NATIONAL CAPITAL AREA CHAPTER
SOCIETY OF TOXICOLOGY NEWSLETTER
Electronic Edition

June 2005 Issue 19

Editor-Gary Burin

MESSAGE FROM THE INCOMING PRESIDENT

On behalf of the Executive Board and the general membership of the National Capital Area Chapter of the Society of Toxicology, I would like to thank outgoing President David Jacobson-Kram for the excellent job he did in leading the Chapter through a most productive year. During David's tenure, the Chapter sponsored a fall symposium on "Toxicology of Dietary Supplements" that was extremely well attended and attracted scientists and members of the press from nationwide. In addition, the spring symposium on "Toxicology of Chemical Mixtures" was another highlight in the Chapter's accomplishments, covering a timely and important topic in toxicology.

Under David's leadership, the Chapter's financial status has grown to a level that allowed the Board to offer significant financial rewards to students who were awarded the Bern Schwetz Travel Awards as well as to those who excelled in their poster presentations at the Spring Symposium. Also this year, the Chapter's Newsletter was ably guided and disseminated by its Editor, Gary Burin, and our website was inaugurated, updated and maintained by Councilor Tom Flynn. Finally, the excellent support and participation of the entire Executive Board of the NCAC-SOT was instrumental in ensuring that the Chapter's membership was well informed and that our Chapter would continue to grow and excel unabated.

As incoming President of the NCAC-SOT, I hope to continue on the road so successfully traveled by all our previous presidents. Our Chapter is one of the most, if not the most, productive Chapters of the Society of Toxicology. Our accomplishments are many and our commitment to outreach to students of all ages is well documented. I thank you all for your trust and I look forward to the coming year.

Harry A. Milman

MESSAGE FROM THE NEWSLETTER EDITOR

The NCAC newsletter is intended to disseminate information of interest to Toxicologists and members of related professions in the National Capital Area. We're happy to publicize upcoming not-for-profit events in Virginia, Maryland and the District of Columbia that may be of interest to toxicologists. Please send these announcements to my attention (Gburin@tsgusa.com).

This issue of the NCAC newsletter contains, in addition to the usual features such as the reports of our President and Treasurer, the abstract from speakers at our Spring Symposium and abstracts from student posters. An application for membership can also be found at the end of the newsletter. Feel free to distribute this edition of the newsletter to colleagues who may be interested in joining our local chapter. The cost is nominal ($20 for full membership, $10 for student membership) and membership in the local chapter is an excellent introduction to local activities in the toxicology field.

Gary Burin

National Capital Area Chapter – Society of Toxicology

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Student	Mashael Al-Namaeb ('05-'06) Representative Howard University drmashael@aolcom
Student Vice- Representative	Devon Graham ('05-'06) University of Maryland 410-550-1532; dgrah001@umaryland.edu

MESSAGE FROM THE STUDENT REPRESENTATIVE

It is my honor and my pleasure to be the Student Representative of our regional chapter (National Capital area Chapter) of SOT. I am really glad that I have an opportunity to serve the society and contribute to its programs in suggesting topics and other information that help to keep it vibrant and interesting to student members. I wanted to thank our past Student Representative Melinda for all her help and advice. I learned a lot in the last year, more than I imagined I would learn. Melinda and I worked very hard to have a successful student day and Melinda's topic which was "writing skills" was very helpful and interesting to all the students.

I would like to introduce our incoming student vice-representative, Devon Graham from the University of Maryland. Devon and I are working hard to have a successful student day that will be held in November 2005. The title of our symposium will be "Conflict resolution and Negotiation Skills for Graduate students and Post Docs". We are looking forward to seeing you in attendance.

The chapter's website was updated in June and you can find all the forms online regarding registration, membership, and the student representative and the vice student representative's e-mail address. I would encourage you to check the website at least once a month so that you can keep up-to-date and be aware of upcoming events in time to register or otherwise participate. Good luck to all of you in the incoming year. If you have any questions please do not hesitate to e-mail us at drmashael@aol.com or dgrah001@umaryland.edu.

