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Report for 11th International Congress of Toxicology

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The 11th International Congress of Toxicology was successfully held in Montreal, Canada from 15th to 19th July, 2007. More than 2000 scientists coming from more than 75 countries presented their latest research findings and discussed recent developments and issues in toxicology. We met scientists from around the world, renewed old friendship and forged new professional relationship. The Congress included 35 symposia and more than 1200 posters covering topic ranging from the latest scientific advances, global toxicological issues and the challenges unique to developing countries. The education program provided an opportunity to enhance our knowledge in new or familiar fields. The Exhibition introduced new products and services that were interested and attractive for toxicological research. Among many symposia and posters, we would like to discuss here some sessions which are related our recent research work.

Immunotoxicology: Hypersensitivity and Allergies

(1) From chemistry to allergy: To cause sensitization, a compound has to penetrate the skin, where it may be metabolized, and react with epidermal proteins to form new chemical structures that are recognized as foreign. The way of low-molecular-weight chemicals can react with skin proteins to form complete antigens and how these structures could be recognized by T-cell receptors were discussed.

(2) Mechanism of dendritic cell activation by chemicals: During in vivo immune responses, the role of antigen-presenting cells is played primarily by dendritic cells (DC) which acting as initiators of the immune response. Recently, it has been shown that haptens directly activate cultured human DCs showing the upregulation of maturation markers (CD83, CD80, CD86, CD40, and MHCII). Haptens induce the phosphorylation of p38MAPK and c-Jun N-termi9nal kinase and inhibition of p38MAPK is correlated with alteration in phenotypic indicators of DC maturation suggesting again similarities between danger signals and haptens for DC activation.

(3) Activation of neutrophils by xenobiotics:in vitro and in vivo aspects of inflammation: The role of xenobiotics on the cellular physiology of human neutrophils is an area of research that had gained increasing attention in the past few years. Interactions between human neutrophils and certain chemicals of environmental concerned were discussed. In addition, the potent pro-apoptotic activity of the two anti-cancer agents, *Viscum album* agglutinin-1 and arsenic trioxide were discussed in relation with inflammation. Knowing the importance of neutrophils in the inflammatory process, research conducted in this field will increase greatly our knowledge of

understanding the potential role of xenobiotics in the regulation of inflammation.

Metals and Neurodegenerative diseases

(1) Manganese and neurodegeneration: Occupational exposure to manganese (Mn) has been associated with the onset of psychological and motor symptoms in some individuals, leading to a phenotype called manganism. Brain Mn accumulation has also been documented in patients with liver failure, those receiving parenteral nutrition or individuals with iron (Fe) deficiency. The transport of Mn into the brain and its molecular/cellular effects in C. elegans and rodents were discussed and the major attention was directed at the effect of dietary Fe levels on brain Mn deposition pattern. From these findings, it has been suggested that any change in dietary Fe levels exacerbates brain Mn accumulation, and alters normal brain Fe distribution in multiple discrete brain regions.

(2) Novel multi-model neuroprotective-neurorescue drugs with various CNS targets for the treatment of Parkinson's and Alzheimer's diseases and amyotrophic lateral sclerosis: New therapeutic strategies in which drug candidates are designed expressly to act on multiple neural and biochemical targets for the treatment of cognitive impairment, motor dysfunction, depression, and neurodegeneration were developed. The development of single molecular entities that combine two or more of the following properties: choline esterase inhibition, monoamine oxidase inhibition, iron chelation, neuroprotection, anti-apoptosis, neurorescue and modulation of components of mitochondrial-dependent cell survival proteins were discussed. These bi- or multi-functional compounds could provide greater symptomatic efficacy, and better utility as potential neuroprotective-neurorescue disease modifying drugs, because of their ability to modulate mitochondrial cell survival/death genes and protein and molecular processes that result in neuronal growth and differentiation.

(3) Chronic effects of mercury and oxidative stress: Hg is a toxic non-essential element to mammals. Methylmercury (MeHg) is an important public concern, particularly for those regularly consuming fish or seafood. MeHg is a potent neurotoxin and can cause permanent injury to mature and developing brain. Literature data have indicated that in vitro oxidative stress and glutamate play a central role in MeHg neurotoxicity. The exposure to MeHg during distinct phase of development alters the glutamatergic system, which can be related to oxidative stress.

Developing Strategies to understand the effects of air pollution on human populations

(1) Low-level exposure to benzene is converted to toxic metabolites much more efficiently than high-level exposures: Although the toxicity of benzene has been linked to its metabolism, the dose-related production of metabolites is not well understood in humans. According to the investigation of benzene metabolites in urine of workers who exposed to benzene in China, indicates that the production of toxic metabolites were greater at low exposure levels. Since cancer risks of benzene exposure are based upon data from

heavily exposed humans and animals, they may underestimate the true risks for persons exposed to low levels of benzene.

