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OFFICERS OF THE STC

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FROM THE EDITOR'S DESK

Michael Prior



Laying in bed waiting for the alarm to ring, I remembered our visit to a public garden in Vancouver en route to the International Airport with a herbalist friend returning to England. We saw the effect of a mass planting of Dusty Miller, whose hairy, silver-gray deeply lobed leaves made the adjacent red geraniums seem to be on fire. Dusty Miller is a cultivar of the genus *Senecio*, of which I have fond memories. During my final year at veterinary school, two of us had written a report on the toxicology of *Senecio jacobaea*, a member of the ragwort family. Being budding scientists, we tried feeding it to the university herd (without permission, of course) but the cows refused to eat it. Why?

We found out later that one of its common English names is *stinking doddie*, because of its malodour. However, if it is accidentally blended into grass cubes, the grasses and alfalfa mask the malodour and it is eaten. I found this fascinating, and it was the start of my life long interest in toxicology.

Ragwort contains a number of pyrrolizidine alkaloids, which may be amongst the most significant plant chemicals causing disease in animals and humans. After absorption from the gut, these compounds are converted to electrophilic pyrroles in the liver which, apart from causing liver damage, may escape and injure other tissues, including lungs, heart and kidneys (Seawright, A. Directly toxic effects of plant chemicals which may occur in human and animal foods. *Nat. Toxins* 3 (4): 227-232, 242. 1995). The pyrrolizidine alkaloids are found mainly in members of three plant families: *Boraginaceae*, *Compositae* and *Leguminosae*. In North America most livestock poisoning is due to ingestion of *Senecio* and *Crotalia* species (Cheeke PR. Toxicity and metabolism of pyrrolizidine alkaloids. *J. Anim. Sci.* 66(9): 2343-2350. 1988). As an aside, there was an informative review article on pyrrolizidine alkaloids published in the 1960s. Unfortunately I cannot find it in the electronic databases, but I do have a copy somewhere in one of my many cartons of references (I

must be about the same age as Don Ecobichon, who describes a similar memory and filing system in his column in this issue).

Our English herbalist friend didn't drink infusions of *Senecio*, for most people are now aware of the risk of veno-occlusive disease, from this and other causes (Rollins BJ. Hepatic veno-occlusive disease. *Am. J. Med.* 81(2): 297-306. 1986). Another source of pyrrolizidine alkaloids is *Symphytum officinale* (*Boraginaceae*), commonly called comfrey; and sometime as knitbone, boneset or blackwort. It is not now recommended for internal use because of its potential health risk (Garland, S. The complete book of herbs and spices. Viking Press: New York.1979). Unfortunately, poisonings still occur (Yeong, ML *et al.* Hepatic veno-occlusive disease associated with comfrey ingestion. *J. Gastroenterol. Hepatol.* 5(2): 211-214. 1990). The small but significant long-term risk that is associated with the consumption of comfrey justifies the need to limit its intake, and also requires further education on the potential dangers of naturally-occurring chemicals of plant origin (Abbott, PJ. Comfrey: assessing the low-dose health risk. *Med. J. Aust.* 149(11-12): 678-682. 1988).

Our English friend was into herbal medicines, or naturally-occurring chemicals of plant origin, in a big way. Amusingly, her aroma therapy routine set off our smoke alarm! Less funny was its effect on my eyes: tears and puffiness. Just what are herbal medicines? Many of us are familiar with therapeutic botanicals, such as the purple foxglove for dropsy, cinchona bark for fever, liquorice for many ailments, and opium poppy for pain or cough. However, variations in potency of the source material meant they could kill as well as cure, or even have no effect whatsoever. Today we use digitalis, quinine, corticosteroids and opiates instead of those particular botanicals. Herbal medicines are a huge and rapidly growing industry, in which pharmaceutical companies are now participating (Canedy D. Real medicine or medicine show? Growth of herbal remedy sales raises issues about value. *New York Times*, July 23, 1998. D1).

In the past year, there was strong opposition to attempts by Health Canada to introduce regulations affecting the herbal medicines used by many people. One thorny issue is how much involvement Health Canada, and the Health Protection Branch (HPB) in particular, should have in the area of herbal and other unconventional products. Where do we draw the line between protecting the public against potential health risks and scams and interfering with personal choice? At a meeting with the Vancouver Sun's editorial board, Assistant Deputy Minister Ian Shugart said the review process should indicate how the HPB can become a more open and transparent agency (*Vancouver Sun*, Sept 30, 1998. B6). For there are valid questions about product verification and quality assurance that need to be asked. Questions no different to those we ask, or should ask, of drug and pharmaceutical manufacturers.

There is also efficacy, often presented as concern about the lack of scientific testing, or participation in the demanding process of providing evidence of safety and efficacy to a government regulatory agency. The Office of Alternative Medicine of the US National Institutes of Health awards research grants on alternative medicines. The resulting final reports are listed in the office's public on-line data base (National Institutes of Health, Office of Alternative Medicine. Grant award and research data. Bethesda, Md: Office of Alternative Medicine). Go to their Web site <http://altmed.od.nih.gov.oam/research/research/grants>).

Even if information on herbal medicines were widely available, would it be read by those who need it? The current debate here in British Columbia on effective and safe orthodox treatments for elevated blood pressure is, in part, an example of information that is apparently readily available but not being read by those who need it. Should we expect any different from the practitioners and patients using herbal medicines?

If there were no merit in herbal medicines, would the field of ethnopharmacology exist, save as an esoteric anthropological sideline? Some years ago I came across a reference to feverfew, *Tanacetum parthenium*, in a 400-year-old text book. It was used then for "*nervous disorders*" but liver complications were also noted. Today we have several friends who chew a small amount of feverfew leaf daily to reduce the frequency of their severe migraine headaches by more than ten-fold. A double-blind study found that treatment with feverfew was associated with a reduction in the mean number and severity of attacks and also in the degree of vomiting, though duration was unaltered. There were no serious side-effects (Murphy JJ et al. Randomized double-blind placebo-controlled trial of feverfew in migraine prevention. *Lancet* 2(8604): 189-192. 1988). So perhaps *some* herbal remedies have their place?

A cautionary view of a broad range of alternative medicines is to be found in the editorial "*Alternative Medicine - The Risks of Untested and Unregulated Remedies*" (*New England J Med* 339 (12)). Incidentally, there was a conference on Alternative Medicines Toxicology on September 12, 1997, in St. Louis, Missouri, USA. This was billed as a state of the art review by leaders in medical toxicology. Does anyone have any information on this conference or proceedings? If so, please contact the Editor.

