

# STC NEWS/NOUVELLES

VOLUME XXXIII, No 1, April, 2004

BULLETIN OFFICIEL DE LA SOCIÉTÉ DE TOXICOLOGIE DU CANADA  
OFFICIAL NEWSLETTER OF THE SOCIETY OF TOXICOLOGY OF CANADA

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VOLUME XXXIII, NUMBER 1

APRIL, 2004

2003-2004

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## **WHAT HAPPENS WHEN YOU CAN'T SAY NO? – Bill Racz**

You become editor of a newsletter! I must confess that I was honoured when Sheldon Roth asked me to assume the role as editor of News/Nouvelles. Of course, I also recognized that this was a considerable amount of work. Since I am due to retire from full time at Queen's University, I hesitated in accepting this role. After six months of saying no, Barbara Hales finally talked me into it. I hesitated, as I recognized that to carry out this function with minimal cost to the society I will need to do most of the assembly of documents and preparation of a printer-ready version. This, of course, raises the question, can an old dog, or, in this case, an old toxicologist, learn new tricks. I will need to improve my computer and word processing skills but I should have more time soon. Right! I now have a retirement project, learning clipart and desktop publishing. I will need the assistance of others.

I would like to acknowledge Michel Prior for the work he did as editor of News/Nouvelles. He did a superb job and his professionalism will be difficult to follow. Unfortunately, due to his untimely death, I was unable to meet with him and tap into the knowledge that he accumulated over the past years as editor of this newsletter.

News/Nouvelles should continue to serve the members of the society, as it has in the past. I would be pleased to receive comments on the contents of the newsletter and, of course, articles are always welcome. For this issue, I have requested articles from Bill Casley and Carol Drury representing issues of interest from government and industry respectively. The winners of the Cantox poster awards have both kindly provided expanded abstracts of their work. This issue also contains tributes to Michael Prior, Francine Denizeau, and Kundan Khera three members of the society who are no longer with us.

### **MESSAGE FROM THE PRESIDENT: BARBARA HALES STC: PAST, PRESENT AND FUTURE, FROM THE NEW PRESIDENT'S PERSPECTIVE**

The Board has met twice since the 2003 December Symposium, first “virtually” in February by teleconference and second “physically” last weekend (April 18) at the Delta in Montreal. Naturally, a major item on the agenda at both meetings was the 2004 Symposium (December 6 and 7, at the Montreal Delta Hotel). Dino Manca and his Scientific Program Committee are assembling a great symposium on the theme “Relationships Between Health and the Environment: The Role of Toxicology”. Outstanding guest speakers, in concert with cutting-edge poster presentations, will create a scientifically exciting meeting! There will be room for everyone to participate in a “round table” discussion aimed at “Identifying, Characterizing, and Addressing Environmental Health Issues on a Local and Global Scale”. To this we add a fun banquet and, new this year, a Sunday evening session geared specifically for trainees on “Careers in Toxicology – from an academic, industrial or government perspective”, accompanied by pizza and beer!

The STC has a new “face” on the world. We hope that you have all had the opportunity to visit our new web site at <http://www.stcweb.ca>. If not, please do, and add it to your favorites! Thanks are due to Jennifer Day, our webmaster, and to members of the newly created web site committee. Among the items we hope to add is a members' only section with expertise information (see below). Your suggestions and input are always welcome. Thanks are also due to Daniel Cyr, our very capable Treasurer, and to Gordon Krip, our hard working Executive Director, for their extraordinary patience and determination in bringing credit card payments into the realm of reality for STC.

2004 is also a busy year for Len Lillie and other members of the ICT XI Executive Committee as they plan their activities at the upcoming ICTX meeting in July 2004 in Tampere, Finland. I know that many of you will be in the land of the midnight sun and I am sure that you will be called upon to help!

Our sympathy goes out to the families and friends of two of our close colleagues, Michael Prior and Francine Denizeau for their loss. We have all benefited from their dedication to STC, and enjoyed working with them over the years. Our new Editor, Bill Racz, has big shoes to fill!

From the past to the present, we arrive at the future. Our continuing goal is for STC to come to mind in Canada when questions are asked and decisions are made on issues relevant to toxicology. One of the things we will work on, as mentioned above, is an update of our registry of scientific expertise. Another, perhaps even more important, is to encourage colleagues with expertise in Toxicology to join STC. It is especially important for the future of the Society that our trainees become involved and join. We could double our membership if each of you sponsored only ONE person. We shall look forward to hearing from you.

Barbara Hales ([barbara.hales@mcgill.ca](mailto:barbara.hales@mcgill.ca))

**MESSAGE FROM THE PAST PRESIDENT SHELDON ROTH**  
**SOCIETY OF TOXICOLOGY OF CANADA**                      **Monday December 8, 2003**  
**REPORT OF THE PRESIDENT**  
**ANNUAL GENERAL MEETING 2003**

Welcome to the 36<sup>th</sup> Annual General Meeting of STC. I would like to begin by expressing my sincere appreciation to the Directors of the STC Board. They have been very active and each member must be acknowledged for their dedication and time commitment; Heather Durham, Past President, Barbara Hales, Vice-President, Jeff Kawamoto, Secretary, Daniel Cyr, Treasurer, Gordon Krip, Executive Director, Councilors, Genevieve Bondy, Mark Goldberg and Daniel Sitar. Len Lillie continued to serve as an ex-officio member of the Board as liaison for the ICT XI. This year we welcomed two new members to the Board, both “Dans” – Daniel Cyr as Treasurer and Daniel Sitar as Councilor.

Many of you may be aware that Gordon Krip has recently retired from Merck. The Board took the liberty of appointing Gordon as full-time Executive Director. Gordon has agreed to serve as “Mr. Executive Director” for the next eleven years. I am confident that without his help the Board would be struggling with the day to day events.

Heather Durham and Mark Goldberg have completed their terms of office. Mark has been a very valuable member of the Board contributing a great deal to the membership and fundraising activities. He has provided a number of ideas and documents that will guide us in the future to attract more members and also acquire better funding. I thank Mark for his contributions and hope that he will continue to serve the society with the same energy he has exhibited over the past few years.

Most of you know Heather Durham. Heather is regarded as one of the “pillars” of this society. She has been an active member for many years and her dedication has been exceptional. Heather has been very influential on a variety of aspects of STC affairs. These include policy, programming, membership and awareness. She is a model member in every respect and I hope that we can continue to count on her enthusiasm and dedication that she has demonstrated.

Once again this year the Board will present Certificates of Appreciation to members who have served as officers at the President's Reception. Please come and express your appreciation to these individuals.

I would like to thank Jack Bend for agreeing to serve as Chair of the Science Policy Committee. Together with Bernard Robaire, I am confident that STC will have a strong voice regarding CFBS affairs and science policy in general. I would also like to thank Adam Socha (Chair) and Thomas Morris for joining the Membership Committee.

Once again we have the opportunity of participating in an outstanding Annual Symposium. Each year seems to get better, and we have been fortunate to have had the talents of the Scientific Program Committee. They have organized a very exciting and timely program. One of the major items of business for the Board is the planning and implementation of the Annual Symposium. However it is the Program Committee that has the major responsibility of developing the theme and attracting high quality speakers. It is evident that the committee has been most successful. I thank and congratulate William (Bill) Casley (Chair), Dino Manca and Louise Winn. I would also like to thank Barbara Hales for informing the Board of the committee's progress and maintaining the schedule during development. The Board has tried to maintain a reasonable registration fee for the Annual Symposium as well as reduced fees for students and postdoctoral fellows. We also have provided some travel assistance to students. Since registration fees are not sufficient to cover all costs, it has been necessary to obtain external funding. Unfortunately, this year, we were not as successful as last year. One of the objectives for next year, and for continued sustainability, will be to secure sponsorship at a sufficient level that will prevent substantial increases in fees. Thank you to Mark Goldberg for his efforts in raising funds for this year.

Michael Prior has served as editor of the STC News/Nouvelles for a number of years. We have managed to convince him on more than one occasion to extend his term of office knowing that one day he would say – this is it! Well, we finally had to accept his resignation this year. Michael has been an outstanding editor. He has created a quality newsletter by acquiring excellent authors, articles of interest to all toxicologists, formatting the newsletter for hard copy and website to be published on time, and providing considerable personal contributions. Our sincere thanks to Michael for his years of service; we wish him good health and happiness for the future. Welcome to Bill Racz as our incoming editor. A better choice could not have been made. As well, we must thank the many contributors to the newsletter; details will be provided by Barbara Hales.