Mashael Al-Namaeb

National Capital Area SOT, Spring 2005 Symposium

Topic: Toxicology of Chemical Mixtures

Location: National Library of Medicine, Bethesda, Maryland
Date: May 24, 2005

Speakers and presentation titles:

Toxicology of Complex Mixtures of Disenfection Byproducts
Jane Ellen Simmons
US Environmental Protection Agency, Research Triangle Park, NC

Chemical disinfection of water is a major public health advance that has decreased dramatically water-borne disease. Chemical disinfectants react with naturally occurring organic and inorganic matter in water to produce a wide variety of disinfection byproducts (DBPs). DBP number, chemical type and concentration are dependent on source-water and treatment-scenario characteristics. Although more than 500 DBPs have been identified, ~50% of the total organic halide (TOX) mass formed during chlorination remains unidentified. Some epidemiological investigations have suggested associations, albeit weak, between human consumption of chlorinated drinking water and adverse health outcomes such as developmental and reproductive effects, and bladder, colon and rectal cancer. The health effects observed in some epidemiological studies are unexpected based on the available data from experimental-animal single-chemical DBP studies. Understanding the human health risk(s) associated with consumption and use of chemically disinfected water will require relevant toxicological information on individual DBPs, defined DBP mixtures of known composition and complex, environmentally realistic mixtures of DBPs. Individual DBP assessments are essential but do not account for potential interactions that influence toxicity. Component-based assessment of simple, defined mixtures are needed as four trihalomethanes (THMs, chloroform, bromoform, bromodichloromethane and chlorodibromomethane) and five haloacetic acids (HAAs, monochloro-, dichloro-, trichloro-, monobromo-, and dibromoacetic acid) are regulated together, respectively, under a total THM and a total HAA standard. Defined mixture data provide important information, but are not by themselves sufficient because a significant portion of the DBP mixture mass remains unidentified. Methods are needed to determine the

portion of any observed toxicity attributable to the unidentified fraction of the mixture. This talk will summarize recent data on individual DBPs and both defined and complex mixture of DBPs. (This abstract does not represent US EPA policy.)

The Use of Interaction Data in the Joint Toxicity of Chemical Mixtures

M.M. Mumtaz and C.T. De Rosa
US Agency for Toxic Substances and Disease Registry, Atlanta, GA.

Health risk assessment is the practice for evaluating the degree of danger associated with environmental exposures to chemicals and other stressors. The recent national report on human exposure to environmental chemicals, through the analyses of blood and urine samples, indicates that over 100 chemicals are found in the US human population. Consequently, risk assessments are performed for chemical mixtures most often using the hazard index approach. The presence of multiple chemicals within a biological system increases the potential for interactions that could enhance or diminish the toxicity of other chemical(s). However, interpretation of the interaction data poses a challenge due to (1) data limitation on chronic exposure to mixtures, (2) lack of higher order mixtures data, (3) lack of statistical power, and (4) equivocal evidence from epidemiological studies. The dilemma of lack of information versus perception of high risk from exposures to mixtures by the exposed population poses an enormous challenge for the risk assessment community. In order to address this challenge, joint toxicity assessment methods have evolved from the initial default generic approaches to the most sophisticated physiologically based pharmacokinetic modeling and *in silico* methods that try to define threshold for interactions. Results from limited but well designed experimental studies will be presented that indicate that environmental level short term exposures to mixtures can be adequately characterized using additivity approaches.