We grow quite a few herbs at home, some of which have reputed medicinal properties, and use them when cooking in our west coast fusion style, often with salmon. Well, one dinner time on one of our west coast ferry routes, there was an announcement over the PA system that the captain was going to turn the ferry, so that the stern became the bow and the bow the stern. Apparently the cook was barbecuing salmon on the front deck and all the smoke was blowing back into the ship (*Vancouver Sun*, Sept 13, 1997 B9). Smoke, whether from barbecuing salmon or the infamous London fog of 1952, contains suspended particulate matter, which may be hazardous for your health. So read the article by Dr. Vincent on particulates in this issue. He addresses some thought-provoking issues, including exposure threshold versus continuum, the necessity of plausible biological explanations of adverse effects, and the biological effects of low level exposure (BELLE).

Dusty Millers of the *Homo sapiens*, not *Senecio jacobaea*, variety are well aware of the health effects of suspended particulates; flour dust is a well-described occupational hazard for them (Brooke, SM, "*Occupational and Environmental Asthma*" *In Environmental and Occupational Medicine* 2nd Ed. Ed. W.N. Rom. Toronto: Little, Brown and Company, 1992).

FROM THE DESK OF THE PRESIDENT

Len Lillie

Whither STC - Are We Y2K Compliant?

Half way up the Eiffel Tower is a very large electronic sign counting down the days to the Year 2000. In our facility, as I expect in many others, people are scurrying around compiling lists of equipment which may or may not have some kind of internal clock which may or may not cease functioning at the turn of the millennium. In the Pacific, micro states are vying for the honour of being able to say that theirs is the site of the first dawn of the new age.

I am not particularly millennium oriented. It is, after all, just the passing of another year in what is primarily a western Christian calendar. Jean and I have not made reservations years ahead to be in the right place at the right time, even if we were able to resolve the question of whether the new millennium actually starts January 1, 2000 or January 1, 2001. I expect that by the time it actually rolls around we may all be a little bored with the whole thing.

Non-the-less, it is a good time to take stock of where our Society and the science of toxicology in Canada is today and where we would like to see it go in the next decade or so. STC as an organization has always been relatively small and has focused primarily on communication and education within the discipline of toxicology in Canada. We maintain no office, secretariat or paid staff and we rely heavily on the voluntary contributions of time and effort by our members. Our dues are modest by comparison with most other organizations. Over the years, many colleagues have contributed substantively to the activities and strength of STC. Each year the Society organizes a Symposium that regularly draws a healthy proportion of our membership as well as a strong submission of posters presentations and (most gratifying) good student participation. I personally consider the STC annual Symposium one of the best small meetings around within my areas of interest.

Of course all of us also belong to other much larger organizations and attend meetings with multiple simultaneous platform presentations, workshops, short courses, satellite meetings and an inexhaustible supply of poster presentations. These organizations will usually have a permanent office, an Executive Director, an elaborate communications machine, and dues and conference fees to match.

Given increasing competition from specialty and subspecialty meetings and decreasing conference travel budgets in every sector, smaller organizations have to work hard to compete. In this increasingly competitive environment, whither STC? Which direction(s) should the Society be taking in the next decade. If we work on the "if it ain't broke, don't fix it " principle, we could

continue on much as we are for some time. Both our membership and attendance at our annual Symposium are stable. We have a core of toxicologists who consider STC as their Society and in an increasingly globalized world it is Canadian. On the other hand, our members too are becoming busier and it is sometimes a challenge to find individuals to stand for office or participate otherwise in the work of the Society. Anyone contemplating allowing their name to stand for Vice-President and President-Elect, for example, is making a six-year commitment. How many of us can tell these days what we will be doing six years down the road or even where we will be?

Downsizing and increased competition in our work environments, not to mention the need to preserve time for our families and communities often make it difficult to take on more elective responsibilities. As a Society, we are well aware of the need to increase the frequency and timeliness of our communications with the members; something which is not always easy to do with an all-volunteer organization. Projects such as our recent ICT X Bid, require substantial amounts of time and can mean that other STC activities get put on the proverbial back burner, at least temporarily.

Do we want to expand our activities in support of toxicology in Canada? Should we look to establishing some kind of secretariat that would enable us to work on a more business-like basis? Are we prepared to support this kind of initiative? Will this just create another expensive bureaucracy? Or are we happy with things pretty much as they are, doing what we can do and focussing our resources on a first class annual Symposium and providing a forum for communication among Canadian toxicologists. Is STC even needed as a separate scientific society. Should we seek to ally ourselves with some other Canadian Society to achieve a greater critical mass. Just as an example, in many places toxicologists are aligned with pharmacologists. Personally, I think we are doing a lot of things right and that there is a niche for a Canadian society of toxicology and STC fills that niche. What do you think? I look forward to hearing your ideas at the Annual General Meeting in Montréal.

On other business, I have to advise you of two important changes affecting the Society. For those of you who don't know, Paul Hough, Executive Director (ED) of the Canadian Federation of Biological Societies (CFBS) has resigned to become Vice-President of BIOTECCanada, an industry association. Paul has served us all well as ED of CFBS. He has helped shepherd CFBS through a difficult time and has directed an extremely active science lobbying program. We wish him the very best in his new position. He will be a difficult person to replace.

Closer to home, Warren Foster has advised us that he is taking a leave-of absence from the Health Protection Branch to take a position as Associate Director Research for the Women's Health Program at Cedars-Sinai Hospital in Los Angeles. This is a tremendous career opportunity for Warren. However it will make it difficult for him to complete his term as Vice-President and President-Elect of STC. Gail Bellward and the Nominating Committee are considering the situation and will make a recommendation to the Board for consideration at the AGM. We will also be electing a Councillor to replace Francine Denizeau. Many thanks to Francine for her support for the last three years.

On a final note, thanks also to Michael Prior and the Newsletter Committee (David Josephy

and Randy Leeder) for their efforts. I am impressed with each issue.

I look forward to seeing all of you at the Symposium/AGM in December.

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NOMINATION AND ELECTION OF STC SECRETARY AND ONE COUNCILLOR

Gail Bellward

Two positions on the Board of directors are open for nominations this year. They are Secretary and Councillor, both with three year terms of office. The Councillor should be from government. Please submit nominations to Gail Bellward by Oct. 16. For details, refer to the Oct.1997 edition 16(3) pp6-7 of the Newsletter

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BOOK REVIEW

Michael Prior

Zero Tolerance: Hot Button Politics in Canada's Universities. Peter C. Emberley. Toronto: Penguin Books. 1996

The cost of university education to the consumer is rising, and the benefits for the rest of us may be lessening. To translate: university tuition fees and political correctness in academe are increasing. According to one reporter, the academic world described by Emberley is "... a set of institutions now choked by right wing pig weed, left wing brambles and much poison ivy." The author sets out to describe in detail the financial, spiritual and political collapse in universities as business, governments and special interest groups hasten to diagnose the illness(es) and prescribe remedies. The picture is not attractive: the Montreal Massacre, the Concordia Fabrikant murders, the Smith Report on teaching and research, Ontario's anti-harassment policy, and charges of systemic racism at UBC.