During the past year, the Board has accomplished a great deal, a few examples:

- Implementation of credit card system for annual dues, registration, etc. (December 2003)
- Electronic directory (sent out September 2003)
- Organization of 36th Annual Symposium
- ICT XI – signing of agreement /contract with NRC at April Board meeting
- Successful interactions with IUTOX
- Acquired a new LOGO (based on original submission by P. Solbeck)
- Development of a new STC Website (in progress)
- Updated STC Constitution
- Publication of Online Sources of Toxicology Information
  - W. Racz, D. Ecobichon, M. Baril [www.sciencedirect.com](http://www.sciencedirect.com)

In addition, the Board has agreed to:

- Develop approaches to increase membership
- Enhance awareness of STC
- Secure better funding for the Annual Symposium
- Become more active in Science Policy activities

- Continue to develop exciting programs for the Annual Symposium
- Continue planning of ICT XI (more about ICT XI later)

Since I have served two years as President, my term has come to an end. I thank all of you and of course the Board members for the opportunity of serving the society. It has been a very rewarding experience and I look forward to the next two years as Past President. We are fortunate to have Barbara Hales take the helm. She will serve the society well and I look forward to working with her.

There is always the need for "new blood". I encourage everyone, and particularly the new members, to volunteer for one of the committees or to indicate their willingness to serve on the Board. Participation is always welcomed.

Thank you,  
Sincerely,  
Sheldon Roth

### **REPORT FROM ICTXI ORGANIZING COMMITTEE – David Josephy**

STC will host the Eleventh International Congress of Toxicology (ICTXI) at the Palais des Congrès de Montréal, 15-19 July, 2007 (Sunday to Thursday). Running this meeting is the most ambitious task that STC has ever undertaken. The ICTXI Organizing Committee is already hard at work, and this report is intended to inform the STC membership of the scope of our ongoing activities.

The Organizing Committee met three times in 2003, in March 2004, and will meet again in June. Len Lillie is Chairing the Committee. Several sub-committees have also been established, including Scientific Program; Communications and Public Relations; Finance and Fund-raising; and Local Arrangements. The National Research Council of Canada acts as the secretariat for the Congress, providing an essential administrative and fiscal-management function.

The next ICT meeting (number 10) will take place very soon (July 2004) in Tampere, Finland, and the Organizing Committee's recent efforts have been focussed on planning for our participation at ICTX. We will send an official delegation of four, plus a staff person from Tourism Montréal, and informal representation by additional STC members. (We will also be sending delegates to relevant future meetings, such as SoT (USA), EuroTox, and AsiaTox.) An ICTXI booth will be open at ICTX, and we will be busy advertising the Montréal meeting, establishing international contacts, and gleaning as much wisdom as we can about the conduct of the meeting - things to do and things to avoid doing. (If you plan to attend ICTX, please let Len know, and he will probably find you a task!) A brochure/announcement has been drafted and will be distributed at ICTX.

The Organizing Committee has chosen a logo for ICTXI (see figure). I think that the logo presents a clean Canadian image, with good visual impact and distinctiveness. (If you don't agree, you must not possess the Committee's high level of aesthetic refinement.) The colours combine a "Canadian" red and a "Quebec" blue. The stylized letter "T" alludes to the widely-used "Toxic Substance" symbol. This logo will appear on all future ICTXI materials.

The Scientific Program Committee (chair, Gaston Chevalier; co-chair Robin Walker) is preparing a detailed plan for the meeting. We hope to attract at least 2,500 participants from as many as 60 countries, with a program including about 100 lectures and as many as 1,500 posters. Potential

commercial exhibitors (we hope to have about 100) are also being contacted. The meeting will be accommodated almost entirely on the fifth floor of the Palais, and we are trying to plan the schedule and room allocation in an efficient manner, so that excessively long walks can be avoided.

An important planning function is liaison and communication with other organizations, such as STC, IUTOX, the various national toxicology societies, and the helpful staff at NRC, the Palais, and Tourisme Montréal.

Planning for ICTXI will shift into a higher gear after the Tampere meeting. The website ([www.ict2007.org](http://www.ict2007.org)) will go on-line (don't click yet - wait until July). Fundraising efforts will be intensified and scientific program planning will move to a more detailed stage. We are also reviewing suggestions for "satellite" meetings.

If you would like further information or are interested in volunteering for one of the ICTXI sub-committees, please write to Len ([len.lillie@pfizer.com](mailto:len.lillie@pfizer.com)) or to me ([djosephy@uoguelph.ca](mailto:djosephy@uoguelph.ca)).



## International Congress of Toxicology Congrès international de toxicologie

July 15-20 juillet 2007 Montréal, Canada

Toxicology: Discovery Serving Society

La toxicologie : La découverte au service de la société

### THE VIEW FROM MY CANOE – Don Ecobichon

Another year gone and a new one here, along with all those resolutions (if you were foolish enough to make any) already broken! Despite a rather mild and wet autumn, winter arrived with a vengeance, colder temperatures than we have recorded since moving to the luxury of country living and, more recently, lots of snow. Our feeders have attracted a variety of bird species, including wild turkeys (groups ranging from 34 to 1), assorted squirrels and three deer (a nice two-point buck and two young does). The buck, "Spike" by name, likes birdseed and cleans off our platform feeder each day, in spite of the fact that I bought cracked corn for him and set up his own feeder. The little does like grass and, since I do not cut the grass after the first part of October, it is quite long, and they dig down through the snow for it. However, they too like corn and birdseed. We have to protect our bushes from foraging, but they have already developed a taste for periwinkle and have pruned these back. While it is pleasant to sit at our kitchen table and see all of this wildlife at arms-length, these deer may pose a major problem come spring. This year, we have a resident, adult, bald eagle, an impressive bird.

The saddest part of a new year is receiving the first newsletters and learning who has died. I lost two good friends/colleagues this past year. Kundan Khera, retired from Health Canada for a few years, died in April. I have known "Kun" since the early 1960s. He made major research contributions in the area of reproductive and developmental toxicology, being one of a number of authors who developed the Canada-U.S.A. guidelines for developmental toxicology in 1973. These procedures are still in use today. He had a great sense of humour, and it was always a pleasure to get together with him at meetings or at lunch when I would be in Ottawa at Tunney's Pasture. His death was not unexpected as he had serious health problems. It was a complete surprise to learn of the death of Perry Gehring in November. Perry was a leading light in the Society of Toxicology and was a dominant figure not only in the pioneering

development of toxicology at Dow Chemical Company but also donating his expertise to many advisory and governing organizations, including the American Board of Toxicology, the Academy of Toxicological Sciences, the National Academy of Sciences and the World Health Organization. It was always an experience to work with Perry. He was a good corporate citizen with a belief in the value of education and training, so much so that he established a scholarship program between the University of Minnesota (his alma mater) and several Chicago inner-city high school students. Two larger than life scientists just “left the room”. They will be sorely missed and my condolences go to their families.

An interesting little article in a recent issue of *The Economist* (Nov. 15<sup>th</sup>) describes a new treatment using leeches, not for their known anticoagulants, but for an anesthetic found in their saliva. It has been tested (University of Duisburg-Essen, Germany) to relieve the pain in arthritic joints. A publication appears in the *Annals of Internal Medicine*. The groups of patients with rheumatoid arthritis, received either twice-daily doses of diclofenac applied to the affected knee OR a one-shot treatment with leeches, allowing 4 to 6 leeches to attach themselves to the knee and to “feed” until they detached themselves after about an hour. The leech “therapy” beat diclofenac for pain relief, particularly in the first week. Longer term benefits included reduced stiffness and better joint function. It is thought that leech saliva may contain an anti-inflammatory agent, as well as the anesthetic and anticoagulant. Who wants leeches fastened to your knee? However, the severity of rheumatoid, arthritic pain may reduce any revulsion to such therapy.

In this column, I have complained about the cancellations of journals by university libraries, and their being replaced by electronic on-line access to “packages” of journals at exorbitant costs whether you want all the journals or not. Academics are fighting back at the University of California campuses, suggesting a boycott of all journals published by Cell Press, an imprint of the global giant Elsevier. Apparently, Elsevier asked the university for an additional \$90,000 annually to provide electronic access to six Cell Press titles, including *Cell*, *Molecular Cell*, *Immunity* and *Neuron*. The University of California (UC), already paying \$8 million for on-line access to other journals, has refused, claiming that the price is too high. The scientists leading the charge want all UC scientists to not send manuscripts to Cell Press journals, claiming that “we can think of better ways to spend our time than providing free services (presumably writing and reviewing manuscripts, editorial duties) to support a publisher that values profit above its academic mission...”. They are also asking that the public and private funding agencies get involved as well, since they pay the lucrative page charges.

In *The Economist* (Nov. 29<sup>th</sup>), there is an article claiming that methamphetamine (meth, crank, ice, tweek, chicken feed, to name a few pseudonyms) is making a big comeback in middle America, with a large number of “factories” being uncovered in 2002 – some 15,353 meth labs, up from 8,971 in 2000. Not environmentally friendly, for every 1 lb of “speed” produced, a manufacturer will leave behind 6 lb of toxic waste! An ancillary problem is the number of young people injured (52) and killed (5) in 2002 who were exposed to either the drug or the noxious fumes during manufacturing. The hotbed for this activity includes Iowa, Missouri, Oklahoma, Tennessee, Illinois, Indiana and Minnesota with these states as well as the federal government pouring money into the problem of “helping speed children”. Perhaps it would be wiser to increase police activities. Each spring, farmers, preparing their fields, find the remains of meth labs in creek beds and old, disused barns. Parks and national forests are also becoming contaminated sites.