Chemical Mixtures Toxicology and Risk Assessment: Guidance and Methods

John C. Lipscomb
US Environmental Protection Agency, Cincinnati, OH

Humans are exposed to at least scores of chemicals daily. This may occur in the form of mixtures of chemicals, where multiple chemicals occur in a given environmental medium, or as a cumulative exposure, where multiple chemicals are encountered from multiple environmental media via multiple exposure routes. Once inside the body, chemicals can interact so that tissue disposition (toxicokinetics; TK) is altered, and/or so that the response at the organ or cellular level (toxicodynamics; TD) is altered. When effects are measured and subsequently expressed at the level of the encountered concentration/dose, separation of TK and TD is not performed. Whether benefit may be gained from such a more intensive investigation should be assessed on a case-by-case basis. Regardless, human chemical exposure is complex, and risk assessors may rely on available guidance and methods to assess the risks of chemical mixtures. Risk assessments for chemical mixtures should address the spectrum of insults possible; site or organ concordance is not a part of the risk assessment approach for the US EPA (US EPA does not develop reference levels anticipated to be without increased risk for liver toxicity, for example). Thus, effects at the level of the whole-organism are assessed. This presents some special challenges. In addition to identifying the affected tissues, organs or systems and the dose-response associated with them, advanced information on mode of action or mechanism of action is critical.

Information on mode or mechanism of action will determine how chemicals in the mixture should be grouped and which mixtures interaction type to apply. Chemicals with the same or similar mode of action are grouped into a common mechanism group (CMG), and the toxicity of these chemicals is expressed as a dose function, based on a selected index chemical from the group. Risk from chemicals in the same CMG is assessed via dose addition; relative potency factors represent one commonly used form of dose addition. Risks from chemicals with different modes or mechanisms of action are assessed through response addition. Though it is recognized that toxic interactions of chemicals in a mixture may represent potentiation, synergistic, or antagonism, the default position for US EPA methods is to assume an additivity type interaction. This lecture will present the fundamentals of chemical risk assessment, and briefly summarize guidance available from the US EPA.

Occupational Exposure to Chemical Mixtures

Frank J. Hearl
National Institute for Occupational Safety and Health, Washington, DC.

Workers are exposed to multiple agents, either as intrinsically complex mixtures or as separate simultaneous exposures to a variety of substances or stressors. Some intrinsically complex mixtures routinely encountered in occupational settings are diesel exhausts, welding fumes, coke oven emissions, and metal working fluids. Other workplace combinations that result in biological interactions are less obvious, such as the combined action of certain organic solvents and noise exposure, which results in hearing loss to an extent greater than would be predicted by either exposure alone. Although the regulatory agencies and consensus standard setting bodies have recognized the existence of combined effects from mixed chemical exposures, and have proposed dose-additivity formulas for adjusting an occupational exposure limit (OEL), in practice most exposures are regulated or controlled as if they occurred independent of any other substance exposures. Little information or guidance is available to assist practicing industrial hygienists for the application of a modified OEL to account for mixed exposures. Research is needed to provide a sound scientific basis to describe interactions, and to assist practitioners in applying appropriate algorithms for controlling exposures where antagonistic, additive, or synergistic effects may be predicted and expected.

Toxicology of Polycyclic Aromatic Hydrocarbon (PAH) Mixtures

Lynn Flowers
US Environmental Protection Agency, Washington DC

The Integrated Risk Information System (IRIS) Program is undertaking a health assessment for PAH mixtures. The IRIS database contains entries for 15 individual PAHs, but these assessments do not consider the environmental occurrence of PAHs as complex mixtures. The PAH mixtures assessment considers three approaches that have been defined for conducting the assessment of health risks of chemical mixtures: the comparative potency, surrogate and relative potency approaches as outlined in the *Guidance for the Health Risk Assessment of Chemical Mixtures* (US EPA, 1986, 2000). These approaches utilize data pertaining to the mixture of concern, toxicologically similar mixtures, or the mixture's component chemicals, respectively. The comparative potency approach assumes that toxicological modes of action are the same for similar mixtures and that the potency of both mixtures in *in vivo* or *in vitro* bioassays is directly proportional to the potency in humans. The surrogate approach

