Renew Your SOT and NCAC Membership at
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 am to be the President of the NCAC-SOT Chapter for the upcoming year and want to thank Dr. Gary Burin for his excellent leadership as President of the chapter last year. He has set a high bar and will be tough to follow. I would like to welcome our new officers. Dr. Jennifer Sekowski, a molecular toxicologist with the Army at the Aberdeen Proving Ground, is the new Vice President/President Elect. Jennifer has been our Treasurer and done a wonderful job in making certain the symposia run smoothly. She will be organizing our upcoming fall and spring symposia for which we are soliciting ideas for topics. Please contact Jennifer (jennifer.sekowski@us.army.mil) or myself (dmendrick@genelogic.com) with ideas. Dr. Thomas Flynn (FDA) who has been our wonderful website guru is now our Treasurer. Syril Pettit (ILSI) joins us as a councilor and will assume responsibility for our website. Amy Delong (Virginia Commonwealth University) is our incoming Student Representative. Continuing in their roles are Mike Orr (FDA) as councilor and Newsletter Editor, Deborah Burgin (EPA) as Secretary, Kathy Squibb (University of MD) as Councilor.

We hosted a successful reception on March 18, 2008 at the Wild Ginger during the national Society of Toxicology meeting in Seattle. There was a good crowd, great food and interesting networking opportunities. A special thanks to Deborah Burgin for organizing this reception.

Our Spring Symposium, held on May 20, 2008, was entitled: “Animal and Human Models of Toxicity Testing” And we had a higher than normal turnout. The presentations have been loaded onto our website. Abstracts for their presentations can be found below. A special thanks to Jennifer and Maureen Gwinn for staffing the registration desk at the meeting.

As we plan our activities for the upcoming year, the executive committee would welcome ideas from all of the members. As noted above, we are looking for topics for our fall and spring symposia that would be of interest to our members. We also would like to strengthen our student activities to encourage people to consider a career in the field of toxicology and would welcome new creative ideas from our members.

I look forward to seeing all of you at chapter activities and I encourage you to contact me or any of the other officers with your suggestions for future NCAC-SOT events.

Donna L. Mendrick
240-364-7633

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 “Animal and Human Models of Toxicity Testing”, up-coming meetings in our area, and NCAC-SOT award.
In addition, a new student mentor program has been developed by the NIH and more details in regards to this new program will be discussed below.

SciMentorNet is a new student mentoring program being offered by the Office of Science Education at the NIH. It is a Web-based program that links prescreened mentors (scientists, healthcare workers, and clinicians) with high school and college students who are interested in exploring careers in biomedical research, health care, or medicine. This mentoring service is free and available to any student who is at least 16 years old and attends high school or college in Washington, D.C., Maryland, or Virginia. Students register for SciMentorNet online through this Web site: http://science.education.nih.gov/SciMentorNet. Students under age 18 must have a parent/guardian sign an agreement and mail or fax it to OSE before being accepted into the program.

Please feel free to pass this information along to administrators, science teachers, and STEM students at D.C., Maryland, and Virginia high schools and colleges. If you need further information about this exciting career-development and mentoring program, e-mail the SciMentorNet coordinator at ariasj@csr.nih.gov.

On a different note, the following local meetings may be of interest to the NCAC-SOT members:

1.) **Americans for Medical Progress International Working Group, International Forum for Animal Research Policy**, June 24–25, 2008, Washington, D.C. Contact: Americans for Medical Progress, 908 King Street, Suite 301, Alexandria, VA 22314 (703) 836-9595 or E-mail amp@amprogress.org

2.) **Genetic Toxicology Association 2008 Meeting: “Current Regulatory and Scientific Issues in Genetic Toxicology”** Wednesday-Thursday, 10-11 September 2008, John M. Clayton Hall Conference Center, University of Delaware, Newark, Delaware  GTA Website: http://www.gta-us.org/

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 that may be of interest to our members.

At the 2008 SOT meeting in Seattle, the NCAC-SOT provided cash awards for graduate students and postdocs with outstanding poster or platform presentations. There were a number of excellent presentations and posters to judge from this year.

