NATIONAL CAPITAL AREA CHAPTER
SOCIETY OF TOXICOLOGY NEWSLETTER
Electronic Edition

July 2007 Issue 23

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http://www.toxicology.org/script/loginredirect2.asp?page=dues

The National Capital Area Chapter of the Society of Toxicology (NCAC-SOT) was established to provide a regional focus for scientists of all disciplines interested in toxicology. The Chapter acts to:

- Sponsor and co-sponsor symposia on current issues in toxicology.
- Provide an annual award to an outstanding student in toxicology to assist in attending the annual meeting of the SOT.
- Maintain communication with the National SOT regarding current toxicology and regulatory concerns.
- Sponsor regional Chapter events at the annual meeting of the SOT.

MESSAGE FROM THE PRESIDENT

First I would like to say how honored I was to serve as the President of the NCAC-SOT Chapter for the past year. Our chapter has had a very productive and exciting several months. Information about all of the activities will be covered in more detail in this newsletter. I would like to welcome our new officers. Dr. Gary Burin is the incoming President of NCAC. I know everyone in the chapter will be giving him support as he carries on the many diverse activities that the chapter sponsors.

I would also like to welcome our new Vice-President/ President Elect, Dr. Donna Mendrick. Donna is a Scientific Fellow and Vice President of Toxicogenomics at Gene Logic. She will be responsible for organizing our fall and spring symposia. And we have a new councilor, Dr. Kathy Squibb. Kathy is already very involved with NCAC student activities.
Special thanks go to Thomas Flynn, our website Webmaster, and to Michael Orr, our Newsletter Editor. Both have done an outstanding job this year in ensuring that our Chapter's activities are well publicized and that the Chapter's membership is informed in a timely fashion of all Executive Board decisions. Thanks also go to Deborah Burgin, Secretary, and to Jennifer Weeks Sekowski, Treasurer, both of whom have been wonderful in performing "above and beyond the call of duty", having the added responsibility of manning the registration desk at our two symposia. Thanks to Devon Graham who has served as our student representative for the past year and she organized the NCAC Student Day in January and advised the board on student issues of concern. Thanks also to outgoing Board Councilor Lynn Flowers for her contributions to NCAC.

We had a great attendance at the NCAC Dinner held at a local restaurant during the National SOT Meeting in Charlotte, NC. This looks like it will become a yearly tradition.
Our Spring Symposium "The Role of Inflammation in Toxicity" was a resounding success. Thanks go to Gary Burin for putting together a very informative program. It was well attended and all of the speakers were excellent. You can find out more information about the symposium in this newsletter.

We had a great turnout for our student poster session held at the spring symposium. Thanks to Kathy Squibb for putting this together and for all the judges who had the difficult job of choosing which posters to give the cash awards to. All of the research presented was top-notch!
Our chapter is also very involved with K-12 activities. We presented several cash awards at local County Science Fairs and plan to sponsor some grants for high school science teachers. More information can be found on our website.

As we plan our activities for the upcoming year, the executive committee welcomes ideas from all of the members and encourages all of you to become more involved with NCAC activities. It's a great way to meet other toxicologists and to contribute to the field of toxicology.

Suzanne Fitzpatrick
301-827-4591

MESSAGE FROM THE NEWSLETTER EDITOR

This issue of the NCAC newsletter contains some of the usual features such as the reports from our president, student representative, and abstracts from the spring symposium on "The Role of Inflammation in Toxicity". The fall symposium will be held on October 24th at the Lister Hill Auditorium, National Library of Medicine, Bethesda, MD. More information in regards to the fall symposium will be coming soon!

Please feel free to contact me with seminars or upcoming not-for-profit events in Virginia, Maryland and the District of Columbia that may be of interest to toxicologists in our area. Please send these announcements to my attention (Michael.Orr@fda.hhs.gov), as we are very willing to publicize upcoming events.

If you are interested in joining NCAC, an application for membership can 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. Additional information on our local chapter can be found at our website (http://www.toxicology.org/isot/rc/ncac/default.htm).

Mike Orr
301-796-1604

MESSAGE FROM THE STUDENT REPRESENTATIVE

Welcome to another exciting year for graduate students in the National Capital Area Chapter! As NCAC's Student Representative for SOT's Student Advisory Committee, I'd like to express my gratitude to Devon Graham (Univ. of Maryland), the outgoing Student Representative, for her hard work and dedication this past year. Devon took on a big challenge in putting together Student Day 2006, which turned out to be one of the most successful and informative to date. I'm looking forward to working with the new Vice-Student Representative, Amy Shaw from Virginia Commonwealth University, in organizing another great Student Day this year!