(2) *Using the workplace as a window to study the role of diesel and gasoline engine emissions in lung cancer development:* Motor engine emissions represent a major environmental health issue. Associations between diesel and gasoline exhausts and lung cancer were investigated by population base case control study, and found that there was on evidence of excess risks of lung cancer with exposure to gasoline exhaust. For diesel engine emissions, results differed by control group used especially at high concentration levels.

(3) *Polymorphism and effect of air pollution:* Genetic polymorphism induced by the air pollution has been associated with increased risk of development of cancer and asthma. In addition, this polymorphism has been linked to an altered level of biomarker of exposure to ambient air pollutants. In development of asthma, it has been reported that deficiencies in either GSTM1 or GSTT1 increases the risk, but mostly in the high exposure group. Integration of information of genetic constitution and proper exposure assessment may provide new information on the adverse health effect of ambient air pollution in genetic susceptible populations.

(4) *Air pollution and asthma:Lessons from animal models*: While allergen exposure is a major risk factor for asthma, especially in children, exposure to air pollution exacerbate asthma symptoms and may even be capable of causing asthma. Studies from animal models confirm that exposure to many components of air pollution can cause airway inflammation and airway hyperresponsiveness and can also prime the lungs of sensitized animals to respond more vigorously to allergen inhalation. Studies using inbred mouse strains and knockout mice have also provided important clues about both the mechanistic basis for the pulmonary effects of air pollution, as well as genetic susceptibility, and have proved predictive for understanding human disease.

Environmental exposure and children's health

(1) *Developmental neurotoxicity of industrial chemicals:* Neurodevelopmental disorders such as autism, attention deficit disorder, mental retardation, and cerebral palsy are comm0on, costly and can cause lifelong disability. Their causes are mostly unknown. A few industrial chemicals (e.g., lead, methylmercury, polychlorinated biphenyls (PCBs), arsenic, and toluene) are recognized causes of neuro-developmental disorders and subclinical brain dysfunction. Exposure to these chemical during early fetal development can cause brain injury at dose much lower that those affecting adult brain function. The toxic effects of such chemicals in the developing human brain are not known and they are not regulated to protect children. New, precautionary approaches that recognize the unique vulnerability of the developing brain are needed for testing and control of chemicals.

(2) *Exposure to urban air pollution in Bangkok school children: Potential health effects:* Urban air pollution resulting from traffic congestion is a major problem in many Asian mega cities such as Bangkok. This type of pollution contains a number of carcinogenic compounds, including

polycyclic aromatic hydrocarbons (PAHs), benzene and 1,3 butadiene. Bangkok school children were exposed to total PAHs at levels more than 6-folds higher than those in the rural area. In addition, DNA damage levels were significantly higher while DNA repair capacity was significantly reduced in urban school children. It is apparent that children living in major cities may have increased risk of the development of diseases due to exposure to carcinogenic substances in air pollution.

(3) *Insecticide exposure during pregnancy and effects on fetal growth and child mental, motor and behavioural development:* Residential pesticide use is widespread in the U. S. but data are limited on use during pregnancy. The organophosphates chlorpyrifos and diazinon and the carbamate propoxur were found in 99%-100% of 48 h personal air samples collected from mothers and repeat two-week integrated indoor air samples from a subset of homes. These three insecticides were found in 29%-55% of blood samples collected from the mothers and newborns at delivery. The more highly exposed newborns were also significantly more likely by age 3 to have early indicators of attentional disorder, attention deficit hyperactivity disorder and pervasive personality disorder by parental report on the Child behavior Checklist.

Overview for 11th ICT

Regarding Continuing Education (CE) Lectures, most of the lecturers were recognized for their novel findings and concepts. Among CE lectures, CE 2; Development and interpretation of toxicokinetic data for risk on safety assessments and CE 4; Drug induced immunostimulation and its relevance to immunotoxicity attracted for attendants.

Regarding symposia and poster sections, toxicologists from various countries presented various points of view such as developmental toxicity, genotoxicity, hepatotoxicity, immunotoxicity, neurotoxicity, toxicity in male and female reproductive systems, cardiotoxicity, and nanotoxicity. In this year, most of the toxicologists gave attention to developmental toxicity and child's health.

From 11th ICT, we have learned

(1) Toxicants and their risks

(2) Mechanism and cell signaling pathway in toxicity

(3) Commonly unaware risk to children living in susceptible areas (e.g., mercury, lead, diesel exhaust particles)

(4) Rules and regulations are needed to control toxic effects and relevant preventive measures and

(5) Modified and newly designed experimental apparatus provided by exhibitors.

In addition, we had a chance to make warmly friendship between toxicologists from many countries. However, there are limited reports for the effect of indoor air toxic chemicals like toluene on pulmonary system, nervous system and behavioral system. Furthermore, presentations for *in vivo* experimental animal model were also limited in this congress. Finally, registration fee was very expensive for scientist who wanted to participate from developing countries.