estimates the potency of the PAH fraction of a mixture of concern, based on the assumption that the cancer risk of this fraction is proportional to the level of an indicator PAH in the mixture. An assumption must be made that the composition of the PAH mixture of concern is sufficiently similar to a surrogate PAH mixture. The relative potency factor approach provides a cancer risk estimate for the whole mixture by summing the carcinogenic potential of individual PAHs relative to an index compound (e.g., benzo[a]pyrene). This approach is outlined in the *Provisional Guidance for Quantitative Risk Assessment of PAHs* (US EPA, 1993) and is extensively utilized for the estimation of risk from exposure to PAH mixtures. The provisional guidance, however, does not reflect the most recent research findings on PAHs and PAH mixtures, nor does it consider some PAHs with carcinogenic potential (e.g., fjord-region PAHs). The PAH mixtures health assessment will encompass all the approaches with a particular emphasis on the relative potency factor approach. (The views expressed are those of the author and do not necessarily reflect the views or policies of the US EPA).

Tools and Data Needed to Assess Multiple Chemical Exposures

Chris DeRosa
US Agency for Toxic Substances and Disease Registry, Atlanta, GA

Literally thousands of chemicals, mostly as mixtures, are found in the environment. Several attempts have been made by various federal agencies to prioritize mixtures so as to accomplish their missions and to meet the needs of their specific mandated programs. These mixtures could be simple or complex in their content or composition. The toxicity and risk assessments of chemicals or their mixtures should represent all the available integrated scientific evidence on their plausible toxicities. According to convention such assessments are performed using the so-called "NAS paradigm" consisting of four steps: hazard identification, dose-response, exposure assessment, and risk characterization. Mostly, single chemical assessments are performed, and only when data lend themselves toxicity or risk assessments are performed for mixture. This is a fundamental deficiency of all the assessments that are performed. Dependent upon the availability of data, three broad approaches are often available for the toxicity evaluation of mixtures. The potency weighted dose or response addition approach is most often used because it utilizes the available single chemical data. This approach until recently did not allow the integration of interaction data in the overall toxicity assessment of the mixture. In the 1990's a weight of evidence method was developed which allows a qualitative, and if data are available, a quantitative factor to include an interaction factor. With advancements in computational techniques and computer capabilities advances are being made to move from the basic default methodologies to more sophisticated tools that will help advances for the assessment methods for mixtures. Research data needs have to be identified and filled as we move towards development and identification of these advanced tools that must be supported by credible science.

Understanding Mechanisms of, and Mechanistic Models for, Chemical Mixtures

Harvey Clewell
Chemical Industry Institute of Toxicology, Research Triangle Park, NC

Because humans are exposed to a wide variety of environmental compounds, it is necessary to consider the potential for interactions that could result in a cumulative toxicity different from the default assumption of additivity. Physiologically based pharmacokinetic (PBPK) models that incorporate information on the mechanism of these interactions can provide useful insights on the health effects of mixed exposures such as gasoline vapors, contaminated food or drinking water. Once validated on the basis of data from animal exposures, a mechanistic PBPK mixture model can be used to provide quantitative predictions of the interactions expected in humans at environmental exposure levels. Examples will be provided for both simple (pesticide) and complex (gasoline) mixtures, illustrating mechanistic modeling of one important kind of interaction: competitive inhibition by substrates for the same enzyme system. Interactions of this kind are probably among the most common in environmental mixtures. Other possible interactions that can be investigated using the PBPK approach include depletion of metabolic cofactors, induction of enzyme synthesis, and destruction of enzyme. For all of these cases, the interaction can lead to either suppression or potentiation of a particular toxic effect, depending on the relationship of the toxic event to the affected metabolic step. In general, interactions are more likely to be seen at the high exposures typical of animal experiments than at the much lower concentrations of concern for human exposures, with the exception of drug-drug interactions and the effect of alcohol consumption on chemical toxicity in humans. As mechanistic modeling of representative interactions accumulates, it will become increasingly possible to draw reliable conclusions about the human risk associated with exposures to mixtures of chemicals.