Surely, one goes to university to be challenged intellectually, shocked by new ideas and thoughts, excited by new knowledge, and encouraged to think? Oh dear, I always thought that "PC" stood for "personal computer". What are the hot buttons of the title? Abolish tenure; back to teaching, university rankings and performance indicators; value-for-money and value-added auditing; tuition as user fee; distance-learning technology; a modularized curriculum; the inclusive university; academic freedom; and accountability.

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Society of Toxicology of Canada - Société de Toxicologie du Canada

Annual Symposium

December 3 -4, 1998

Holiday Inn Montréal Midtown

Advances in the Scientific Basis of Safety/Risk Assessment

Day One: December 3, 1998

8:50 Welcoming Remarks (Dr Len Lillie, President STC)

New Approaches to Risk/Safety Assessment

(Chair:)

9:00 Overview of Advances in Risk Assessment: Robert Willis (Cantox)

9:30 Probabilistic Risk Assessment: Sheryl Bartlett (Health Canada)

10:30 Contribution of PBPK Modelling to Risk Assessment: Kannan Krishnan (University of Montreal)

11:00 Advances in Dose Response Assessment/Unified Approach to Risk Assessment: David Gaylor
(US FDA NCTR)

11:30 Discussion and Chairperson's Concluding Remarks

11:45 *Posters*

12:30 *Lunch*

Use of Carcinogenicity Data From Transgenic Animals in Toxicology & Safety Assessment

(Chair: Jay Goodman)

1:55 **Introduction** Jay Goodman

2:00 **Overview:** Sylvia Furst (Boehringer Ingelheim)

2:30 **Industry Perspective:** Douglas Bryant (Cantox)

3:00 **Regulatory Perspective:** Joseph DeGeorge (US FDA, not confirmed)

3:30 **Discussion and Chairperson's Concluding Remarks**

4:00 *STC - Annual Business Meeting*

6:30 *President's Reception*

8:30 *Dinner*

Day Two: December 4, 1998

8:30 *Henderson Award Speaker*

Biomarkers in Safety Assessment

(Chair: Mark Feeley)

9:00 **Introduction** Mark Feely (Health Canada)

9:05 **Immunologic:** Judy T Zelikoff (NYU University, New York)

9:35 **Human & Rodent AH Receptors: Can Variations in Their Properties Assist in Assessing Human Risks From Dioxin Exposure?:** Alan Okey (University of Toronto)

10:30 **Molecular Epidemiology/ ultrasensitive Assay of DNA Damage In Humans:** Chris Le (U of Alberta, Edmonton)

11:00 **Indicators of Adverse Effects on the Endocrine System:** Warren Foster/Michael Wade (Health Canada)

11:30 **Discussion and Chairperson's Concluding Remarks**

11:45 *Posters*

12:00 *Lunch*

Safety Assessment of Nongenotoxic Carcinogens

(Chair: M Charbonneau)

1:00 **Introduction** Michel Charbonneau

1:05 **Epigenetic Mechanisms:** Jay Goodman (Michigan State University)

1:35 **a₂-Globulin Nephropathy and Renal Carcinogenicity:** Lois Lehman-McKeeman (P&G, Cincinnati)

2:05 **Peroxisome Proliferators:** Jack Vanden Heuvel (Penn State University)

2:35 **Discussion and Chairperson's Concluding Remarks**

2:50 *Overall Conclusion*

PLEASE NOTE: THIS DRAFT WAS CORRECT AT THE TIME OF EDITING.

ANY LAST MINUTE CHANGES WILL BE AVAILABLE

AT THE TIME OF REGISTRATION

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HEALTH IMPACTS OF PARTICULATE MATTER IN AMBIENT

Renaud Vincent

It has been known for 15 years that ambient levels of sulphate in Canada are associated with respiratory morbidity (*Bates and Sitzo, 1983*). In eastern Canada, sulphate levels are highly correlated with fine particulate matter. Much of the day-to-day variation in fine mass can be explained by daily fluctuations in sulphate concentrations. Sulphates and fine mass have many sources of pollution in common, such as industrial activity and transportation. Fine particulate mass, which contains metals and combustion products, also correlates with photochemical air pollution. What has emerged from epidemiological investigations published over the past 5 years is that severe health outcomes can be associated with surprisingly low levels of air pollution (*Burnett et al., 1994, 1995, 1998a, 1998b*). For example, daily increases of $13 \mu\text{g}/\text{m}^3$ in ambient sulphate are associated, on the following day, with 3.7% increase of cardiac hospital admissions and 2.8% increase of respiratory hospital admissions (*Burnett et al., 1995*). This concentration of sulphate corresponds to about $30 \mu\text{g}/\text{m}^3$ PM_{2.5} (particles with aerodynamic cut diameter of $2.5 \mu\text{m}$) or $50 \mu\text{g}/\text{m}^3$ PM₁₀ (cut diameter $10 \mu\text{m}$). For comparison, occupational exposure limits (8-hour time-weighted average) for a number of respirable particulate materials are well above those ambient levels of particles that can be associated epidemiologically with acute health impacts: e.g. amorphous silica, $3 \text{ mg}/\text{m}^3$; quartz, $100 \mu\text{g}/\text{m}^3$; copper fumes, $200 \mu\text{g}/\text{m}^3$ (*ACGIH, 1995*). It is unlikely that acute exposure to low levels of air pollution could result in the rapid, overnight development of respiratory and cardiac conditions in otherwise healthy individuals, and with such severity that hospitalization becomes required. Rather, it is thought that air pollution may precipitate symptoms in individuals already compromised with a respiratory infection, chronic obstructive pulmonary disease, or cardiac disease.

There are troubling aspects of this association between low level episodes of air pollution and metrics of population health impacts such as hospitalization and daily mortality rates. For one, current toxicological paradigms do not provide satisfactory, biologically plausible mechanisms for acute adverse effects of such low levels of air contaminants. That is, even if we admit as probable that individuals primarily affected, or at least accounting for the epidemiological signal, are those with established pulmonary and cardiac conditions, we still cannot explain, in terms of the pathobiology and pathophysiology, the pathway(s) of primary and secondary effects between the deposition of an almost trivial dose of particles in the respiratory tract and the deterioration of a pathological condition to the extent that the physician must to admit the patient to the hospital. There are practical consequences of these gaps in understanding. It is possible that the biological effects of particles are very subtle, adding little to those of an overwhelmingly large number of individual and environmental factors. The statistical relationship between hospitalization rates and ambient particulate matter at levels below current air quality objectives could merely reflect the sophistication and power of the methods in population epidemiology. In that sense, air pollution would constitute a set of factors, variable in time but common temporarily to millions of individuals, which would simply synchronize those individuals with unique sensitivities in their clinical manifestations of established diseases. This synchronization phenomenon, after filtering out or ignoring all of those more important factors that are independent of time, would be sufficient to cause an audible statistical blip attributable to episodic fluctuation of particles in ambient air. For a basin of a few million individuals, and one hundred hospitals, a 4% increase in hospital admissions may represent less than one

more admission on any given day. If this overall reasoning is correct, it places the issue in a different perspective. Indeed, a statistically significant association between low levels of air pollution and morbidity becomes an interesting phenomenon, but with little significance with respect to the actual etiology of disease. It follows that improvement in air quality at great societal costs would not improve the overall incidence of health outcomes, but simply leave them a little more randomized through time, removing a statistical association and bringing a false conclusion of health benefits.