An extensive cover story in *Business Week* (Jan 26<sup>th</sup>) deals with insomnia and other sleep disorders, exploring the “diseases” and the pharmaceutical companies’ responses with “sleep medications”, a whole battery of new agents that are either still in Phase 2 or 3 trials or awaiting U.S. FDA approval. What is the situation here in Canada? Would anyone in Health Canada care to comment? An interesting comment in the article – “We have to prove it’s healthy to take sleeping pills”!!

As a philatelist (stamp collector to the uninitiated), I found the Morning Smile (Globe and Mail Nov 19<sup>th</sup>) particularly fitting. – A woman goes to the post office to buy stamps for her Christmas cards. She says to the clerk –“May I have 50 Christmas stamps?” The clerk says “What denominations?” Her response – “God help us! Has it come to this? Give me 6 Catholic, 12 Presbyterian, 10 Lutheran and 22 Anglican.”

Ethanol as a fuel is in the news again. The U.S. government subsidy to the industry (75 plants producing 2.8 million gallons with another dozen more facilities under construction) is worth 50cents/gallon (\$1.4 million/yr). While touted to be the clean fuel of the future, there are discrepancies in the supporting data. David Pimentel (Cornell U) argues that each gallon of ethanol takes 29% more energy to make than it produces, while the USDA claims that corn-ethanol yields 34% more energy than it take to produce. However, Pimental says the USDA study omits about half the inputs in corn production, including the cost of water to grow the corn, not a problem in rain-rich Minnesota but a significant problem in Nebraska and other drier states where irrigation is necessary and natural-gas powered pumps are required (*The Economist*, Jan 17<sup>th</sup>).

The Alzheimer-like neurological disease found in the Chamorro people native to Guam was attributed to the peculiar toxicant found in the fruit of the cycad plant, the fruit being used during times of privation and food shortages to make a flour. Within two decades of WWII, the disease appeared and, shortly thereafter, the incidence began to decrease. Recent evidence suggests that the source of the toxin is not the cycad seeds but flying foxes (fruit bats) which are a delicacy to the Chamorro and which were hunted to extinction during the 1940s. It appears that these bats love cycad seeds, ingest the toxic agent which does not harm them but affects the human consumer. It appears that the introduction of rifles during wartime made hunting these bats much more efficient with consumption increasing dramatically. A scientist, Paul Alan Cox, has been analyzing museum specimens stored since WWII and has found high levels of neurotoxins in the dried flesh. An interesting case study of biomagnification (*Discover*, Dec/03).

## **BOOK REVIEW – Don Ecobichon**

“The New Killer Diseases. How the Alarming Evolution of Mutant Germs Threatens Us All”, E. Levy and M. Fischetti, Crown Publishers, New York (Random House) 2003, pp.312. \$60 CD.

This is a timely book dealing with invasive Group A streptococcus (flesh-eating disease), anthrax and bioterrorism, malaria, West Nile virus, BSE (mad cow disease), coliforms (*E. coli* 0157), bacterial resistance and antibiotic use, influenza, resistant tuber-culosis strains, hepatitis C and AIDS. In fact, this book was ready for publication just prior to the SARS outbreak and was held up so that an Introductory chapter could be written to cover this new invasion. The authors are a respected immunologist (Dr. Levy, Boston University) and a veteran science writer (M. Fischetti, contributing editor to *Scientific American*). The book discusses the rapid evolution and global migration of bacteria and viruses in well written chapters with many good examples of incidental cases, as well as discussing gene swapping that allow these organisms to evade and fight off the best and (and sometimes only) drugs available. The authors also discuss the ineffective pathogen alert system that has not been on top of such problems as “imported” organisms and what must be done. Remember how long it took to get on top of the SARS epidemic, not only here in Canada but in Southeast Asian countries, the WHO and the CDC in the U.S.? It is astonishing how rapidly such an organism as West Nile virus or SARS can disperse globally and throughout countries. We still do not completely understand the vectors involved for West Nile virus, but

horses, frogs and many species of migrating wild birds carry the virus in addition to globe-trotting humans.

The book has an excellent index for finding things again if you don't make marginal notes like me. There are additional references for each chapter in a bibliography at the back of the book. All-in-all, a good book for your shelf, well worth the cost.

### **HEALTH CANADA PERSPECTIVE – Bill Casley**

Bill Casley is a Research Scientist in the Centre for Biologics Research of The Biologics and Genetic Therapies Directorate of Health Canada's Health Products and Food Branch. He is also a member of the Society of Toxicology of Canada.

On January 1<sup>st</sup> of this year, new regulations governing the licensing of natural health products for sale in Canada came into effect. This development was driven both by the report of the House of Commons Standing Committee on Health on the need to regulate such products and also by the awareness at Health Canada of the increasing desire among Canadians to have access to alternative modes of therapy, including natural health products. Natural health products include plant or plant materials such as herbal products, isolates extracted from plant materials, vitamins, minerals, amino acids, essential fatty acids and homeopathic products that are used to diagnose, treat and/or prevent disease, restore or correct function or maintain or promote health.

It is the responsibility of the Natural Health Products Directorate (NHPD) to license these products for over the counter sale. The NHPD is part of the Health Products and Food Branch (HPFB) of Health Canada. The NHPD regulates the licensing of natural health products while the HPFB Inspectorate is responsible for post-market surveillance of these products. The mission of the NHPD is "To ensure that all Canadians have ready access to natural health products that are safe, effective and of high quality, while respecting freedom of choice and philosophical and cultural diversity".

The criteria for the evaluation of natural health products may differ significantly, depending on the product, from those required of conventional small molecule drugs or biotherapeutics with respect to the burden of proof required to demonstrate safety and efficacy. A key element in the evaluation of traditional herbal remedies, for example, is historical evidence of safety and efficacy in human use. In fact, according to the NHPD guidance on safety and efficacy of NHPs, when sufficient evidence from prior human use exists, no animal or *in vitro* toxicological data may be required in the submission for approval of a natural health product.

From a toxicological perspective, the evaluation of a natural health product may provide some interesting challenges. While a vitamin preparation may be amenable to physico-chemical methods of analysis to establish purity and concentration, a traditional herbal remedy may contain numerous plant parts with, in some cases, no established chemical entity as the purported active ingredient. Since these products are typically used in self-administered treatments, the possibility of interactions with conventional pharmaceuticals exists. This is certainly true in the not uncommon case where a physician may be prescribing a drug while unaware that the patient is self treating with a natural health product. An example of this phenomenon is the well established reduction in Cytochrome P450 CYP3A4 among individuals using St. John's wort, a popular natural remedy for depression.

While the evaluation of the safety of these products can draw from historical data on human use and, in some cases, defined and testable standards of purity and potency, there is still a need to monitor safety post-licensing. For this reason, the NHPD has established an Adverse Reaction Reporting system

for natural health products and the HPFB inspectorate maintains a surveillance system to track post market safety issues. The inspectorate was recently involved in the withdrawal from market of a natural health product purported to improve male potency. Analysis by the HPFB Inspectorate laboratories, with confirmatory analysis by the mass spectrometry and nuclear magnetic resonance facilities in the Centre for Biologics Research laboratories of the Biologics and Genetic Therapies Directorate, HPFB, showed that these preparations had been spiked with pharmaceutical sildenafil, at physiologically active doses. There certainly exists the possibility of a severe ADR or drug interaction involving such a preparation. Such cases emphasize the need for effective post market surveillance of natural health products.

These issues and others have driven the NHPD to expand the knowledge base around natural products and facilitate the development of new and existing Canadian expertise in this field, as well as fostering communications between the scientific and practitioner communities. Of particular interest to the research community was the request for proposals put forth by the NHPD in January, with the intention of providing a total of \$400K to Canadian researchers, from July 2004 to March 2005, as seed funding to develop research programs through grants, contracts and contributions. The goals of this funding were to build research capacity and enhance knowledge transfer and information retrieval among the various interested parties. The NHPD requested research proposals addressing the key themes of; biomedical and clinical science; product quality; health services and systems; societal, cultural and environmental influences on the health of individuals and populations; regulatory issues; information and knowledge transfer. Such a funding initiative will hopefully lead to the increasing application of scientific methods to the evaluation of safety and efficacy in this group of products.

The implementation of regulations governing licensure for sale in Canada, along with the establishment of an Adverse Reaction reporting scheme and the announcement of funding initiatives to support scientific assessment of these products are all indications that Health Canada is responding to the potential benefits and risks posed by the increasing use of natural health products by the Canadian populace.

### **PERSPECTIVE SELON SANTÉ Canada – Bill Casley**

Le Dr Casley est chercheur scientifique au Centre de recherche sur les produits biologiques de la Direction des produits biologiques et thérapies génétiques sous l'égide de la Direction générale des produits de santé et des aliments. Il est aussi membre de la Société de toxicologie du Canada.