Spring 2005 Symposium Graduate Student/Postdoc Poster Awards

May 24, 2005

Congratulations to the winners from the recent Graduate Student/Postdoctoral Poster exhibition. Six excellent posters were shown and the following were selected by our hard-working judges and NCAC-SOT Councilors (Lynn Flowers, Laurie Roszell and Thomas Flynn) for special recognition:

1st Place ($ 300)
Kim Barnett — University of Maryland Program in Toxicology

2nd Place ($ 250)
Rosemary Schuh, PhD — University of Maryland Program in Toxicology

3rd Place ($ 200)
Christopher Toscano, MS, PhD — Johns Hopkins University

Spring 2005 Symposium Graduate Student/Postdoc Poster Abstracts

May 24, 2005

A. *The* Aryl Hydrocarbon Receptor (AhR) Regulates Ovarian Follicle Growth In Vitro

Barnett KR; Tomic D; Flaws JA. University of Maryland School of Medicine, Baltimore, MD

The AhR plays an important role in mediating the toxicity of various environmental toxicants that cause adverse effects on the development and function of the female reproductive tract. Studies using AhR-deficient (AhRKO) mice have shown that the AhR has an important physiological role in the mouse ovary. Previous studies in our lab have demonstrated that AhRKO ovaries have a decreased number of antral follicles compared to wild-type (WT) ovaries. Since our previous studies also indicate that AhR deficiency does not affect atresia (follicle death via apoptosis) of antral follicles, the purpose of these studies was to determine whether AhR deficiency reduces follicle numbers by slowing follicular growth. Further, since antral follicles produce estradiol (E_2) and E_2 is required for normal follicular growth, these studies also tested whether AhR deficiency results in decreased synthesis of E_2 by antral follicles. To test these hypotheses, antral follicles were isolated from AhRKO and WT ovaries and cultured for 168 hours. During culture, follicle growth was assessed by daily measurements of follicular diameter. After culture, media was collected and E_2 levels were measured using an enzyme-linked immunoassay (ELISA). AhRKO and WT ovaries were also subjected to measurements of proliferation using immunohistochemistry (IHC) for proliferating cell nuclear antigen (PCNA) antibody. Our results show that WT follicles grew significantly larger than AhRKO follicles by 168 hours of culture (WT: 615.5±17.15μm; AhRKO: 489±17.03μm; $p<0.001$; n=3 mice per genotype, 10 follicles per mouse). The results also show that WT follicles produced significantly more E_2 compared to AhRKO follicles (WT: 2463±508 pg/ml, n=15 follicles; AhRKO: 971±316 pg/ml, n=9 follicles; $p=0.007$). Further results from IHC show that AhRKO follicles had less PCNA staining in granulosa cells compared to WT follicles. These data suggest that in addition to mediating toxicity of environmental chemicals, the AhR is an important regulator of ovarian follicle growth and E_2 production. Supported by NIH grants GM072195-01, HD38955, and R25-GM55036.

B. Methoxychlor Inhibits Expression of Antioxidant Enzymes in the Mouse Ovary

Gupta RK, Miller KP, Tomic D and Flaws JA. Program in Toxicology, University of Maryland-School of Medicine, Baltimore, MD, USA

Females are born with a finite number of primordial follicles, of which a small fraction reaches the antral stage. Antral follicles are responsible for releasing an egg for fertilization and maintaining cyclicity. *In vivo* studies with the organochlorine pesticide methoxychlor (MXC) have shown that antral follicles are the primary targets of MXC exposure. Specifically, MXC exposure decreases the number of antral follicles and increases the percentage of antral follicles undergoing atresia (cell death via apoptosis). While different pathways lead to toxicant-induced cell death, oxidative stress is known to cause apoptosis in non-reproductive and reproductive tissues. Certain toxicants produce reactive oxygen species, which are detoxified by antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT). Thus, this work tested the hypothesis that MXC inhibits the expression of selected antioxidant enzymes in antral follicles. To test this hypothesis, 39-day old CD-1 mice