However, absence of toxicological evidence for effects is not evidence for absence of effects. Even if we trivialize the issue, a problem remains for toxicologists, since one of our central assumptions in toxicology is that there should be a threshold for adverse effects of inhaled particles. What must be kept in mind here is not so much the fact that there is a temporal statistical association between low level air pollution and respiratory and cardiac morbidity, but more significantly the fact that there is a continuum in this relationship between the levels of air pollution and the intensity/frequency of health impacts. There is little doubt that high episodes of air pollution, such as the historical episodes of London smog, were directly causing deleterious biological effects resulting in death. This is the high end of the dose-response curve. The low end of the dose-response curve is clean air. Somewhere in-between these two points there is, it is hoped, an air quality target that should allow reconciliation of the protection of human health and the necessary human activities in an industrialized society. To locate this target, we look for a break or inflection in the slope of the dose-response relationship, for example a threshold for the production of adverse effects. This is where trade-offs are allowed in order to balance a variety of inter-related economic and health imperatives. Safety margins can be used to account for uncertainties and to increase the comfort zone around a standard. The recent epidemiological evidence suggests that air pollutants actually behave as non-threshold substances, removing the luxury of safety margins. The simple fact that there is a clear continuum even in the bottom part of this association between ambient particles and the frequency of severe, quantal outcomes such as cardiac hospitalization or death is an indication that biological systems respond to environmental stressors in ways not previously suspected, with practical, tangible, measurable consequences on health costs and quality of life.

What appears as a trivial statistical association then becomes a major public health issue. If particles act as non-threshold contaminants, there is the distinct possibility that epidemiology time-series allow us to see only the tip of the iceberg. Those few sensitive or sick individuals admitted to the hospital the day after an air pollution episode could actually be sentinels. What could hide under the water level is the recurrent alteration, over years and years of exposure, of defense and homeostatic mechanisms even in healthy individuals, predisposing them to infections or precipitating development of pathologies, which outcomes would be diluted in time and difficult to relate with air pollution through epidemiology investigations. Science must stand between alarmism and snapping shut the lid on the can of worms.

A second troubling aspect of the issue is the pervasive nature of the particulate effects, for example across age groups, across different types of pathologies, across geographical regions with seemingly different combinations of air pollutants, but yet with definite patterns of health impacts. We currently have few clues on how inhalation of ambient particles in the population can impact simultaneously on such diverse outcomes as pulmonary infection, airway obstruction, asthma, infarct of the myocardium, heart arrhythmia etc. It should be clear that not everything in the air correlates with hospital admissions at large. For example, particles correlate with hospital admissions for both pulmonary diseases and cardiac diseases

(*Burnett et al.*, 1995). So does carbon monoxide (*Burnett et al.*, 1998a). However, ozone correlates with pulmonary admissions but not with cardiac admissions (*Burnett et al.*, 1994, 1995). Furthermore, particles correlate with hospital admissions for heart infarct and arrhythmia, but not with admissions for stroke (*Burnett et al.*, 1998b), and so on. This implies toxicodynamic differences between different pollutants, something which does not come as a surprise. It also implies that pollutants do not simply recruit sick or weak individuals, in a generic sense, into a temporal phenomenon. What emerges from all of this is that a number of different things in the air may affect different people, for a number of different reasons. What toxicologists can also expect, from their experience with occupational stressors, is the existence of some still obscure toxic interactions between the different compounds or substances in ambient air. At this time, the potential combined effects of simultaneous exposure to carbon monoxide and particles on pulmonary and cardiac outcomes, or from particles in combination with ozone, are not defined by the epidemiological data.

In short, while the current regulatory emphasis may be on the development of valid and defensible air quality objectives for particulate matter, in the mind of toxicologists the picture is more complicated. Recent data actually indicate that only 20% of all air pollution-related morbidity is attributable to particulate matter. The bulk of the air pollution-related hospital admissions, about 80%, are attributable to the gaseous mix (*Burnett et al.*, 1998b). We will not be able to independently substantiate the epidemiological findings without understanding the basic aspects of the phenomenon. In turn, we may not be able to fully understand the health impacts of particles without considering at the same time those of ozone, carbon monoxide, oxides of nitrogen, and so on. The immediate need is the identification of the various agents of those adverse effects as well as the diversity of mechanisms of action. Then will we have the tools to define the toxicodynamics, and move toward quantifiable models. To do this will undoubtedly require the development of a rich and diversified hypothetical framework, the utilization of a plurality of experimental models, concerted research efforts, resources, and time.

Several laboratories in North America and Europe have been studying the toxicology of ambient particulate matter for a number of years. The National Academy of Sciences in the United States has recently recommended a 13-year research agenda on ambient air particulate matter, estimated at close to half-a-billion dollars, a significant portion of which should be targeted at resolving the toxicological and clinical aspects of the health impacts of particles (*NRC*, 1998). In Canada, the resources should remain proportionately more modest. Nevertheless, we may be able to maximize the returns by looking beyond the direct issue of ambient particulate matter. The apparent difficulties in reconciling toxicological evidence and epidemiological evidence is not limited to low concentrations of particles. This problem extends also to low levels of ozone, oxides of nitrogen, and carbon monoxide. The heart of the scientific challenge is two-fold: to determine how the acute exposure of sensitive individuals to low levels of contaminants can possibly cascade into such severe health impacts as hospitalization or mortality; and to define the significance of the phenomenon to recurrent exposure of healthy individuals or the population at large. The answer to these practical questions should have impacts beyond environmental toxicology and air quality objectives, and actually teach us a lot about pulmonary and cardiac diseases.