Below are the names and pictures of the award winners this year:
Graduate Student Awards
First place - Matthew Smith, ($500); Poster, Abstract # 2135

Second place - Suma Vavilala ($350); Platform presentation, Abstract # 696

Picture Not Available

Postdoc
First place - Zhenguan Jia ($500); Poster, Abstract # 2051

Congratulations to the winners from the executive committee members at NCAC-SOT!!!
If you are interested in joining NCAC, an application for membership can be found at the end of the newsletter. Alternatively, you may want to use the on-line membership renewal method by clicking on the following link SOT Membership. 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
MESSAGE FROM THE STUDENT REPRESENTATIVE

Hello everyone, and thanks for making this past year another exciting one for graduate students in the NCAC-SOT. It was great seeing students from across the region in attendance at the Student Day Symposium at Virginia Commonwealth University in Richmond, VA as-well-as at the national SOT meeting in Seattle, WA. As the outgoing NCAC-SOT Student Representative, I’d like to express my gratitude to Amy Delong (Virginia Commonwealth University), the incoming Student Representative, for her hard work and dedication this past year as the Vice-Representative. Amy will be working diligently on planning the Student Day for the 2008/2009 school year.

This year’s Student Day is going to be held sometime near the end of or shortly after the Fall Semester. Stay tuned to the Newsletter and to the NCAC-SOT website for more information about the location, topic, and speaker line-up for the next Symposium. It’s been an honor and a pleasure to serve the chapter, and I wish everyone the best of luck in all your pursuits. I’m sure Amy is looking forward to meeting each of you at this year’s events, so come out and have some fun with the NCAC-SOT. If you have any comments, questions or suggestions, please feel free to contact us at shethcm@vcu.edu or shawae@vcu.edu.

Christopher Sheth and Amy Delong
EXECUTIVE COMMITTEE MEMBERS

National Capital Area Chapter – Society of Toxicology

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240-364-7633
DMendrick@genelogic.com

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Student Vice-Representative: Amy Delong (‘07-’08)
Virginia Commonwealth University
shawae@vcu.edu
Predictive Teratogenicity Assessment: Current Applications and Future Directions

Karen Augustine, Ph.D. Discovery Toxicology, Bristol Myers Squibb, Hopewell, N.J.

Unexpected teratogenicity is a prevalent cause for toxicity-related attrition of drug candidates. It is a costly liability and tends to be identified relatively late in the pre clinical phase of drug development, following significant engagement in pre clinical and clinical studies. The origins of teratogenicity are related to the intended pharmacology having an essential role in embryo-fetal development and/or to an undesired “off-target” effect. Teratogenicity identified with endothelin receptor antagonists provides a classic example where proactive assessment of target-based liabilities could have been undertaken earlier, specifically in the discovery phase, potentially enabling better alignment of indication in context to the developmental toxicity risk. Such proactive approaches include thorough assessment of the literature to obtain an understanding of potential liabilities, additional follow up work conducted on the level of target expression and functional characterization using molecular biology and developmental model systems and applying in vitro teratogenicity screens. This presentation will describe the case study of unexpected teratogenicity associated with endothelin receptor antagonists under development in the 1990s and the types of proactive approaches that can now be utilized to proactively problem solve and potentially reduce later phase teratogenicity-based attrition.

The Rodent Chronic Assay Database for Pesticides: Using Mode of Action Data to Assess the Human Relevance of Animal Tumors.

Vicki Dellarco, Ph.D., Senior Science Advisor, US EPA, Office of Pesticide Programs, Washington DC.