were dosed with either sesame oil (control) or MXC (32 or 64 mg/kg/day) for 20 days. After treatment, ovaries were collected and antral follicles were isolated from the ovaries and subjected to real time polymerase chain reaction for measurement of mRNA levels of SOD, GPX, and CAT. The results indicate that MXC significantly decreases mRNA expression as compared to controls of SOD (control=2.98 ± 0.30 genomic equivalents (ge); MXC 32 mg/kg/day=0.94 ± 0.08 ge; MXC 64 mg/kg/day=1.28 ± 0.16 ge; n=3; $p \leq 0.003$), GPX (control=2.36 ± 0.48 ge; MXC 32 mg/kg/day=0.90 ± 0.03 ge; MXC 64 mg/kg/day=1.09 ± 0.10 ge; n=3; $p \leq 0.05$), and CAT (control=2.02 ± 0.24 ge; MXC 32 mg/kg/day=0.98 ± 0.05 ge; MXC 64 mg/kg/day=1.13 ± 0.07 ge; n=3; $p \leq 0.01$). Collectively, these data indicate that MXC inhibits the expression of SOD, GPX, and CAT in antral follicles. Therefore, it is possible that MXC may cause atresia of ovarian antral follicles by inducing oxidative stress through inhibition of SOD, GPX, and CAT detoxifying pathways. (Supported by NIH HD38955, T32 ES07263, and a Colgate Palmolive Fellowship)

C. <u>The Organochlorine Pesticide Methoxychlor Alters Brain Mitochondrial</u>
Respiration, H2O2 Production and Calcium/cAMP Response Element Binding Protein Levels.
R.Schuh1,2 T. Kristian1, J. Flaws2 and G. Fiskum1,2 Department of 1Anesthesiology, 2Epidemiology and Experimental Therapeutics, Program in Toxicology, University of Maryland School of Medicine, Baltimore, MD, USA

Methoxychlor, an organochlorine insecticide with endocrine disruptive properties has been demonstrated to affect the reproductive system. However, this environmental contaminant is also implicated in decreasing antioxidant enzyme activity and increasing hydrogen peroxide production resulting in oxidative stress. Phosphorylation of the Ca^{2+}/cAMP response element binding protein (CREB) has been demonstrated in many studies to increase in response to oxidative stress. In the current study, we tested the hypothesis that methoxychlor inhibits mitochondrial respiration, increases mitochondrial hydrogen peroxide production and alters the phosphorylation state of mitochondrial CREB. Mitochondria isolated from rat brains were exposed *in vitro* to methoxychlor (0-10 μg/ml). In addition, mitochondria were isolated from brains of mice chronically exposed *in vivo* to methoxychlor (0-64 mg/kg/day) for 20 days by intraperitoneal injection. *In vitro* methoxychlor exposure inhibited state 3 (ADP-stimulated) O_2 consumption and respiration-dependent H_2O_2 production was stimulated, both in a dose-dependent manner. ADP-stimulated O_2 consumption was inhibited in isolated mitochondria from mice exposed *in vivo* to methoxychlor but without stimulation of H_2O_2 production suggesting a compensatory mechanism had been invoked. Analysis by ELISA demonstrated a dose-dependent increase in phosphorylated CREB in the mitochondrial lysates exposed *in vitro* to methoxychlor in the absence or presence of respiratory substrates. These results suggest that methoxychlor exposure causes mitochondrial metabolic stress (*in vitro* and *in vivo*) and oxidative stress (*in vitro* only). *In vitro* methoxychlor also increases mitochondrial pCREB but in a manner that does not require mitochondrial H_2O_2 generation. (Supported by NIH grants ES07263 (R.S.) and NS34152 (G.F.), and USAMRMC grant DAMD 17-99-1-9483 (G.F.)

D. <u>Temporal Parameters of Environmental Enrichment-Induced Cognitive Enhancement in a Rodent Model of Lead Neurotoxicity.</u> CD Toscano, JL McGlothan, JR Moss, TR Guilarte, Johns Hopkins University, Baltimore, MD.