Recent work in our laboratory indicates that there appears to be a biological basis for the epidemiological evidence of acute health impacts of ambient particles. One series of experiments was aimed at defining the pulmonary toxicity of urban particulate matter (*Vincent et al.*, 1997). We have found

that inhaled urban particles are relatively innocuous to the structural integrity of the lungs of healthy rats. However, if a limited epithelial lesion is introduced in the lungs, for example by co-exposure of the animals to ozone, then the particles can amplify the primary injury. These observations validate the notion that toxicological data obtained from exposure of healthy animals to particles, which is essentially the classical approach in toxicology, can vastly underestimate the impact of particles in sensitive lungs. A second interesting series of observations have come from our subsequent attempts to define some of the mechanisms of the toxicological interaction between ozone and urban particulate matter (*Bouthillier et al.*, 1998). Although urban particles by themselves did not cause structural lesions in rat lungs, we have observed an increase in plasma endothelin-1 levels in the rats. Changes in plasma ET-1 were not affected by a co-exposure to ozone. Here, vascular effects can apparently be caused by inhalation of particles without the need for any significant structural impact on the lungs. While a fluctuation of plasma ET-1 levels may be innocuous to healthy individuals, because of rapid compensatory mechanisms, the impact may be quite different in an individual with a heart condition. The important clue here is that the absence of structural lesions in the lungs after inhalation of particles is clearly not evidence of innocuity since systemic effects may be introduced, possibly via alteration of ET-1 metabolism in the alveolar capillary bed. This model should eventually give us a better insight into why particles in ambient air have been associated epidemiologically with cardiac impacts, while ozone has not (*Burnett et al.*, 1994, 1995).

The limited toxicological evidence at this point is consistent with the epidemiological evidence. However, the difficult part is still before us, which is to verify the pathophysiological significance of the biological effects in animal models of disease, to begin long-term inhalation exposures to complex mixtures of air pollutants, and to perform quantitative extrapolations of the experimental data to the human experience.

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air pollution on cardiorespiratory hospitalizations. Arch. Envir. Health 1998b:*in press*.

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THE VIEW FROM MY CANOE

Don Ecobichon

Where has the summer gone? The wild purple asters (they are *not* weeds) are in full bloom, small flocks of Canada geese are present in our area, and the trees are starting to turn colour, particularly the ash with their russet and purple foliage. The maples and birches will soon follow. The wood is piled high and I think there is enough for the winter, barring another ice-storm. There is still more piled in our woodlot, with more to be cut from storm damage. I think that we are ready for winter.



My canoe feels abandoned. We have been out on the water very few times. Our kayaks haven't even been out of storage this year. When we used to come to the cabin for the summer, we made great use of these vessels but, now that we live here full time, there is always tomorrow. But there is always something to do tomorrow. Our 15-month-old Labrador dog is not really convinced that he likes water, and sitting in a tippy canoe is not his idea of fun. On his first "trip", someone passing commented on how well behaved Max was. Heck no, he was petrified!

Since Betty feels that she is "isolated from the world", we bought a StarChoice dish. Big, big mistake! Not only about 30 television channels but also 29 music (no picture) channels in surround sound. There is always something that you want to see in the evening, thus interrupting gardening, fishing, walks, reading or juts goofing off. We are still learning! We didn't die, just retired!

Published a book in September that I edited, entitled "*Occupational Hazards of Pesticide Exposure. Sampling, Monitoring, Measuring*" from Taylor and Francis. I coerced some great people to write succinct chapters on various aspects of exposure and monitoring. They made it easy for me.

I think that it will be a definitive piece for some years to come, certainly updating what was considered "exposure" a few years back. With about eight people involved for a year, we brought the book to publication on time, within budget, within the allotted page limitations and even provided the pictures for the cover! It is available in both hard- and soft-covered format. I am pleased with it and with the co-operation and assistance of the folk at Taylor and Francis.

An interesting article and accompanying editorial appeared recently in *Science* (Sept 4, 1998) on intellectual property and who should own scientific papers. A Working Group of the American Academy of Arts and Sciences propose that authors receiving funding from the U.S. government should not relinquish their copyright to publishers - "retention of the copyright benefitting scientific progress for the public good by permitting scientists to rapidly distribute, read and respond to new results through the electronic channels of the Internet." Since 1976, the U.S. Copyright Act shifted the legal control from publishers to authors. All journal publishers require authors to transfer copyrights that the law has vested in creators, a standard procedure. Research results created by employees of the U.S. government as part of their duties are considered in the public domain, free for use by anyone, without infringement on copyright since the work was funded by the U.S. taxpayer. This freedom extends even beyond the border, since, on trying to obtain copyright for a figure, I received a polite letter stating that I did not need to apply. While researchers can and do place their results on Internet websites, citing that they are sharing their discoveries widely and promptly, the veracity of much of this information is questionable. As the computer whizzes say - GIGO (garbage in, garbage out). I have no problem of scientists using websites to present results to their friends and colleagues. However, these sharings are not publications, have not been peer-reviewed for accuracy, and could not be considered to be quality information even though they might be freely available if you know where to look. We all know of incidents that received media hype to the point of public paranoia. Dr. Bloom, editor of *Science*, maintains that *Science* holds the copyright of its authors because of the belief that the journal materially improves and protects the product created by the author, peer reviewers and the journal, whether people read the article in the Journal; or obtain the information from *Science OnLine*. Both the article and editorial make thought-provoking reading.

Recently I attended a pesticide-related neurotoxicology meeting in Little Rock, Arkansas, as an invited speaker. It was an interesting meeting, relating global use of pesticides and their impacts on acute and chronic toxicity. I was there because of my involvement in South America and southeast Asia. Government policy-makers presented on the first day and then disappeared - the usual scenario of "don't confuse me with science, our minds are already made up and we are busy people, making a speech tomorrow in Cincinnati or Timbuktu, etc." The scientists, academic, industry and government, remained to present lots of good research, interesting results and generate engaging discussion. Still, it was a case of preaching to the converted whereas it is the pagans we needed to reach. However, it was a good chance to meet old friends, renew acquaintances and to meet new people.

The one thing that I find about having gray hair and being retired is that I have become a memory bank for younger investigators who cannot find research carried out before 1972, the starting year for many computer-based scientific data banks. They don't know how to use *Index*

Medicus, *Chemical Abstracts*, etc and therefore are totally unaware of earlier literature. Esterases, particularly cholinesterases, were a "going concern" in the 1940s, 1950s and 1960s; a base of literature that I am familiar with. I still get calls starting off with "*I know that you will know something about*". A real challenge to my interneuronal tracts and one reason why I am re-classifying, by first author, any reference that I have used in pesticide writings for easier retrieval. However, it still leaves several cartons filled by subject/topic that I have to paw through to locate some obscure paper that I know I have a copy of. No wonder that I cannot get out in the canoe.

Right now, I am looking at eight cubic yards of sifted soil delivered this morning that Betty wants moved from the pile to new flower beds, one bucket at a time ...

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NEWS FROM OTTAWA

Doug Arnold

The local CBC morning program is at it again. They air items about the Health Protection Branch (HPB) that the Ottawa print media do not seem to be interested in. However, with all that is going on in Washington, DC, there is hardly any space left for *As the World Turns at HPB!*



HPB caught CBC's attention during the early part of September, when a Toronto pediatrician requested the evaluators' report under the Access to Information Act for a drug that the reporter indicated was used as a diuretic and for diarrhea. The Director General for the Therapeutic Products Directorate, Mr. Dan. Michols, issued the physician a sixty-some page document of which 90-95% was deleted/whitened out. White out was used because the information deleted was considered proprietary information. Apparently, the CBC then asked the US Food and Drug Administration for the same information requested from HPB by the physician and received a completely uncensored document. In fact, Judy Erola, a spokesperson for the Pharmaceutical Industry, deplored Mr. Michols actions, claiming the pharmaceutical industry wanted a more transparent system as they had nothing to hide.