Le nouveau *Règlement sur les produits de santé naturels*, un outil de réglementation nécessaire à l'attribution de permis pour la vente de produits de santé naturels (PSN) au Canada, fit son entrée en vigueur le 1<sup>er</sup> janvier dernier. L'élaboration de cet instrument fut motivée d'une part par les conclusions d'un rapport publié récemment par le Comité de Santé de la Chambre des Communes et, d'autre part, par le désir croissant manifesté par le public d'avoir accès aux thérapies alternatives, comme celles offertes par les PSN.

Les PSN sont formulés à partir de plantes ainsi que de matériaux dérivés de celles-ci. On retrouve, entre autres, les remèdes à base d'herbes, les extraits botaniques, des vitamines, des minéraux, des acides aminés, des acides gras essentiels ainsi que plusieurs produits homéopathiques utilisés pour le diagnostic, le traitement et/ou la prévention de maladies ou encore employés pour corriger ou stimuler certaines fonctions physiologiques ou promouvoir un état général de bonne santé.

La Direction des produits de santé naturels (DPSN; une sous-division de la Direction générale des produits de santé et des aliments - DGPSA) est responsable de la réglementation en vue de l'attribution de

permis pour la vente au comptoir des PSN. La DPSN est appuyée par l'Inspectorat de la DGPSA qui concentre plusieurs de ces activités à la surveillance des PSN suite à leur mise en marché. La DPSN a pour mission de 's'assurer que la population canadienne ait un accès rapide à des produits de santé naturels sécuritaires, efficaces et de grande qualité, tout en respectant la liberté de choix ainsi que la diversité philosophique et culturelle.

Les critères d'évaluation des PSN peuvent différer de façon significative, selon le produit, de ceux présentement requis pour les remèdes conventionnels (petites molécules) et agents biothérapeutiques, surtout en ce qui concerne les éléments de preuve nécessaires pour en démontrer l'efficacité et l'innocuité. Le constat d'utilisation historique sécuritaire et efficace au sein de la population, par exemple, constitue un des éléments principaux du processus d'évaluation des remèdes traditionnels à base d'herbes. En fait, selon les lignes directrices de la DPSN, la soumission d'une demande d'approbation pour la vente d'un PSN ne requiert aucune étude de toxicologie s'il existe suffisamment de preuves fondées sur l'utilisation préalable par le public.

Ceci dit cependant, l'évaluation d'un PSN pose plusieurs défis en matière de toxicologie. Un remède traditionnel à base d'herbes, par exemple, peut être constitué de plusieurs éléments végétaux dont aucun ne peut être identifier avec certitude comme étant l'agent actif. Cette situation est très différente de celle rencontrée au cours de l'évaluation d'une préparation de vitamine. Cette dernière qui se prête aisément aux diverses méthodes d'analyse physico-chimiques pour en assurer la pureté et la concentration. De plus, les PSN sont très souvent adoptés comme traitements auto-administrés. Il est donc possible que de tels produits puissent interagir avec d'autres agents pharmaceutiques conventionnels. Ce scénario est d'autant plus plausible dans le cas d'un médecin qui pourrait prescrire un médicament sans savoir que le/la patient(te) utilise déjà ou prévoit utilisé un PSN en parallèle. À ce chapitre la réduction des niveaux de cytochrome P450 CYP3A4 chez les usagers de l'herbe de Saint Jean, un PSN populaire contre la dépression, est bien documentée.

Même si l'évaluation de l'innocuité d'un PSN peut s'inspirer de données historique auprès des usagers, et même si cet exercice peut s'appuyer, dans certains cas, sur des standards bien caractérisés qui facilitent l'analyse de sa pureté et de son activité, il n'en demeure pas moins nécessaire d'assurer l'innocuité du produit licencié une fois ce dernier mis sur le marché. C'est pourquoi la DPSN a mis sur pied un système de documentation (base de données) de réactions indésirables reliées aux PSN et que l'Inspectorat de la DGPSA maintient un programme de surveillance pour les produits mis en vente sur le marché. L'Inspectorat a récemment participé au retrait d'un PSN dont le fournisseur vantait les mérites en matière de virilité chez le mâle. Des analyses dans les laboratoires de l'Inspectorat, appuyées par des études de spectroscopie de masse et de résonance magnétique nucléaire par les chercheurs du Centre de recherche sur les produits biologiques (DGPSA, Direction de produits biologiques et thérapies génétiques) ont démontré clairement que ces préparations avaient été additionnées de doses physiologiques de sèdanafil, un produit pharmaceutique. Ce cas illustre bien le risque de réactions indésirables encouru par les usagers d'un tel produit et renforce d'avantage le besoin de maintenir un programme de surveillance accru pour les PSN.

De telles considérations, parmi plusieurs autres, ont incité la DGPSA à accroître ses connaissances en ce qui concerne les PSN, à favoriser le développement d'expertise canadienne dans ce domaine et à encourager une plus grande communication au sein des communautés scientifiques et médicales. Par conséquent, la DPSN a récemment annoncé qu'elle mettait à la disposition de la communauté scientifique canadienne \$400K (sous forme d'octrois, de contrats et de contributions) dans le but d'augmenter la capacité de recherche et d'échange de connaissances dans le domaine. La DPSN invite donc les intéressés à soumettre, en vue d'un premier exercice financier réparti entre juillet 2004 et mars 2005, leurs propositions de projets d'études selon les thèmes suivants - sciences cliniques et biomédicales; qualité des

produits; réseaux et services de santé; influences sociales, culturelles et environnementales sur la santé des individus et des populations; problèmes concernant la réglementation; information et transfert de connaissances. Par le biais de cette initiative, la DPSN espère favoriser l'application de la méthode scientifique en vue de l'évaluation de l'efficacité et de l'innocuité des PSN.

L'élaboration du nouveau règlement concernant les PSN, la mise en disponibilité d'une base de donnée sur les réactions indésirables associées aux PSN et l'annonce d'un programme de subvention thématique visant à favoriser l'évaluation scientifique de ce type de produit de santé témoignent de l'importance qu'accorde Santé Canada en matière de risques et bénéfices que pose l'utilisation de PSN par la population canadienne.

## **THE NATIONAL FRAMEWORK FOR PETROLEUM REFINERY EMISSION REDUCTION (NFPRER) – Submitted by Carol Drury**

In 1992 the National Pollutant Release Inventory (NPRI) was established by Environment Canada to begin tracking where industrial pollutants were coming from and what kinds were most prevalent. Since then, most industries have been required to provide a yearly report on what they emit to the land, water or air above certain threshold quantities. The list of chemicals which require accounting and reporting has grown each year and currently numbers 250 to 300 chemicals. The information is used by Environment Canada in its toxics management programs, and is made publicly available to Canadians each year at <http://www.ec.gc.ca/pdb/npri/>.

The NPRI data provides a starting point for the development of methods to reduce the major contributors to industrial pollution and to identify and manage health effects potentially associated with air pollution. As a part of that process, the Canadian Council of Ministers of the Environment (CCME) is developing a new approach to reduce emissions of air pollutants from the petroleum refining sector in Canada. This approach is called the NFPRER and is a unique example of an industry-proposed initiative. It was initiated in 2001 by the Canadian Petroleum Products Institute and all levels of government, industry and non-governmental environmental and health organizations are working together on it. The document referenced at the end of this article was developed by a multi-stakeholder committee and was released for discussion on February 3, 2004. Among the stated goals of the NFPRER initiative are:

- 1 . the protection of human health and the environment
2. achievement of real, quantifiable, verifiable emission reductions that will contribute to improved air quality on a local and regional basis
3. converging the emission performance of Canadian refineries with comparable U.S. refineries, while preserving the competitiveness of the Canadian refining sector and maintaining any superior performance which already exists in Canada.

There are currently 19 refineries operating in 8 provinces. The national framework will allow for the individual jurisdictions (the provinces, the Greater Vancouver Regional District and the City of Montreal) which regulate these sites to develop their own rules with their own reduction requirements.

Examples of the pollutants which will be the probable focus of this initiative are: SO<sub>2</sub>, NO<sub>x</sub>, VOCs. Total particulate matter: PM<sub>10</sub>, PM<sub>2.5</sub>, CO, Benzene

It is intended that annual emission "caps" will be set for each facility for these pollutants, allowing the refinery more flexibility in determining the most cost-effective way to control the total emissions.

The first step in the program was benchmarking to provide a basis against which progress can be measured. Data from both Canadian and U.S. refineries is being used to look for correlations between some parameter (such as volume of crude oil processed) and mass of air emissions. Charts have now been prepared for each pollutant for each refinery but it is expected that these will continue to evolve as more data becomes available from the U.S. refineries.