Environmental enrichment (EE), a non-pharmacological therapy that combines social interaction with a complex living environment, reverses molecular and cognitive deficits observed in a rodent model of lead intoxication (Guilarte et al, Ann. Neurol., 53:50, 2003). In order to translate this finding to the human condition, it is important to further understand the temporal parameters of this therapy. We tested whether the benefit of EE on cognitive function persists in adult rats after EE was removed and if a critical window exists for the application of this therapy. Rats were exposed to 0 or 1500 ppm lead acetate from conception until postnatal day (PN) 21 and then housed singly in standard rat cages (isolated) or in groups of 8 (enriched) in multi-level cages that contained toys until PN79. To test if the benefits of EE are long lasting, rats were raised in enrichment cages from PN21 until PN50 and then transferred to isolated cages until PN79 (permanence). To determine if a critical window existed for the benefit of the intervention, animals were placed in EE from PN50 to PN79. In all studies, spatial learning was assessed at PN79. Blood and hippocampal lead levels were elevated in lead exposed rats, however, no significant Pb^{2+}-exposure effect was observed on the acquisition of the task. A significant housing effect was observed on the acquisition, probe and cue tests with rats currently receiving EE (enriched and critical window) performing significantly better on all three tasks. Nearly twice as many rats in the isolated and permanence groups exhibited a place strategy in the cue test which contributed to the significantly elevated latency in the cue test. In summary, these studies could not detect a significant cognitive deficit in lead exposed rats at PN79, which could be due to the degree of difficulty of the task. Further, EE is effective in enhancing cognitive performance but this benefit is lost after cessation of EE. [Supported by NIEHS grant # ES006189 to TRG]

E. Induction of Oxidative Stress in Response to Ingestion of Lead, Cadmium and Arsenic Mixtures

M. Whittaker, M. Lipsky, G. Wang, X. Chen, and B.Fowler. Toxicology Program, University of Maryland, Baltimore.

Human populations are commonly exposed to mixtures of chemicals. To date, relatively few studies have examined potential interactive effects using a statistical factorial design. Multiple drinking water studies were performed to test the hypothesis that exposure to arsenic, lead, or cadmium (or their combinations) for 30, 90, or 180 days at lowest-observed-effect levels (LOELs) results in increased levels of oxidative stress in the kidney, which is a target organ for trace element-induced toxicity. Male Sprague-Dawley rats were exposed to lead, cadmium, arsenic, or mixtures of these three trace elements for 30, 90, or 180 days via drinking water. Oxidative stress levels (as measured by increases in kidney carbonyls) were generally increased at 30 days and decreased at 90 and 180 days. At 30 and 180 days, cadmium appeared to attenuate carbonyl increases among mixture groups. Among all treatment groups, increases in kidney carbonyls were lowest among the PbxCdxAs group at all three timepoints. Cellular adaptation to trace element-induced oxidative stress is suggested by the attenuation of increases in kidney carbonyls at the 90 and 180 day timepoints. Statistically significant increases in kidney glutathione levels (measured as nonprotein thiols) were measured after 30 and 180 days of exposure among most treatment groups, with some of the greatest increases measured among the four combination groups at the 30 day timepoint (96%-145% increase) and the 180 day timepoint (20%-70% increase). In contrast, kidney non-protein thiols were statistically significantly decreased in 4 of 7 treatment groups after 90 days of exposure (28%-33% decrease). These data demonstrate that low-level exposure to trace elements or their mixtures results in measurable increases in oxidative stress and upregulation of cellular defensive mechanisms [Supported by U.S. EPA Star Grant R827161-01-0].

F. Characterization of the nAChR in Rat Heart During Development and Regulation by Nicotine. Al-Namaeh, M., , Das J.R., and Dávila-García, M.I. Department of Pharmacology, College of Medicine, Howard University, Washington. D.C.