This story led into a side bar story about how the HPB Transition Team was trying to retool HPB for the new millennium by holding consultative meetings across the country. The consultative process has just started in Halifax and Mr. Michols indicated his hope that these meetings would help to point out that HPB currently operates under a series of outdated laws which should be

updated and that the new laws would hopefully make the HPB regulatory process more open. About the same time, a column in *The Globe and Mail* by Hugh Winsor (Sept. 9, 1998), was suggesting that "*whenever a government department strikes a Transition Team beware. If, in addition, it begins to boast about that transition process, put up two red flags.*" The article went on to suggest that Health Canada will lessen its current responsibilities "*...to protect Canadians from bad food, bad drugs, bad pesticides and other health hazards... (and) ... turn the responsibility for testing and research back to the pharmaceutical and chemical companies.*" Those of us in HPB can readily relate to Mr. Winsor's column. A Transition Team document entitled "*Keeping Faith with Canadians, Final Report*", went through six drafts before the staff had a chance to see a copy of it as part of the internal consultation process. Staff identified several errors in this draft and made several comments for textual improvements. The final version still contained some of those errors identified by staff. Further, many staff comments were omitted even though management had indicated they would be included in the final version. It appears that Mr. Rock and the people he has brought in to manage various aspects of the Transition Team are being outflanked by those managers who have already closed down the drug research labs and appear to be on a course to eliminate as many of the remaining research laboratories as possible.

Not to be outdone in the media attention department, the Food Directorate and its Bureau of Veterinary Drugs caught the interest of CBC about a week later. The stories started out by updating the Bovine Somatotropin (BST) situation, wherein the evaluators indicated that the managers were imposing their views upon the evaluators and were not allowing the evaluators to do their jobs properly, etc. It seems that the evaluators had filed grievances about managerial interference but to no avail. When CBC inquired as to whether staff had "whistle blower" protection when managers do unethical things and/or act in an inappropriate manner, a Health Canada spokesperson assured the CBC interviewer that employees would be protected. However, CBC concluded that the employees who did "blow the whistle" on their managers received no protection in this situation. CBC then presented an interview with some HPB critics who are concerned that managerial interference will become more commonplace if measures currently being discussed by the Transition Team are enacted.

A few days later, both the local CBC morning program as well as the CBC's *The National* ran a story about the six evaluators taking their case to the Public Service Commission Staff Relations Board. While managers had ordered the evaluators not to speak publically about this matter, the Sierra Club of Canada and the Council of Canadians made several comments about the data being evaluated. Their comments were purportedly based on information obtained by a researcher for a Senator who is a member of the Senate Agriculture Committee. The irony is that the Senate Agriculture Committee asked Health Canada, under Freedom of Information, for the scientific evidence supporting the safety of BST in animals and humans. Approximately 30-40% of the report the committee received was whitened out. However, Health Canada purportedly provided additional information to the Senator's researcher following her personal intervention. Subsequently, a Health Canada spokesperson indicated that due to the concerns raised by the six evaluators, Health Canada had set up two expert panels consisting of medical doctors from the Royal College of Physicians and Surgeons and veterinarians from the Canadian Veterinary Medical Association. To be continued ...

On a less contentious matter, one of the recommendations contained in the Transition Team's report entitled "*Keeping Faith with Canadians*", authored by the Laboratory Science Review Committee, is to "*develop and implement appropriate internationally recognized quality management systems (e.g. ISO/IEC Guide 25) across HPB laboratories in order to become accredited by a qualified party*" (i.e. The Standards Council of Canada). A business plan is being drafted with the hopes that HPB will achieve ISO/IEC Guide 25 accreditation on or before January 1, 2001. There has also been some talk that, if ISO accreditation is achieved, that this could possibly serve as a base from which a Good Laboratory Practices "management system" might be developed.

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BOOK REVIEW

Don Ecobichon

"Pest Control" by Bill Fitzhugh, New York: Avon Books, 1996. pp 310, Can \$7.99

This is one of the funniest books that I have read in a long time. I read it on a long flight to Chile recently, my chuckles arousing the curiosity of the in-flight attendants. The hero is a down-on-his-luck New York bug exterminator who finally refuses to use a triple dose of parathion to kill cockroaches in a building and gets fired for taking this position. His firing also might have had something to do with the fact that the nozzle of his sprayer was up the left nostril of his nasty supervisor at the time. The hero is a true entomologist, looking for the optimal biological control too, busily breeding and cross-breeding assassin bugs with other voracious predators in attempts to create the ultimate killing machine. He goes into business for himself, developing a flyer with the title "Exterminator". Quite by accident, this is seen by a Frenchman who is the go-between for people who want others killed and assassins for hire. You get the picture now? Completely misunderstanding one another, the first contract to get rid of someone is successful - the intended victim managing to kill himself in an car accident, to the delight of his family who wanted him dead. Success follows success without our hero ever leaving New York. The world's supply of contract killers come gunning for him because he is bad for their business. While dodging these murderers, our hero is experimenting with his hybrid insect assassins, with hilarious results. Lots of entomological terms, used correctly, regarding species, some good information on house hold pests, some subtle references to insecticide toxicology and some good jokes, e.g. what is the last thing a bug sees when it hits your windshield? Its rear end. It may be a bit difficult to find although it can be ordered through any bookstore, but it is worth the effort. It sits on my shelf beside Casarett and Doull.

COFFEE AND LONG TERM MEMORY

Michael Prior

A recent article examined the inverse relationship between the financial health of the university and the quality of the coffee it serves (Joseph, D. A Second Cup at Starbucks. *STC NEWS/NOUVELLES* XVII (I):12. 1998). Might there also be a relationship between coffee and long-term memory?

Memory storage includes a short-term phase (STM) which requires the phosphorylation of pre-existing proteins and is protein synthesis independent, and a long-term phase (LTM) which is dependent upon the novel synthesis of RNA and proteins (Yin JC *et al.* Induction of a dominant negative CREB transgene specifically blocks long-term memory in *Drosophila*. *Cell* 79(1):49-58. 1994). Cyclic AMP response element binding protein (CREB)-responsive transcription plays a central role in the formation of long-term memory in *Drosophila*, *Aplysia* and mice (Yin JC & Tully T. CREB and the formation of long-term memory. *Curr. Opin. Neurobiol.* 6(2):264-268. 1996).