At the same time another subgroup (the Health Prioritization Subgroup, HPSG) which includes a number of STC members, was conducting a review of information available in the literature on the health implications of exposure to refinery emissions. This subgroup was also charged with an assessment of human health risk-based prioritization schemes for setting of priorities in emissions reductions. They commissioned consultants, largely also made up of STC members, to address these concerns. Conclusions to date are:

1. SO<sub>2</sub> is the highest priority pollutant
2. reductions in NO<sub>x</sub> are a clear priority
3. VOCs are a clear priority
4. other concerns exist but are not as clearly defined

Starting from this data, the NFPRER is intended to provide methodology, a strategy for monitoring and reporting and a 10-year forward plan. The CCME will provide these tools to the individual jurisdictions, who will develop and administer their own regulations.

This is still very much a plan in the works. As it proceeds, it will move Canadian refineries to lower emissions overall, in line with their American counterparts, and will address the highest priority issues first.

The HPSG is currently developing a tool to aid future prioritization of pollutants. STC members may be very interested in this tool: keep checking the website!

For more information, go to the CCME website,  
[http://www.ccme.ca/initiatives/climate.html?category\\_id=69](http://www.ccme.ca/initiatives/climate.html?category_id=69)

## SOCIÉTÉ DE TOXICOLOGIE DU CANADA/SOCIETY OF TOXICOLOGY OF CANADA (STC)

### STC AWARD OF DISTINCTION

*But:*

*Purpose:*

The purpose of the STC Award of Distinction is to honour those individuals who have made outstanding and sustained contributions to the science of toxicology in Canada and/or the Society of Toxicology of Canada.

Le but de Prix du mérite est d'honorer les personnes qui ont apporté une contribution remarquable et soutenue au domaine de la toxicologie au Canada ou à la bonne marche de la Société de toxicologie du Canada.

*Selection Committee:*

### STC PRIX DU MÉRITE

Recipients shall be chosen by a committee of four members drawn from the

Society: the Past President who shall act as chairperson, one of the Councillors, and two members appointed by the Board from the general membership and who are not members of the Board.

#### *Nominations:*

Nominations must be made by two regular members of STC, in good standing, but no member may nominate more than one candidate during any one year. Nominations for the Award shall be made to the Chairperson of the Selection Committee before July 1 of the year of the award. Nominations must be accompanied by:

- 1 A summary, not to exceed two pages, describing the nominee's contribution to the science of toxicology and/or to the STC;
- 2 Copies of no more than five manuscripts and other documents considered by the sponsor to be pertinent to the award.
- 3 The nominee's curriculum vitae and a brief biographical sketch suitable for press release.

Nominees who are not granted the award in the year of nomination will be automatically included among the nominees in the two subsequent years unless the sponsors express otherwise. Sponsors will be invited to update previously submitted information.

#### *Award and Presentations:*

The award will be in the form of a plaque or other suitable memento. Presentation of the award will be made at the President's Reception during the Annual Meeting.

#### *Comité de sélection:*

Les récipiendaires seront choisis par un comité de sélection formé de quatre membres de

la Société, le président sortant de la Société qui présidera la comité, un des conseillers, ainsi que deux membres réguliers choisis par le bureau de direction, mais qui ne font pas partie.

#### *Candidatures:*

Les candidatures doivent être soumises par deux membres réguliers de la Société. Un membre ne peut soumettre plus d'une candidature chaque année. Les candidatures doivent être déposées auprès du président du comité de sélection avant le 1<sup>er</sup> Juillet de l'année de la remise du Prix. Les documents suivants doivent être soumis à l'appui des candidatures:

- 1 un résumé d'au plus deux pages décrivant la contribution du candidat ou de la candidate au domaine de la toxicologie ou au fonctionnement de la STC;
- 2 des copies d'au plus cinq manuscrits ou documents pertinents produit par le candidat ou la candidate.
- 3 un curriculum vitae du candidat ou de la candidate, ainsi qu'une notice biographique à l'intention du monde de la presse.

À moins que les parrains des candidats ou des candidates ne souhaitent qu'il ne soit autrement, les candidatures non retenues l'année de leur dépôt seront réactivées automatiquement lors des deux années suivantes. Les parrains verront alors à mettre à jour les dossiers soumis.

#### *Le Prix et sa remise:*

Le Prix consistera en une plaque ou en toute autre marque tangible de reconnaissance. La remise du Prix se fera lors de la réception du Président, à l'occasion du Colloque annuel de la Société.

#### *Criteria:*

The following criteria will guide the Selection Committee:

- 1 The recipient should have demonstrated outstanding and sustained contributions to the science of toxicology in Canada and/or the recipient should have provided outstanding and sustained service to the Society of Toxicology of Canada.
- 2 The Selection Committee will exercise discretion regarding the relative contribution of the recipient to the science of toxicology in Canada and service to the Society of Toxicology of Canada.
- 3 The decision of the Selection Committee shall be final. Only one award may be made annually, and there is no obligation or duty to make the award when, in the opinion of the Selection Committee, there is no qualified candidate.

Information about STC's activities, awards, and/or membership application forms may be obtained by contacting:

Secretary STC  
C.P./ P.O. Box 517  
Beaconsfield, Quebec

*Critères:*

H9W 5V1

Le comité de sélection se basera sur les critères suivants:

- 1 le ou la récipiendaire devra avoir apporté une contribution remarquable et soutenue au domaine de la toxicologie au Canada ; à ceci pourrait se substituer une contribution sous la forme d'états de service remarquable et soutenues au sein de la Société de toxicologie du Canada.
- 2 c'est au comité de sélection qu'il incombera de porter un jugement éclairé sur le mérite de la candidature.
- 3 la décision du comité de sélection sera finale et un seul prix sera remis chaque année. Si, de l'avis du comité de sélection aucune candidature n'est méritante, le Prix ne sera pas remis.

On peut obtenir des informations sur les activités et les prix de la STC ainsi que sur la façon de joindre les rangs de la Société, en écrivant à l'adresse suivante:

Secrétaire de la STC  
C.P. / P. O. Box 517  
Beaconsfield, Québec  
H9W 5V1

## SOCIÉTÉ DE TOXICOLOGIE DU CANADA/SOCIETY OF TOXICOLOGY OF CANADA (STC)

### STC VEYLIEN HENDERSON AWARD

This STC award honours an individual who has made a significant contribution to the discipline of toxicology in Canada. The conditions of the award are as follows:

- 1 the candidate must be a Canadian citizen;
- 2 the candidate must be under 45 years of age as of July 1 of the year in which the award is given;

### STC PRIX VEYLIEN HENDERSON

Par ce Prix, la STC cherche à reconnaître l'importante contribution à la toxicologie d'une chercheuse œuvrant au Canada. Les conditions d'éligibilité sont les suivantes:

- 1 être citoyen(ne) canadien(ne)
- 2 être âgé(e) de moins de 45 ans en date du 1<sup>er</sup> Juillet de l'année de l'obtention du Prix;

3 the candidate must be nominated by one ordinary member of the society (in good standing) who will supply the Secretary with:

- a) a supporting letter of recommendation;
- b) a two page resume describing the significant contribution made;
- c) a complete curriculum vitae and publication list; and
- d) reprints of not more than 5 papers best reflecting the candidate's research.

All of the above should be sent to the Secretary, at the STC address by July 1 of the year of application for this award.

Secretary STC  
C.P. / P.O. Box 517  
Beaconsfield, Quebec  
H9W 5V1

3 être mis(e) en nomination par un membre régulier en règle de la Société. Ce membre devra faire parvenir au secrétaire;

- a) une lettre d'appui à sa recommandation;
- b) un résumé de deux pages soulignant la contribution remarquable du candidat ou de la candidate;
- c) un curriculum vitae complet et une liste des publications du candidat ou de la candidate;
- d) des tirés à part d'au plus cinq (5) publications reflétant bien les activités de recherche du candidat ou de la candidate.

Le tout doit être transmis au secrétaire, à l'adresse habituelle de la société, avant le 1<sup>er</sup> Juillet de l'année de la remise du Prix

Secrétaire de la STC  
C.P. / P.O. Box 517  
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### Report on the STC annual symposium - 2003 ----- Louise Winn and Bill Racz

The 2003 annual symposium “Evolving Models In Toxicology” was very much a success. We as participants were treated to two days of interesting and in some cases controversial presentations. The four sessions covered the topics of emerging models, emerging technologies, alternatives to animal testing and the changing regulatory environment regarding animals in research. The highlights of the meeting are described below.

The first session on “Emerging Models” began with Dr. E. Calabrese giving us a brief history of his studies on hormesis. For those readers who are not familiar with the concept of hormesis, it is defined by Dr. Calabrese as follows: “Hormesis is the U shaped dose response model, characterized by a low dose stimulation and a high dose inhibition. The dose response may take the shape of inverted U or J depending on the endpoint measured”. Dr. Calabrese cited several examples, most of which can be found in his article “The Maturing of Hormesis as a Credible Dose-Response Model” published in *Nonlinearity In Biology and Medicine*, 1: 319-343, 2003.