The dates for this year's annual student symposium have yet to be determined. Tentatively, it will be held in December or January at one of the campuses in our region. The topics covered this year will be geared towards students and post-docs who are involved in the broad and ever expanding field of toxicology. Within the next couple weeks, we will also send out a survey. Again, these are relatively painless, so I would appreciate if we can get everyone's input on what they would like to see the NCAC do for them. Please keep an eye out for more details regarding the survey and the symposium.

I look forward to meeting each of you at this year's symposia. If you have any comments, questions or suggestions, please feel free to contact me at shethcm@vcu.edu or Amy at shawae@vcu.edu.

Chris Sheth and Amy Shaw

EXECUTIVE COMMITTEE MEMBERS

National Capital Area Chapter – Society of Toxicology

President:	Gary Burin (’06-’09) Technology Sciences Group Inc. 202-828-8980 gburin@tsgusa.com
Vice-President/ President-Elect	Donna Mendrick (’07-’10) Gene Logic Inc. 240-364-7633 dmendrick@genelogic.com
Immediate Past President	Suzanne Fitzpatrick (’06-’07) US FDA 301-827-4591 sfitzpat@oc.fda.gov
Secretary:	Deborah Burgin (’05-’08) US Environmental Protection Agency 202-566-0269 burgin.deborah@epa.gov
Treasurer:	Jennifer Weeks Sekowski ('05-‘08) US Army CHPPM 410-436-8774 jennifer.sekowski@us.army.mil
Councilors:	Michael Orr ('06-'09) US Food and Drug Administration 301-796-1604 michael.orr@fda.hhs.gov Kath Squib (‘07-‘10) University of Maryland ksquibb@umaryland.edu Thomas Flynn (‘05-‘08) US Food and Drug Administration 301-827-8382 thomas.flynn@fda.hhs.gov
Student Representative	Christopher Sheth (’06-’08) Virginia Commonwealth University shethcm@vcu.edu
Student Vice- Representative	Amy Shaw (’07-’09) Virginia Commonwealth University shawae@vcu.edu

ABSTRACTS FROM MAY, 2007 NCAC-SOT SYMPOSIUM

Alcohol and Liver Inflammation

Vishnudutt Purohit, Ph.D., and Bin Gao, M.D., Ph.D
National Institute on Alcohol Abuse and Alcoholism
National Institutes of Health

Alcoholic Liver disease (ALD) is a major complication of heavy alcohol consumption and is characterized by progressive pathologic stages such as fatty liver (steatosis), steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. Inflammation is a mechanism whereby alcohol triggers the process of alcoholic hepatitis characterized by infiltration of neutrophils, macrophages, and/or lymphocytes as well as hepatocyte degeneration, ballooning, and necrosis.

Kupffer cells (Hepatic macrophage) activation by alcohol-mediated gut-derived endotoxin (LPS) appears to be a key event in the initiation of alcoholic liver inflammation. Binding of endotoxin to Kupffer cells through CD14 and TLR4 receptors triggers a cascade of events leading to generation of free radicals (ROS and RNS), activation of transcription factors (NF-kB, AP-1 and Egr-1), and increased production of pro-inflammatory cytokines (e.g., TNF-), chemokines, and adhesion molecules.

Increasing evidence suggests that TNF released from Kupffer cells plays an important role in the pathogenesis of alcoholic liver inflammation. Serum concentrations of TNF-α are elevated in alcoholic hepatitis patients and in animals exposed to chronic alcohol. Alcohol up-regulates the expression of TNF-mRNA in the liver, which is especially localized in Kupffer cells. TNF- antibodies attenuated alcohol-induced hepatic necro-inflammation in rats, and TNF- receptor 1 knockout mice were refractory to alcoholic liver injury. TNF- may initiate liver inflammation by inducing apoptosis/necrosis of hepatocytes, and by increasing the synthesis of chemokines, adhesion molecules and other pro-inflammatory cytokines. Alcohol appears to render hepatocytes susceptible to TNF-induced liver injury by inducing oxidative stress, impairing methionine metabolism and inducing steatosis. IL-1 (another pro-inflammatory cytokine) may contribute to alcoholic liver inflammation by increasing the production of MIP-1 chemokine.