The protein kinase A pathway and CREB appear to play a critical role in the consolidation of short-term changes in neuronal activity into LTM storage. Memory storage is mediated not only by positive but also by negative regulatory mechanisms, analogous to cell division control through proteins encoded by oncogenes and tumour suppressor genes. This suggests that there are memory suppressor genes whose protein products impede memory storage (Abel T & Kandel E. Positive and negative regulatory mechanisms that mediate long-term memory storage. *Brain Res. Brain Res. Rev.* 26(2-3):360-378. 1998). Agents that disrupt the activity of CREB specifically block formation of LTM. Conversely agents that increase the amount or activity of CREB increase LTM.

Some of us are familiar with "benign senescent forgetfulness" (as opposed to severe dementias such as Alzheimer's), perhaps in ourselves, friends, family members or even colleagues. It has been suggested that this condition is in part the result of deterioration in the production of activator CREB, which has a positive effect on LTM. Observations that middle-aged people drink twice as much coffee as everyone else is tempting evidence in support of the reduction of benign senescent forgetfulness through the consumption of coffee, effected by counter-acting deterioration in the production of activator CREB. Of course, coffee's effects on memory, memory performance and coordination as well as anxiety and sleep are well known (Nehlig A *et al.* Caffeine and the central nervous system: mechanisms of action, biochemical, metabolic and psycho stimulant effects. *Brain Res. Brain Res. Rev.* 17(2): 139-170. 1992).

So where does that Second Cup at Starbucks fit in all this?

- The university faculty population is ageing, and
- Coffee counters forgetfulness and enhances LTM.

Therefore, it would seem that providing good quality coffee would enhance efficiency, effectiveness and productivity of faculty members. At the personal level, the Second Cup enhances our second wind. At the university level, administration gets a bigger bang for the Starbucks.

I rest my case.

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CYANIDE AGAIN

In the New Year, there was a report that a man found dead in Agatha Christie's favourite hotel had died from cyanide poisoning (*The Province* Jan 26, 998, pA22). He was found in room 131 of Torquay's Grand Hotel, where Dame Agatha spent her wedding night on Christmas Eve 1914. The detectives on the case said cyanide *"is very, very rare these days. It's something we haven't seen since the early 1900s."*

Maybe not in Devon, England, but a cancer patient in California was caught stuffing 100 envelopes with cyanide packaged to look like free samples of a nutritional supplement (*Vancouver Sun*, August 25, 1998. pA8).

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CANADIAN INSTITUTES FOR HEALTH RESEARCH: The biggest new idea in Canadian science in a generation

David Josephy

How should the Canadian government spend its "fiscal dividend", now that the deficit has been brought to zero (and assuming that the world economy does not "tank" in 1999)? Many government departments are vying for a place in line when the much-anticipated cheques are handed out. A Task Force established by the Medical Research Council is developing the concept of "CIHR" or the Canadian Institutes of Health Research. The idea is to provide the government with a well-founded plan for spending hundreds of millions of dollars of "new" money on Canadian health

research. The concept was presented to the Minister of Health in March and is now being developed further, with a view to funding in the next federal budget, to be presented early in 1999. Politically, the plan has an obvious attractive feature: it allows the federal government to make a huge and politically-attractive investment in Health Care, without stepping on provincial toes --- because the investment would be in health RESEARCH, a field which is clearly within federal jurisdiction.

The dream is to boost annual health research spending from the present \$250 million range to about \$750 million. This proposal will be simplified with the slogan "I'm 100% for 1%", that is, "I support spending 1% of total Canadian health care expenditures (\$76 billion) on health research". This slogan is going to be the basis of a big publicity campaign towards the end of 1998, as the political decisions are being made in Ottawa.

If funded, the CIHR would pump a vast amount of new money into health research programs across Canada, with the priority being personnel support and research grants, not buildings and equipment. The CIHR would NOT be a "campus", like NIH USA, but would be a set of "virtual" institutes, centred at the medical schools across Canada and radiating out to other institutions. Efforts are now being made to reach out to other branches of government, to the pharmaceutical industry, to private charitable organizations like NCIC, and to other interested parties, and to obtain their active support for CIHR.

You can expect to hear a great deal more about this bold new proposal very soon. A Web site is being created at <http://www.cihr.org/> and I urge everyone to have a look and get involved in this initiative. If it is successful, it will be the biggest new development in Canadian science in decades - much bigger in scope even than the NCEs or the recently-funded CFI programme.

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BOVINE SOMATOTROPIN

EDITOR'S NOTE. This Executive Summary was downloaded from the Web site of the National Farmers Union at <http://www.nfu.ca/>, please go there for the rest of the report, which was the subject of an interview on CBC Radio One. If anyone can validate this report or wishes to comment on it, please contact the Editor./P>

Executive Summary

... genetically engineered bovine growth hormone (BGH), technically called recombinant bovine somatotropin (rBST), is a uniquely controversial veterinary product throughout the world. Approved by US FDA but not yet approved by Health Canada and several other national regulatory agencies, it is claimed to increase the average milk yield in dairy cows by 10-15 percent. The reason

for this report is to determine whether the required human safety review and evaluation for this drug were adequately addressed and, if not, to provide a critical "gaps analysis" of same.

Both procedural and data gaps were found which fail to properly address the human safety requirements of this drug under the Food and Drugs Act and Regulations. The question of the oral absorption of rBST and IGF-1 was not adequately addressed.

Evidence from the subchronic rat study submitted by Monsanto had shown that rBST was absorbed intact from the GI tract following oral administration, albeit at high doses, and elicited a primary antigenic response (IgG antibodies). The full immunological and potentially toxicological consequences of this observation were not investigated.

IGF-1 also can survive the GI tract environment to produce local effects. Under exposure conditions, which would mimic the human scenario (i.e., in milk), IGF-1 appears also to be absorbed intact from the GI tract. The full significance of this finding also was not investigated.

In addition, based on the proposed label supplied by Monsanto, the increased risk of mastitis that may be associated with the use of rBST (Nutrilac) has human health implications (antibiotic resistance in farm-borne human pathogens).

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SMOKING

When will people learn? Young people in Kelowna, BC, have been smoking some wild weeds, enough to land at least one of them in hospital overnight. He had been smoking *Datura stramonium* or jimson-weed (*Vancouver Sun*, Oct 3, 1996. B7).

Jimson weed has narcotic and hallucinogenic properties, including blurred vision and unconsciousness. It is usually smoked or drunk as an infusion. Rarely, the victim dies. The entire plant is toxic, including the nectar; but the seeds and dried leaves are used most often for their deliriant effect.

Interestingly, there is a condition known as "cornpicker's pupil", a mydriasis that may occur when operating farm machinery in cornfield containing jimson weed. Enough hyoscyamine and related parasympatholytic substances from the plant can reach the eye to dilate the pupil over a period of days (Goldey *et al.* Cornpicker's pupil: a clinical note regarding mydriasis from Jimson weed dust (*Stramonium. Ohio State Med. J.* 62:921. 1966).

