRNA were inefficient in eliminating CPD, but did not have any effect on removal of 6-4PP compared to control cells. By using chromatin immunoprecipitation method, we showed that Brg1 is recruited to CPD site, but not to 6-4PP site. The recruitment of Brg1 to the CPD site depends on the damaged DNA binding protein, DDB2. We also showed that both Brg1 and SNF5, physically interact with XPC and this interaction is enhanced in response to UV treatment. Furthermore, SNF5 associates with XPC at the UV damage site. Even though the loss of Brg1 affects XPC protein level, the loss of SNF5 did not affect the



## Abstract-Topic A

XPC level. Nevertheless, RT-PCR failed to demonstrate any detectable difference in the XPC transcription level in Brg1-proficient and deficient cells, indicating that Brg1 protects XPC from degradation after UV irradiation. We also revealed that the ATM activation and recruitment at the UV damage site were affected in SNF5 knockdown cells whereas ATR activation and recruitment were not affected. Accordingly, the phosphorylation of H2AX, and the recruitment and phosphorylation of BRCA1 were also affected in SNF5 knockdown cells. Strikingly, Chk1/Chk2 phosphorylation and cell cycle checkpoint was intact in SNF5 knockdown cells. Taken together, these data suggest that SWI-SNF complex associates with UV damaged chromatin through its interaction with XPC and helps stabilization of XPC at the damage site. Furthermore, SWI-SNF influences the access of ATM at the damage site, which promotes assembly of ATM-H2AX-MDC1-53BP1-BRCA1 complex, which eventually influences NER. We propose that SWI-SNF complex positively modulates NER by facilitating stability and accessibility of NER and checkpoint factors at the UV damage chromatin sites.



## Abstract-Topic A

<b>Author</b>	<b>Rutao Liu*, Zhiyong Li, Shifeng Yan Zhenxing Chi, Fengmei Yang, Dong Yuan</b>
Institution	Shandong University
Email	rutaoliu@sdu.edu.cn
Origin	Shandong, China
Paper NO.	A610

### Title:

Gene-toxic and detoxic interaction process of calf thymus DNA with cationic/anion surfactants

### Abstract:

Using resonance light scattering (RLS) and absorption spectra, we studied the gene-toxicosis and detoxification process of calf thymus (ct) DNA with cationic surfactants like cetylpyridine bromide (CPB) and/or anion surfactants like sodium dodecyl benzene sulfonate (SDBS). Our experimental findings suggest that RLS intensity is enhanced by the long line assembly of cationic surfactant on DNA macromolecules. The interaction between surfactant and DNA is governed by electrostatic attraction together with hydrophobic forces. In the current study, the  $\pi$ - $\pi$  stack interaction between the pyridine ring in the cationic surfactant CPB and the DNA base which lead to the gene-toxicosis process was shown to produce a new absorption at a long wavelength, while no such phenomenon was observed for the interaction of cetyltrimethyl ammonium (CTAB) with DNA. In fact, there is no obvious interaction between anion surfactants and DNA except weak hydrophobic and electrostatic repulsion forces. We found that the addition of SDBS to the CPB-ct DNA system removed CPB from the CPB-ct DNA complex, freeing the ct DNA from the ion-associated complex which is corresponding to the detoxification process. Keywords: gene-toxicosis and detoxification; resonance light scattering; mixed cationic/anion surfactant