The rodent cancer bioassay has formed the basis for health risk assessment and regulatory decisions for over 40 years. Several extrapolations or inference methods are necessary when using the results of this animal model to predict human health consequences. Unless there is evidence to the contrary, it is assumed that rodent data predict human effects, findings at high experimental doses predict effects at environmental exposure levels, and adult animals provide adequate coverage for predicting responses at different life stages, including children. Irrespective of the data base, the rodent liver is the most target organ most frequently showing a tumor response. An examination of the pesticide data base revealed that the mouse lung is also a common target which is consistent with the data showing that some frequently used mouse strains spontaneously develop pulmonary tumors. In addition to liver in the rat and mouse and lung in the mouse, thyroid follicular cell and Leydig cell tumors are frequently diagnosed in the rat following pesticide treatment. The hormone sensitive tumors in the rat thyroid and testicle typically represent species sensitivity. Unlike the rodent, the incidence of liver cancer in humans occurs at a much lower frequency compared to the much higher frequency of prostate and breast cancer. Prostate tumors rarely are diagnosed in rodents. Because of significant differences between rodent and human tumor incidences, data from the rodent cancer bioassay should be interpreted in combination with all available data to predict human hazard. The consideration of mode of action is extremely valuable to assess species differences and to inform dose-response extrapolation and modeling approaches. An approach that provides rigor and transparency to the weight of evidence evaluation of mode of action has
developed through collaborative efforts of the US EPA, Health Canada, International Programme for Chemical Safety (IPCS), and the International Life Sciences Institute (ILSI). This approach uses a conceptual framework for assessing the weight of evidence for a postulated mode of action for a given toxic effect (including carcinogenicity). The IPCS/ILSI Framework is based on the Bradford Hill criteria. These criteria are used to evaluate the causal relationship between quantifiable key events in the animal that are necessary elements in the mode of action and tumor development. Once an understanding of the animal mode of action is established then the human relevancy can be assessed. This next step involves a qualitative and quantitative concordance analysis of the key events between animal and human (e.g., consideration of comparative biology, kinetics/metabolism, anatomical variations, and relevant human disease states). The USEPA Office of Pesticide Programs has used this framework approach for several years with great success. In the case of pesticides that are rodent liver carcinogens and are not direct acting mutagens, two general modes of action are observed, a receptor mediated pathway (e.g., PPARα agonism or CAR activation) or a non-receptor pathway (e.g., chronic cell injury/death and regenerative proliferation). Thiamethoxam, a broad spectrum insecticide that induces mouse liver tumors will be used as an example of the application of the IPCS/ILSI human relevance framework. This case study demonstrates how the framework is utilized, that it promotes the use of all relevant data (chemical specific and generic) and provides a structure to clearly present the evidence in a transparent manner. (*This abstract represents the view of the author and does not necessarily represent the decisions or stated policies of the USEPA. Mention of trade names does not imply endorsement.)*

**Use of Transgenics in Carcinogenicity Testing**

Richard Storer, Ph.D., Senior Scientific Director, Dept. of Laboratory Sciences and Investigative Toxicology, Safety Assessment, Merck Research Laboratories.

International guidelines allow for use of a short-term cancer bioassay (26 weeks) in transgenic mice as a substitute for one of the two required long-term rodent bioassays in the preclinical safety evaluation of pharmaceuticals. The substitution may be allowed, or encouraged, when preclinical safety and/or pharmacology data suggest that an alternative assay could provide additional information not likely to be obtained from a second long-term bioassay. Utilization of these models in preclinical safety evaluation can significantly reduce animal use, time and manpower. The two models which have gained general acceptance by both sponsors and regulators are the CB6F1-RasH2 mouse hemizygous for the human H-ras transgene and the B6.129N5-Trp53 mouse heterozygous for a p53 null allele. These models have shown potential to provide, in addition to a short-term tumorigenicity endpoint, insight into mechanisms involved in tumor induction. Utilization of the p53+/− model is of particular value for compounds with residual concern that genotoxic activity may contribute to tumorigenesis; the rasH2 model however may be accepted as an alternative without regard to evidence of genotoxic potential. In considering the utility of the p53 model, many genetic toxicologists view the ICH test battery and available adjunct assays as sufficient for evaluating the potential risk of genotoxic carcinogenesis and for making decisions with respect to initiation of clinical trials. However, results from a p53 assay can make an important contribution to the weight of evidence assessment of mode of action (genotoxic vs non-genotoxic) from any tumor findings in the long-term bioassay. In addition, since results from a short-term bioassay can be obtained relatively early in drug development, there is the potential for more timely assessment of cancer risk for individuals in clinical trials. For the rasH2 model, responses to non-genotoxic carcinogens and the rationale for use of this model will be discussed in the context of the debate as to which
classes of compounds in this category are most important to detect.