Next Dr. K Almeida described her work measuring homologous recombination of DNA and its role in cancer. She described a mouse model that provides a tool for revealing genetic and environmental factors that modulate mitotic homologous recombination. The FYDR (fluorescent yellow direct repeat) mice carry two non-functional, mutant copies of an expression cassette for the enhanced yellow fluorescent protein (EYFP). Homologous recombination can restore the EYFP sequence and Dr. Almeida described how this model can be used to detect sister chromatid exchange, gene conversion and homologous repair.

Then Dr. S. Kennedy discussed the application of “open methods” of gene expression technologies to wildlife susceptibility to the toxic effects of environmental agents. This approach is based on the assumption that most, if not all, toxicants cause up or down regulation of multiple genes, some of the changes observed in gene expression are mechanistically associated with toxic effects and many of the changes in the expression of mRNAs and protein are not predictable. The methods used include RNA arbitrary primed polymerase chain reaction, fluorescence differential display PCR and long-serial analysis of gene expression.

To end the first session, Dr. A. Hontela described the importance of screening environmental endocrine toxicants. While most studies have focussed on the estrogenic effects of environmental pollutants, her work has focussed on the effects of environmental pollutants on adrenal function. Her laboratory has found that metals and agricultural pesticides including cadmium, endosulfan, mancozeb,

and diazanon are potent adrenotoxicants. Of particular interest was the finding that there is important species differences in the adrenotoxicity of these xenobiotics.

To start the second session on “Emerging Technologies” Dr. F. Gonzalez explained the utility of humanized mouse lines expressing *CYP2D6*, *CYP2E1*, and *CYP3A* genes. These genes accurately expressed the corresponding enzyme and exhibited catalytic activity at levels comparable or higher than those expressed in humans. These P450 humanized mouse lines overcome some of the species differences in P450 expression and offer an appropriate system for the study of xenobiotic biotransformation and toxicokinetics. Additionally, Dr. Gonzalez also described a PPAR $\alpha$  humanized mouse model, which is responsive to peroxisome proliferators and which should provide insights into species differences in response to peroxisome proliferators.

Following this, Dr. C. Yauk reported on the success of Health Canada, Healthy Environments and Consumer Safety Branch in establishing a Mutagenesis Microarray facility. This facility is currently using both the high-density commercially available arrays and their own custom oligonucleotide chip (HC ToxChip) that includes approximately 1100 genes known to respond to toxicants, to evaluate the predictive validation of gene expression in toxicology.

To end the first day Dr. D. Chelsky introduced the audience to the use of proteomics to detect the effects of drugs and toxicants and cellular proteins. Identifying the protein content of plasma and the changes that occur in the proteins in response to disease and toxicants can serve as a window into the toxic effects of xenobiotics.

The session examining several aspects of “Alternatives to Animal Testing” began the second day of the symposium. In the first presentation Dr. D. Sauder reviewed the dysregulation of cytokine cascades and T-cell activation after xenobiotic exposure and the usefulness of microarray technology in furthering our understanding of xenobiotic induced cutaneous reactions.

In the second presentation Dr. M. Jurima-Romet described the application of cell-based bioassays in drug development. Recent advances have improved the sensitivity and reliability of bioassays. Successful bioassay development is contingent on the careful selection of the appropriate cell line, coupled to studies of functionally relevant and easily measurable endpoints that are conducted according to GLP and GMP.

Next Dr. M. Griffith described a unique innervated tissue engineered human corneal model. These cells demonstrate similar innervation patterns to natural corneas and the in growing nerves can be excitable and propagate action potentials. Furthermore, neurotransmitter release, differential wound healing and nerve-epithelial cell interaction is observed in this model. These properties make these model a more complete alternative to animal testing for ocular irritancy testing.

To end the third session Dr. T. Zacharewski explained that to fully assess the potential adverse effects of xenobiotics, a more comprehensive understanding of the molecular, cellular and physiological effects is required within the context of the whole organism, its genome, proteome and metabolome. The omic technologies generate vast amounts of data that must complement the existing toxicological investigations and this vast amount of data requires the use of computational approaches, or in silico toxicology. Dr. Zacharewski described a supportive toxicogenomic database and quality control measures that can be taken to improve the outcome of omic technologies.

The final session of the symposium was titled “The Changing Regulatory Environment for Animal Research”. This session began with Dr. C. Gauthier describing the guidelines and policies of the Canadian

Council on Animal Care and the underlying approach of Reduction, Replacement and Refinement in animal use.

Following this Dr. A. Rowan spoke on the Humane Society's perspective on animal research in the US. He gave an un-biased history of the development of regulatory oversight and discussed some weaknesses and some suggestions on how to improve the regulation of animals used in research.

To end the symposium Dr. B. Borwein discussed the economic impact of the animal rights movement. Dr. Borwein used the case example of the Stop Huntingdon Animal Cruelty campaign against Huntingdon Life Sciences to illustrate the impact of Animal Rights organizations.

Finally the symposium was greatly enhanced by trainees who participated in the very successful poster session.

## **WINNERS OF THE CANTOX GRADUATE STUDENT POSTER AWARDS 2003**

**FOLIC ACID PROTECTION AGAINST VALPROIC ACID INDUCED NEURAL TUBE DEFECTS IN CD-1 MICE.** Jennifer E. Dawson<sup>1</sup> and Louise M. Winn<sup>1,2</sup>. Queen's University, <sup>1</sup>Dept. Pharmacology and Toxicology and <sup>2</sup>School of Environmental Studies. Kingston, Ontario, Canada K7L 3N6.

Neural tube defects (NTDs) are a common type of human congenital malformation, with an incidence frequency of 1-2 per 1000 live births. The use of the antiepileptic drug valproic acid, (VPA), during pregnancy has been associated with a 5-20 fold increase in the rate of human NTDs. *In utero* exposure to VPA in rodents has been shown to induce NTDs in a dose and strain dependent manner. The etiology of VPA induced NTDs remains unknown, however alterations in tumor suppressor genes and other embryo protective genes are implicated as playing a role. Neural tube closure is a complex morphogenic developmental event, dependent on a fine balance between apoptosis, cell cycle arrest, and differentiation. Any alteration in this balance could lead to a detrimental developmental outcome such as failure of the neural tube to close. The well-known tumor suppressor gene *p53* is thought to play an important role in development. The exact nature of its role has not been elucidated; however congenital malformations have been associated with modulation of *p53* expression. We hypothesize that VPA exerts its teratogenic effect on the neural tube by altering the normal level of expression, via post-translational modifications, of *p53* and other tumor suppressor genes regulating cell cycle arrest and apoptosis.

There is substantial evidence in the literature that VPA can alter the expression of genes, and studies have shown that VPA decreases blood folate levels in humans and rodents, suggesting that dietary folic acid supplementation may be beneficial in alleviating teratogenicity. Folic acid (FA) is a critical vitamin in mammals, and its implications in mammalian development have been an important field of study the past two decades. In 1991, the Medical Research Council established that therapeutic supplementation of folate provides a 75% decrease in the risk of pregnant women giving birth to children with NTDs. The mechanism through which FA prevents NTDs is presently unknown; however FA is known to play an essential role in the maintenance of genomic DNA integrity, specifically as a facilitator in the transfer of one-carbon units from donor molecules to pathways involved in the methylation of DNA. FA is also important in DNA synthesis and repair. Changes in the distribution of this vitamin can result in alterations in the expression of genes, such as *p53*. Folic acid supplementation during pregnancy

has been shown to protect human and some rodent embryos from teratogenic insult, however FAs ability to protect embryos from VPA induced NTDs is controversial. Human epidemiological studies provide evidence leaning toward a protective effect, in the mouse model this protection appears to be strain dependent. As recently highlighted in the January 8<sup>th</sup> 2004 issue of the New England Journal of Medicine, a greater understanding of the molecular mechanisms involved with FA supplementation is required. Elucidations into the doses required for protection is suggested to help guide these controversial FA public health policies (Wald, N 2004).

The purpose of the current study was to investigate the protective effects of FA against VPA induced NTDs in the CD-1 mouse strain. Pregnant CD-1 mice (vaginal plug = day 1) were treated with 4 mg/kg of FA via subcutaneous injection 3x's daily on gestational days (GDs) 5-10 and a previously demonstrated teratogenic dose of VPA, (400mg/kg, i.p.) on GD 9, just prior to neural tube closure in this strain. Our results demonstrate that VPA treatment alone caused a 24% incidence of NTDs in CD-1 mice, which was completely blocked by the prolonged FA treatment ( $p < 0.05$ ). To investigate the molecular mechanism mediating FA protection against VPA teratogenesis, CD-1 embryos exposed to VPA on GD 9 were analyzed for protein expression of p53 and downstream transcriptional targets, using Western Blot analysis. Embryo's exposed to VPA showed a 9-fold increase in p53 protein levels compared to litter controls ( $p = 0.02$ ). Our results also demonstrate that exposure to VPA during the critical period of neural tube closure in CD-1 mice also leads to increased expression of the cell cycle arrest modulator pRb ( $p = 0.02$ ). The ratio of apoptotic proteins Bax and Bcl-2 significantly decreased in VPA treated embryos ( $p = 0.01$ ). We are currently investigating if protection from VPA-induced NTDs is mediated by alterations in expression of these genes, and also examining the protection elicited by other types of maternal vitamin supplementation, such as pantothenic acid.