Chronic alcohol exposure may regulate infiltration of neutrophils in the hepatic parenchyma by upregulating the production of CXC chemokines (IL-8, CINC and MIP-2) and adhesion molecules (-integrins and ICAM-1). On the other hand, recruitment of mononuclear inflammatory cells (lymphocytes and macrophages) in alcoholic liver inflammation appears to be mediated through increased expression of CC chemokines (RANTES, MIP-1 , KC, MCP-1). Adhesion molecules such as integrins, ICAM-1, VACM-1, and VAP-1 participate in the migration of lymphocytes. Inflammatory cells may damage heaptocytes by releasing free radicals, proteases and cytokines.

The role of inflammation in the safety assessment of medical device materials

Ron Brown
FDA/CDRH

Patients can be exposed to endotoxin either exogenously from contaminated or improperly cleaned medical devices or endogenously during infection with Gram-negative bacteria. The inflammatory response seen during preclinical testing of some medical device materials

(bioresorbables, nanoparticles) may be due to the presence of residual endotoxin, not the material itself. This finding emphasizes the need for allowable endotoxin limits for devices and the need for preclinical testing to assess inflammatory potential of some device materials.

Sepsis is the systemic inflammatory response to infection and is an important public health issue for critically ill patients. The pro-inflammatory state associated with sepsis/endotoxemia and resulting target organ damage has been shown to potentiate the toxicity of a number of compounds and, therefore, has the potential to also increase the toxicity of compounds released from medical device materials. Conversely, compounds released from medical devices materials have the potential to either suppress or potentiate the inflammatory response to endotoxin. For example, preliminary *in vitro* studies in our lab have shown that DEHP, a plasticizer commonly used in PVC medical devices, has an anti-inflammatory effect in LPS-stimulated RAW 264.7 macrophages. Hyperglycemia is also associated with the pro-inflammatory state seen in critically ill septic patients. Studies in our lab have shown that DEHP inhibits insulin release in rat pancreatic islet cells, a finding that is consistent with the increased glucose levels seen in DEHP-treated rats. Since hyperglycemia is common in critically ill and septic patients, and since these patients can be exposed to relatively high doses of DEHP, the potential exists for DEHP released from PVC medical devices to increase the blood glucose values in these patients. Fever is another common response to inflammation produced by endotoxin. Studies in our lab and others have shown that even mild hyperthermia can potentiate the *in vitro* cytotoxicity of extracts of medical device materials. Collectively, the results of these studies indicate that a pro-inflammatory state and hyperthermia have the potential to increase the toxicity of compounds released from biomaterials; however, in some cases, compounds released from medical device materials may be anti-inflammatory.

Application of the Neuro-Immune-Endocrine System Model to Evaluate the Role of Inflammation in Systemic Toxicity

Larry Garthoff PhD
Food and Drug Administration
Laurel, Maryland

Recently, one of our research efforts in the Office of Applied Research and Safety Assessment (Center for Food Safety and Applied Nutrition) at the FDA has involved an investigation of the utility of a Neuro-Immune-Endocrine System (NIES) model for toxicological evaluation in food safety and food security programs. This model is based on an experimental model developed to investigate the interactions between the classical nervous, immune, and endocrine systems. The concept was initiated over three decades ago, but became a large and rapidly growing body of research within the last 10-15 years. The inflammatory process is one of the central features of this physiological system. A commonly used name for the discipline is *Psychoneuroimmunology*, but several slightly different names have been and continue to be used. The pioneers of this discipline have suggested the name could be changed to reflect its current key role in biomedical science, i.e., *Integrative Biology and Medicine* (Besedovsky and del Ray, 2007). *Psychoneuroimmunology* offers a new perspective and attempts to provide a unified and highly integrated concept of mammalian health and disease as an alternative to the

compartmentalization and reductionism of the biological sciences. For this reason it also appears to provide a useful platform for investigating some of the complex issues that may help to define the future direction of toxicology. I will introduce this model and provide examples of how it represents a significant paradigm shift from past toxicological approaches. I will present evidence showing that this paradigm is a valuable tool in understanding the role of inflammation in toxicology as well as in the pathogenesis of many disease processes. In reference to recent concerns for the future of Toxicology, (Liebler, 2006) we believe a model of this kind can provide a mechanistic base that will demonstrate the important and close relationship between toxicology and mammalian health and disease. This is especially useful with respect to the key group of human disorders that currently have a major public health impact such as obesity, cardiovascular disease, and neurodegenerative disorders. I will also present some of our results that show the effects of inflammation on the acute toxicity of deoxynivalenol and colchicine that support the utility of the NIES model.