Cigarette smoking during pregnancy increases the incidence of perinatal mortality and cardiovascular diseases. We know nicotine exposure alters neuronal nicotinic acetylcholine receptors (nAChRs) in cardiac vagal parasympathetic preganglionic neurons (cVPN) that project to cardiac parasympathetic ganglionic neurons (GPNs), which also contain nAChRs. Therefore, our goal was to determine the identity of the nAChR subtypes in the heart, determine their developmental profile, and assess if they were regulated by prenatal nicotine. Our working hypotheses were that 1) nAChRs will increase with developmental age and 2) that nicotine upregulates these receptors. We tested our hypotheses using [3H]EB receptor binding assays and [125I]EB binding and autoradiography. Pregnant rats received continuous infusions of saline or nicotine (4mg/Kg/day) from embryonic day 7 through birth. The results show that nAChRs are developmentally regulated with a peak at P7. The developmental profile, seems to be identical between control and nicotine exposed hearts tissues. [3H]EB binding assays were performed in the presence of 15 nM A85380 or 200 nM cytisine. The data shows that in the whole heart, approximately 38% of nAChRs are β2-containing, since A85380 is selective for these receptors. The residual binding in the presence of A85380 (~62%) represent all non β2-containg receptors. Since cytisine displaces all the nAChRs except α3β2 or α3β4 or α3β4α5, its displaced binding (~43%) also represents the β2-containing receptors, while the residual binding (~57%) represent β4-containing receptors, Since there was no difference in the levels of residual binding between A85380 and cytisine, therefore, it is unlikely any α3β2 receptors are present in the rat heart. The data demonstrates that there are at least two potential types of nAChRs in rat heart, in addition to the known α7 receptors (Ji et al., 2002), a β2-containing receptor, but not an α3β2, and high levels of a low affinity α3β4* receptor. Furthermore, these receptors are upregulated by nicotine only at E18. Thus, during the critical period of rapid development and synaptogenesis, prenatal nicotine affects nAChRs expression. These changes may contribute to the higher incidence of morbidity and mortality of those exposed to nicotine in utero through maternal smoking.

This work was supported by NIH-MBRS S06 GM 08016-32-2 to MDG & by Kuwait University grant KU0653 to AM & MDG

TREASURERS REPORT

by Laurie Roszell

Spring Meeting: May 24, 2004

Meeting-related income:

		Cost	Rc'd	
Registration:				
	Members			
	Students (early-bird)	($0)	7	$ 0.00
	Students (on-site)	($5)	0	$ 0.00
	Regular (early-bird)	($35)	20	$ 700.00
	Regular (on-site)	($40)	3	$ 120.00
	Non-Members:			
	Students (early-bird)	($10)	2	$ 20.00
	Regular (early-bird)	($45)	15	$ 675.00
	Students (on-site)	($15)	2	$ 30.00
	Regular	($50)	2	$ 100.00
Membership				
	Regular	($20)	6	$ 120.00
	Student	($10)	4	$ 40.00

Gross Symposium income **$1805.00**

Meeting-related expenses (final):

Printing (programs)		$ 74.87
Supplies (Badges)		$ 0.00
Plaque		$ 106.52
Speaker (estimated):	Dr. Lipscomb	$ 300.00
	Dr. Mumtaz	$ 300.00
Room rental		$ 0.00
Catering:		$ 615.00
Posters		$ 1465.95
Student Awards		$ 750.00

Total meeting expenses (estimated) **$ 3612.34**

Net meeting income **-$ 1807.34**

Checking account balance (April 30, 2005) **$14,744.65**
Net assets (estimated) **$12,937.31**

Respectfully Submitted,
Laurie Roszell
8 June 2005

National Capital Area

MEMBERSHIP APPLICATION

Name: _____

Affiliation: _____

Address _____

_____

City: _____

State: _____ Zip Code: _____

Area Code: _____ Phone: _____FAX:_____

E-mail: _____

Membership Type _____ Full Member ($20) _____ Student ($10)

Please check the most appropriate responses:

SOT Member

_____ Yes

_____ No

Highest Degree Attained

_____ A.S.
_____ B.A.
_____ B.S.
_____ D.V.M.
_____ D.V.M./Ph.D.
_____ M.D.
_____ M.D./Ph.D.
_____ M.P.H.
_____ M.S.
_____ M.A.
_____ Ph.D.
_____ Sc.D.
_____ V.M.D.
_____ V.M.D./Ph.D.

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