Support: JP Bickell Foundation

## **INVESTIGATING THE MECHANISM OF FELBAMATE-INDUCED IDIOSYNCRATIC REACTIONS – M. Popovic<sup>1</sup>, W. Santos<sup>3\*</sup>, S. Nierkens<sup>2\*</sup>, R. Pieters<sup>2\*</sup>, J. Uetrecht<sup>1</sup>.**

<sup>1</sup>Pharmaceutical Sciences, University of Toronto, Toronto, ON, Canada; <sup>2</sup>IRAS-IT, Utrecht, Netherlands, <sup>3</sup>Department of Chemistry, University of Virginia, Charlottesville, Virginia.

Felbamate is an antiepileptic drug used for monotherapy and adjunctive therapy in the treatment of partial and generalized seizures, including the Lennox-Gastaut syndrome in children. Shortly after its release on the market, more than 50 cases of aplastic anemia and liver toxicity were associated with felbamate treatment, putting felbamate in the category of drugs that can induce idiosyncratic reactions. Although little is known with certainty about the mechanisms of idiosyncratic drug reactions (IDRs) their characteristics suggest that they are immune-mediated. Previous research has accumulated data on the importance of chemically reactive metabolites of drugs, rather than parent drugs themselves in the development of IDRs. Consequently, we were interested in elucidating the role of reactive felbamate metabolite, in triggering idiosyncratic immune response. It has been proposed that the reactive metabolite responsible for felbamate-induced IDRs is the  $\alpha,\beta$ -unsaturated aldehyde, 2-phenylpropenal, however this metabolite is more extensively formed in humans than in rodents and this may account for the lack of good rodent models of felbamate-induced idiosyncratic reactions. Given our present state of knowledge, we are aware of the two properties of reactive metabolites that may contribute to them initiating IDRs, first being their ability to covalently modify host proteins, and second their immunogenicity.

The objective of this study was to examine both of these properties of 2-phenylpropenal.

Our initial goal was to develop an animal model of felbamate-induced hepatotoxicity and aplastic anaemia, and to observe covalent binding of 2-phenylpropenal in liver or bone marrow tissues of the treated animals. Previous to analyzing the tissues for the presence of covalently bound 2-phenylpropenal, we tested the quality of the polyclonal 2-phenylpropenal antiserum, using standard sandwich and a competitive inhibition ELISA. Both approaches confirmed our antibody to be highly specific for 2-phenylpropenal, and not to share cross-reactivity even with a structurally similar 2-phenylpropanoic acid. Nevertheless, we were unable to detect covalent binding of 2-phenylpropenal *in vivo* in various strains of rats and mice treated with felbamate.

Furthermore, we performed *in vitro* studies, in which we preincubated MCF with rat liver and bone marrow tissues to check for the 2-phenylpropenal formation. Unfortunately, obtained results were not positive. Nevertheless, when we directly preincubated MCF with an equine alcohol dehydrogenase in the presence of NAD<sup>+</sup>, our immunoblotting analysis showed the presence of 2-phenylpropenal binding to alcohol dehydrogenase under non-reducing conditions. It is still not known whether MCF is oxidized by P450 or alcohol dehydrogenase action to CBMA, but we suspect the more likely candidate to be alcohol dehydrogenase.

As idiosyncratic reactions are believed to be immune-mediated, we were interested in elucidating whether 2-phenylpropenal is an immunogen. We performed the reporter antigen popliteal lymph node assay (RA-PLNA) using TNP-Ficoll as a reporter antigen, and we investigated the immunogenicity of felbamate and its metabolites MCF and CBMA in female Balb/c mice. Felbamate and MCF treatment did not induced immune response in mice PLNs, because both of these two chemicals need to be enzymatically converted to CBMA before they could trigger an immune response in the mice PLN. However, CBMA treatment appeared immunogenic, causing footpad inflammation, hardening, crusting and an increase in thickness. CBMA is a highly unstable molecule at physiological pH with a half-life of less than 30 s, which spontaneously converts to 2-phenylpropenal, losing carbon dioxide and ammonia. The reason we used CBMA instead of 2-phenylpropenal for our experiment was that former is less sensitive to light and oxidation, and does not easily polymerize, unlike 2-phenylpropenal. Analysis showed that the total PLN cell count in CBMA-treated mice was eight times increased in comparison to the remaining treatment groups. Immunohistochemical analysis of the CBMA-exposed PLNs revealed germinal center formation, indicating B cell proliferation, plasma and memory B cell formation, later confirmed by flow cytometry. Popliteal lymph nodes of CBMA treated mice, showed an increase in IgG1 and IgM specific responses to TNP-Ficoll. As there are no TNP-Ficoll specific T cells present in the PLN, antibody switch from IgM to IgG1 isotype could only have taken place due to the 2-phenylpropenal presence, which induced T helper cell formation. Upregulation of IL-4 production and to a much lesser extent IFN- $\gamma$  cytokine production in PLNs also alludes as to the specific role of Th2 cells in helping B cells mount an immune response against 2-phenylpropenal. Observed increase in the IL-4 production is higher than previously reported for D-penicillamine, and IFN- $\gamma$  levels even though significantly increased in comparison to the control, still did not appear high enough to suggest a Th1 mediated immune response in the presence of 2-phenylpropenal. In the case of streptozotocin, IFN- $\gamma$  levels as much as forty times higher than those observed in the presence of 2-phenylpropenal, were previously observed in Balb/C mice. Flow cytometry analysis of popliteal lymph node cells confirmed the previous findings by ELISA, ELISPOT and immunohistochemistry. The total number of B cells increased from 26% in controls to 43% in the CBMA-treated mice, with 11% of the B cells expressing activation marker ICAM-1 (CD54) on their surface. Our findings confirmed the previous hypothesis, indicating that 2-phenylpropenal is a very potent immunogen, which once formed could possibly be involved in felbamate-induced liver toxicity and aplastic anemia.

## **STC TRAVEL AWARDS**

The following students were the recipients of STC Travel Awards:

Jennifer Billinsky (University of Saskatchewan)

Marija Popovic (University of Toronto)

Leanne Bedard (Queen's University)

Kirsten Bielefeld (University of Toronto)

Jacintha Shenton (University of Toronto)

Natasha Thadani (Queen's University)

Jennifer Dawson (Queen's University)

## **IN MEMORIAM: MICHAEL GEOFFREY PRIOR**

**March 24, 1934 to February 24, 2004**

**A Colleague and a Friend**

**- Leonard E. Lillie**

**Michael was born in London, England, educated at Whitgift School in Croydon and graduated in veterinary medicine from the University of Bristol. After working as a veterinarian in Gloucester, England, Michael and his wife Muriel immigrated to Canada in 1966 to pursue a career in research. Michael earned an M. Sc. in Immunology (1968) and a Ph. D. in Toxicology (1978) from the University of Saskatchewan.**

I first met Michael in about 1975 when he was serving as Head of Agriculture Canada's Animal Pathology Laboratory on the University of Saskatchewan campus and I was working at the Manitoba Veterinary Services Branch Laboratory in Winnipeg. For reasons that I no longer remember I had traveled to Saskatoon for a meeting with Michael and a few other laboratory diagnosticians from western Canada. What I do remember is that Michael graciously invited me home to have dinner with him and his family.

Our paths crossed again in 1979 when, after I had relocated to the small town of Vegreville, Alberta (about 100 Km. east of Edmonton) to participate in establishing a major new facility for research and services in environmental sciences, Michael expressed interest in a position as Head of the Inhalation Toxicology Section. One of the ever-present challenges in Alberta is the issue of the effects (real and perceived) of sour gas emissions associated with the extraction of petroleum and natural gas. The Alberta Environmental Centre had a mandate to investigate the effects of sour gas both on the human population and on one of the other major industries in Alberta, the production of beef cattle. The predominant component of sour gas is hydrogen sulphide. In addition to being highly toxic in high concentrations, and with a toxic mechanism not unlike that of cyanide (albeit potentially reversible), sour gas was also widely perceived to have effects at very low concentrations over long periods of time, although there was little hard data to support this perception. In Alberta, research into the effects of sour gas also came with a full panoply of acute and chronic political issues.

Toxicologists know that inhalation toxicology is inherently one of the most technically difficult (not to mention expensive) areas in which to work, and working with sour gas is also potentially dangerous. Michael cheerfully accepted this challenge that began with establishing a new research group from scratch and designing a purpose built facility in which controlled studies could be conducted safely. Over the next thirteen years (1980 –1993) Michael and his co-workers succeeded in completing and

publishing an important series of studies on the biochemistry and pathology of hydrogen sulphide toxicity as well as contributing to the technology of inhalation toxicology. Along the way Michael and I with the aid of our colleagues and in cooperation with the University of Saskatchewan Faculty of graduate Studies managed to mount a week long intensive and very much hands on short course in Inhalation Toxicology. Although this was a one-time event all reports indicated that it was a much appreciated success.