NEWS OF STC MEMBERS

Dr Tee Guidotti, a long time member of STC, will be leaving his position as Professor of Occupational and Environmental Medicine in the University of Alberta Faculty of Medicine at the end of 1998. He will be going to George Washington University, in Washington DC, to head their Department of Environmental and Occupational Medicine. All the best, Tee.

CONFERENCES, MEETINGS AND WORKSHOPS

1998

Nov 23 - 28: X Congreso Latinoamericano de toxicologia IRA Reunion de directores de centros de toxicologia de america latina, Cuba. Contact: Lic Zosima Lopez Ruiz, Organizadora Profesional de Congresos, Palacio de Convenciones de la Habana, Apartado postal 16046, Cuba.

Dec 4-5: Thirty-First Annual Symposium, Society of Toxicology of Canada. Holiday Inn Montreal Downtown, Montréal, Québec. Contact: Society of Toxicology of Canada, P.O. Box 517, Beaconsfield, Québec H9W 5V1. Tel: 514-428-2676, Fax: 514-428-4946.

1999

Jan 16-23: Clinical Toxicology Short Courses, Adelaide, Australia. Contact: "Clinical Toxicology Short Courses", c/o Hyperbaric Medicine Unit, Royal Adelaide Hospital, Adelaide SA 5000, Australia. WebSite: <http://www.wch.sa.gov.au/paedm/clintox/index.html>

Feb 1-3: Advanced Industrial Hygiene Chemistry, Salt Lake City, Utah, USA. Contact: Registration Coordinator, The Rocky Mountain Center for Occupational and Environmental Health, 75 South 2000 East, University of Utah, Salt Lake City, Utah 84112, USA

March 14-18: Society of Toxicology Annual Meeting, New Orleans, Louisiana. For information or registration, contact: SOT HQ, Tel: 703-438-3115 or Fax: 703-438-3113

April 12-16: Xvth World Congress on Occupational Safety and Health. Sao Paulo, Brazil. Contact: Secretaria XV Congresso Mundial Sobre Seguranca e Saude no Trabalho Fundacentro, Rua Capote Valente 710, 05409-002 Sao Paulo, Brazil

April 19-22: Ninth Symposium on Environmental Toxicology and Risk Assessment. Recent achievements in environmental fate and transport. Seattle, Washington, USA. Contact: Fred T. Price, Booz-Allen & Hamilton, Inc, 8283 Greensboro Drive, McLean, VA 22102, USA. E-mail: price_fred@bah.com

May 2-7: 10th International Symposium on Trace Elements in Man and Animals, Evian, France. Contact: A. Alcaraz, Laboratoire de Biochimie C, Hopital Albert Michallon, BP 217-38043 Grenoble cedex 9, France. E-mail: ane-marie.rousseau@ujf-grenoble.fr

June 2 - 5: Canadian Federation of Biological Societies, Winnipeg, Manitoba.

June 6-8: Third Colloquium on Particulate Air Pollution and Human Health, Durham, North Carolina, USA. Contact: Ms Toni Moore, Planning Coordinator, Department of Environmental Medicine, New York University School of Medicine, 57 Old Forge Road, Tuxedo NY 10987, USA. E-mail: moore@charlotte.med.nyu.edu

June 13-17: 18th International Symposium of the Society of Toxicologic Pathologists. Toxicologic Pathology of the Central Nervous System. Washington DC, USA. Contact: STP Registration, 19 Mantua Road, Mt. Royal, New Jersey 080061, USA

June 27-30: Eurotox '99. 37th Congress of the European Societies of Toxicology. Oslo, Norway. Contact: Erik Dybing, National Institute of Public Health, Department of Environmental Medicine, PO Box 4404 Torshov, N-0403 Oslo, Norway

July 4-10: 7th International Neurotoxicology Association Meeting, University of Leicester, UK. Contact: Dr David Ray, MRC Toxicology Unit, Hodgkin Building, Lancaster Road, Leicester LE1 9HN

August 22-26: 7th European ISSX Meeting, Budapest, Hungary. Contact: ISSX Office, PO Box 3, Cabin John, MD 20818, USA.

Sept 28-Oct 5: 1999 North American Congress of Clinical Toxicology. La Jolla, CA, USA. Contact: Registrar, Contemporary Forums, 11900 Silvergate Drive, Dublin CA 94568-2257, USA.

Oct 10 - 13: 7th International Symposium on Particle Toxicology, Maastricht, The Netherlands. Contact: Conference Agency Limburg, P.O. Box 1402, 6201 BK Maastricht, The Netherlands. Tel: +31-(0)43-361-91-92 Fax: +31-(0)43-361-90-20 e-mail: cal.conferenceagency@pi.net

Oct 24-28: 9th North American ISSX Meeting, Nashville, Tennessee, USA. Contact: ISSX Office, PO Box 3, Cabin John, MD 20818, USA.

Nov 6-10: 4th Congress of Toxicology in Developing Countries, 4th CTOX-DC, Antalya, Turkey. Contact: Prof. Dr. Semra ardas, (4th CTOX-DC), Gazi University-Faculty of Pharmacy Toxicology Department (Eczacilik) Hipidrom 06330 Ankara, Turkey.

December: Thirty-Second Annual Symposium, Society of Toxicology of Canada, Montréal, Québec.

2000

March 13-16: Society of Toxicology Annual Meeting, Philadelphia, Pennsylvania. For information or registration, contact: SOT HQ, Tel: 703-438-3115 or Fax: 703-438-3113

June 24-28: 15th International Symposium of the Society of Toxicologic Pathologists. Reproductive Biology/Endocrine Disrupters. Phoenix, Arizona, USA. Contact: STP Registration, 19 Mantua Road, Mt. Royal, New Jersey 08061, USA.

Sept 17-20: 38th Congress of the European Societies of Toxicology. Contact: Alan Boobis, Imperial College, London W12 0NN, England.

December: Thirty-Third Annual Symposium, Society of Toxicology of Canada.

2001

March 25-29: Annual Meeting of The Society of Toxicology. San Francisco USA. Contact: SOT, 1767 Business Centre Drive, Suite 302, Reston, Virginia 22090-5332, USA.

June 24-28: 20th International Symposium of the Society of Toxicologic Pathologists. Orlando, Florida USA. Contact: STP Registration, 19 Mantua Road, Mt. Royal, New Jersey 08061, USA.

July 8 - 13: Ninth International Congress of Toxicology, ICT-IX, Brisbane, Australia. Contact: Congress Secretariat, Intermedia Convention and Event Management, 11/97 Castlemaine Street, P. O. Box 1280, Milton, QLD 4064 Australia. Website: <http://www.uq.edu.au/ICT9> or e-mail: ictix2001@im.com.au

December: Thirty-Fourth Annual Symposium, Society of Toxicology of Canada.

2004

July: Tenth International Congress of Toxicology, ICT-X, Tampere, Finland.

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