**Hepatotoxicity Testing; Predictive Strengths and Weaknesses**

Rich Miller, DVM, PhD, VP, Safety Assessment, GlaxoSmithKline

Hepatotoxicity is a significant cause of discontinuation of drugs in development, as well as withdrawal of marketed medicines. Hepatic structure and function are generally similar across species used for preclinical testing and humans; specifically, hepatic cell make up and major roles (e.g., metabolism, detoxification, energy storage, bile formation, endocrine and immune function) are conserved across species. These similarities underpin the rationale for use of preclinical species in identifying potential human liver hazards. However, there is clearly a need to improve our ability to predict hepatotoxicity outcomes early in drug development due to varying hepatotoxic sensitivities in diverse patient populations and the multitude of mechanisms that can lead to hepatotoxicity. Increasingly sophisticated in vitro, imaging and molecular biology approaches offer promise in this regard. Hepatic transcriptome alterations representing well annotated toxicity pathways interpreted in the context of clinical and anatomic pathology endpoints can bolster sensitivity and predictivity of preclinical studies. In vitro assays including cellular, enzymatic and binding assays such as those using primary hepatocytes or hepatic cell lines, CYP inhibition assays, and reactive metabolite signal detection assays (i.e., GSH trapping), may also aid in identifying potential hepatotoxic properties early and can supplement in vivo studies. In summary, improvements in hepatotoxicity detection and prediction can be made by complementing sound preclinical testing paradigms with additional relevant endpoints in standard in vivo studies, coupled with detection of undesirable biologic properties using a variety of in vitro assays.

**The Generation and Use of Human Data in the Safety Evaluation of Pesticides, Personal Care Products, Food Ingredients and Pharmaceuticals**

Gary Burin, MPH, Ph.D., D.A.B.T., Director, Toxicology and Risk Assessment, Technology Sciences Group Inc., Washington DC

Human data have played an important role in the safety assessment of chemicals found in a variety of products including pesticides, pharmaceuticals, personal care products and food ingredients. The types of intentional human studies that have been used in risk assessment include safety, efficacy and exposure studies. There is a well-established process for ensuring ethical conduct of these studies. In the absence of human data, risk to humans is assessed from animal models through the use of default values for interspecies and intraspecies sensitivity. Chemical Specific Adjustment Factors which are based upon human data have the potential to improve the accuracy and scientific basis of risk assessment by replacing the default values for interspecies and intraspecies uncertainty.

**ToxCast: Developing predictive signatures of chemically induced toxicity.**


ToxCast, the United States Environmental Protection Agency’s chemical prioritization research program, is developing methods for utilizing computational chemistry, bioactivity profiling and toxicogenomic data to predict potential for toxicity and prioritize limited testing resources. In the
proof-of-concept phase, we are focused upon evaluating chemicals with an existing, rich toxicological database in order to provide an interpretive context for the high through put screening data. This set of 320 reference chemicals are largely derived from the active ingredients in food use pesticides and represent numerous structural classes and phenotypic outcomes, including tumorigens, developmental and reproductive toxicants, neurotoxicants and immunotoxicants. The goal of the program is to develop signatures based on the combined use of physico-chemical properties (the traditional independent variables in structure activity models) and the bioactivity data (derived from a broad spectrum of more than 400 readouts from biochemical assays, cell-based phenotypic assays, and genomic analyses of cells) that are predictive of responses in animal bioassays. The signatures derived for chemicals with toxicity data gaps could then be compared with those of the well characterized chemicals, and those with significant signatures would become priority candidates for testing in traditional animal bioassays. These data are being generated through a series of external contracts, and through collaborations within EPA and with the National Institutes of Health Chemical Genomics Center. Results of the proof of concept phase and supporting chemo-informatic infrastructure will be presented. This is an abstract of a proposed presentation.

TREASURERS REPORT

NCAC-SOT Treasurer’s Report
June 2008

I. Official checking account balance (4/30/08 statement): $16,354.66

II. Spring Symposium financial data:

Gross proceeds
  Registration and membership fees $3,420.00

Gross costs
  Catering $1,374.04
  Speaker travel $0
  Admin. & supply costs $0

Gross cost of Symposium $1,374.04

Net proceeds from Symposium $2,045.96

III. Data on Attendees:

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IV. New memberships:

V. Unofficial Balance as of 03 June, 2008: $18,400.62

Respectfully Submitted,
Tom Flynn
03 June, 2008
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      Highest Degree Attained      Type of Affiliation

_____ Yes   _____ A.S.   _____ M.P.H.   _____ Academia

_____ No    _____ B.A.   _____ M.S.    _____ Consulting

_____ B.S.   _____ M.A.   _____ Contract Lab

_____ D.V.M.  _____ Ph.D.  _____ Government

_____ D.V.M./Ph.D.  _____ Sc.D.  _____ Industry-

_____ M.D.   _____ V.M.D.  Chemical/Petroleum

_____ M.D./Ph.D.  _____ V.M.D./Ph.D.  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:

Tom Flynn, Treasurer
NCAC-SOT
9707 Baltimore Ave.,
Laurel, MD 20723-1861