Of course Michael and I did not interact only at work. We shared not infrequent family dinners and the Prior children (Robert, Sarah and Jonathon) who were a little older than ours were frequent hosts and mentors for our oldest son Jeff in intensive sessions of Dungeons and Dragons. And I specifically remember the year Jonathon had set his heart on a somewhat traumatized 1972 Plymouth Satellite that I was preparing to dispose of. After a quiet word with Michael to ensure that Jonathon's parents were on board, this resulted in a classic win-win deal. I got rid of a vehicle I no longer wanted and Jonathon got his car, battle scars included, for a very modest price.

One year, our family took a camping trip up the Sunshine Coast of British Columbia. This involved traversing a series of ferry rides and passing through a series of colourful places; Horseshoe Bay, Howe Sound, Gibson's (of Beachcomber fame - and yes we did see an episode being filmed), Sechelt, Porpoise Bay, the reversing falls of Skookumchuk Narrows, Earl's Cove, Jervis Inlet and Powell River. We returned home and spoke glowingly of the Sunshine Coast to many people including the Priors. We said that this was the place that Jean and I wanted to retire to some day.

Well Jean and I never did retire to the Sunshine Coast but Mike and Muriel did. The next year they went out to Sechelt and bought a house high up overlooking Georgia Strait with a clear view of boats going up and down the Inside Passage and Vancouver Island in the distance. Michael left Vegreville in 1993 and served as a Consultant to Alberta Health in Edmonton until 1996. In 1996 Mike and Muriel retired to their house with the majestic westward view. Muriel continued her work as a fiber artist, teaching weaving and creating beautiful works of art on the loom. Michael as he always did became deeply and enthusiastically involved in the Anglican Church and in his community and offered his services as a consulting toxicologist.

Michael and I became separated by time and by geography beginning when I relocated to southern Ontario in 1990. However in 1996 when Don Ecobichon advised the STC Board that he wished to retire as editor of the STC newsletter NEWS/NOUVELLES, I immediately thought of Michael. Fortunately for all of us, Michael agreed to take on this task and both the Society and the newsletter are the better for it. Even though Michael's contact with STC was essentially all electronic and at a long distance, he undertook the job of Editor with the same commitment and enthusiasm that he put into anything to which he put his hand. We have all seen the consistent quality and timeliness of the newsletter, Michael's thoughtful editorial essays at the beginning of each issue and the subtle sense of humour that infused his writing.

We had hoped that Michael would be able to join us at the 2003 STC Symposium in December. Unfortunately Michael's illness was more serious than we knew. Michael passed away peacefully at home February 24, 2004, after a valiant struggle with esophageal cancer.

Our sincere sympathies go out to Michael's wife Muriel, to his children Robert, Sarah and Jonathon, to his son-in-law Fred and to his grandchildren Mitchell and Morgan.

Donations in Michael's memory may be made to the B.C. cancer agency, 600 West 10<sup>th</sup> Avenue Vancouver, British Columbia, V5Z 4E6.

**IN MEMORIAM: FRANCINE BEAUDOIN DENIZEAU**  
**(1950-2004)**  
**- Gaston Chevalier**

Francine nous a quittés le 24 mars, de façon inopportune, frappée trop tôt, après une vaillante lutte contre le cancer. Si je vous disais qu'elle était professeur à l'UQAM depuis 1978, ayant formé plus de vingt étudiants et étudiantes aux 2<sup>e</sup> et 3<sup>e</sup> cycles et au post-doctorat, qu'elle a marqué pendant ce temps de son influence en particulier le programme de doctorat de biochimie qu'elle a fondé, la direction de la maîtrise en chimie, le poste de décanat des études supérieures et de la recherche.

Très tôt, Francine a développé avec énergie et enthousiasme, un programme de recherche en toxicologie *in vitro*, qui a été la marque de son équipe depuis 25 ans; l'étude des mécanismes de cytotoxicité des métaux et minéraux comme le cadmium et l'amiante chez l'hépatocyte, puis la signalisation cellulaire et l'apoptose lui ont valu une belle renommée dans des secteurs de recherche fondamentale et appliquée. Je pourrais aussi vous témoigner que notre Francine avait le sens du travail d'équipe, ayant participé à la fondation et à l'animation avec ses collègues de l'UQAM, du Centre TOXEN qu'elle a dirigé de 1997 à 1999, en plus de participer à l'implantation du Réseau Canadien des Centres de toxicologie comme directrice intérimaire. On se souviendra aussi de son influence dans des organismes comme la STC, Environmental Mutagen Society et les comités d'organismes subventionnaires.

Mais je voudrais vous dire de façon plus personnelle l'excellence et l'amitié chaleureuse de cette collaboratrice au quotidien, comme pour plusieurs collègues à différentes phases de sa trop courte carrière. Oui Francine était une battante, qui ne baissait pas les bras, pour la cause de l'idéal de la science toxicologique et avait inspiré le thème de notre futur congrès ICT XI de 2007, « La découverte au service de la société » La perspective du congrès de 2007 l'enthousiasmait, comme elle avait dynamisé le Congrès International de Biologie Cellulaire de 1988.

Bien que nous pleurons sa perte, elle nous a apporté à chacun de diverses manières mais nous sommes plus riches d'avoir connu la femme de style qu'elle était. Partager un set de tennis ou nager quelques kilomètres à ses côtés dans « son » lac Massawipi ne fut jamais banal.

Si la quête d'immortalité donne tous son sens à la recherche scientifique, Francine nous a montré un total engagement à bâtir une œuvre dont elle ne verrait pas la fin. Que restera-t-il quand l'encre de ses publications sera séchée ? Dans le cas de Francine, beaucoup....

The untimely and early loss of our colleague and friend Francine Denizeau has left many of us devastated, but many also felt enriched by her short presence in our lives.

After her appointment as professor at UQAM, her influence grew rapidly in many directions. Francine will be best remembered by some 20 students at the M.Sc., Ph.D. and PDF levels which she trained as a rigorous and demanding mentor in the field of *in vitro* toxicology of metals. Francine was best known for her consistent contributions to the study of cytotoxicity and genotoxicity and more recently of cell signalisation and apoptosis - in both fundamental and applied toxicology.

She helped to establish the Ph.D. program of biochemistry and was instrumental as co-founder of the TOXEN Center at UQAM and of the Canadian Network of Toxicology Center (CNTC) in '85 and '91, respectively. Francine's vision, energy and practical sense were applied to various administrative positions including Dean of Graduate Studies and Research. She participated in scientific council committees and societies such as the STC Board.

Our beloved colleague believed in quality and that science should serve society – a theme she proposed for our 2007 ICT XI. She was very enthusiastic about the perspective of this future international meeting as she was a real dynamo in the organisation of 1988 International Congress of Cell Biology in Montreal.

Everyone could appreciate that “Professor Denizeau” had a colourful style. Whether on a tennis court or swimming a few kilometres along side her was never trivial and could make one appreciate the kind of fighter she was. After the dust has settled, our recollection of Francine's contributions will be timeless. “Yes, science was fun with you, Francine!”

### **Conferences, Meetings and Workshops:**

#### **2004**

- June 8-10 The 3<sup>rd</sup> International Conference on Non-Linear Dose-Response Relationships in Biology, Toxicology and Medicine. Univ. of Massachusetts, Amherst, MA. [belle@schoolph.umass.edu](mailto:belle@schoolph.umass.edu)
- June 13-17 Society of Toxicologic Pathology Annual Meeting, Salt Lake City, UT  
<http://eshow2000.com/STP/index.cfm>
- June 16-20 Northern Lights Conferences - 47<sup>th</sup> Annual Meeting of the Canadian Federation of Biological Societies. Vancouver, BC.  
<http://www.cfbs.org/annual.html>
- June 16-18 3<sup>rd</sup> International Conference on Idiosyncratic Drug Toxicity, San Diego, CA. [www.isciencex.com](http://www.isciencex.com)
- July 11-16 10<sup>th</sup> International Congress of Toxicology, ICT-X, Tampere, Finland. Contact: e-mail: [ictx@tsgcongress.fi](mailto:ictx@tsgcongress.fi)
- Aug 28-Sept 3 FBI Laboratory Forensic Toxicology Symposium & Joint Meeting of the Society of Forensic Toxicologists (SOFT) and The International Society of Forensic Toxicologists (TIAFT). Washington, DC, USA. Contact: Marc A. LeBeau, Federal Bureau of Investigation, FBI Laboratory, Phone: 202-324-8472, Fax: 202-324-4633, E-mail: [mlebeau@fbi.gov](mailto:mlebeau@fbi.gov) Websites: <http://www.soft-tox.org> or <http://www.tiaft.org>

#### **2007**

- July 14-21 11<sup>th</sup> International Congress of Toxicology, ICT-XI, Montréal, Québec, Canada.