References:

Besedovsky, H. and del Ray, A. (2007) Physiology of psychoneuroimmunology: A personal view. *Brain Behav. Immunity* **21**:34-44.

Liebler, D.C., (2006), The Poisons Within: Application of Toxicity Mechanisms to Fundamental Disease Processes, *Chem. Res. Toxicol*., **19**: 610-613. Part of the *Chemical Research in Toxicology Perspectives Open Forum*, http://www.acspublications.blogs.com/crtopenforum/

Pulmonary Inflammatory Responses in Rats Related to Particle Exposures: Role of Surface Reactivity and Particle-types

David B. Warheit, PhD,
DuPont Haskell Laboratory for Health and Environmental Sciences
Newark, Delaware, USA

The results of several lung toxicology studies in rats have demonstrated that ultrafine or nanoparticles (generally defined as particles in the size range < 100 nm) administered to the lungs produce enhanced inflammatory responses when compared to fine-sized particles of similar chemical composition at equivalent doses. However, the common perception that nanoparticles are always more toxic than fine-sized particles is based upon a systematic comparison of only 2 particle-types, namely, titanium dioxide and carbon black particles. Apart from particle size and corresponding surface area considerations, other factors may play more important roles in influencing the pulmonary toxicity of nanoparticles. These include, but are not limited to the surface reactivity of particle-types. Perhaps more importantly, assessments of particle-induced pulmonary toxicity in rats can be predicted on the basis of responses such as sustained inflammation, cytotoxicity and enhanced cell proliferation. These observed effects usually result in the development of adverse lung tissue responses.

Results of pulmonary bioassay hazard/safety studies in rats will be presented demonstrating that fine-sized quartz particles (0.5 μm) may produce greater pulmonary toxicity

(inflammation, cytotoxicity, cell proliferation and/or histopathology) in rats when compared to nanoscale quartz particles (50 nm), but not when compared to smaller nanoquartz sizes (e.g., 12 nm). In addition, other studies have demonstrated no measurable differences in pulmonary toxicity indices among particle-types when comparing exposures in rats to 1) fine-sized TiO_2 particles (300 nm – 6 m^2/g (surface area); 2) TiO_2 nanodots (6-10 nm – 169 m^2/g); or 3) TiO_2 nanorods (25 m^2/g). Finally, the results of intratracheal instillation and inhalation studies, respectively, with fine and ultrafine TiO_2 particles as well as zinc oxide particles will be presented which demonstrate that surface reactivity rather than particle size influences pulmonary responses following particulate exposures.

TREASURERS REPORT

NCAC-SOT Treasurer's Report
July 10, 2007

I. Official checking account balance (5/30/07 statement): $16,367.30

II. Spring Symposium financial data:

Gross proceeds (include: Registration fees and new memberships)	$1,990.00
Gross costs	
catering	$1,095.52
poster boards	$320.00
speaker travel	$196.50
student awards	$1,350.00
Gross cost of Symposium	$2,962.02
Total (net) cost of Symposium	**$972.02**

III. Data on Attendees:

Type of Attendee	Pre-registered	On-site	Total
Full member	18	4	22
Student member	10 (no fee)	7	17
Non-member	20	5	25
Student non-member	6	0	6
Speaker	6 (no fee)		6
Total	**60**	**16**	**76**

IV. New memberships: $100.00
full (2x $20)- $40, student (6x $10)- $60

V. Unofficial Balance as of 7/10/07: $15,395.28

Respectfully Submitted,
Jennifer W. Sekowski
10 July, 2007

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.

Type of Affiliation

_____ Academia
_____ Consulting
_____ Contract Lab
_____ Government
_____ Industry-Chemical/Petroleum
_____ Industry- Pharmaceutical
_____ Industry- Other
_____ Other- _____

Please complete the information above and send with a check, money order or credit card (payable to [specific RC], no POs) to the address below. The chapter to which you are applying will review your application and you will be notified within 30 days. Those not accepted will receive a full refund. *Current RC members: please do not use this form since your renewal dues are billed annually through SOT.*

Payment Type: Money Order_____ Check _____ Credit Card _____
Credit Card # _____ Exp date _____
Name on Card _____

Send to:

Jennifer Weeks Sekowski, Treasurer
US Army
CHPPM ATTN MCHBS TS THE, 5158 Blackhawk Road
Aberdeen Proving Ground, MD 21010