President’s Message

by Timothy Pastoor, PhD, DABT

When the past-past president, Jim Lamb approached me a couple of years ago with the opportunity to join the RSESS leadership, I have to confess that I knew little about RSESS. I paid my dues and went to a couple of annual meetings at the SOT, but never connected with the role RSESS plays in our professional lives until I joined the leadership team for RSESS as vice-president elect two years ago. In the intervening years I discovered a lot about RSESS. Each year gave me a better chance at seeing what RSESS does and what it could do. I can recount this year-by-year education through my experiences – a cook’s tour, if you will, of the RSESS leadership team.

I first discovered that there is an orderly process for learning the RSESS “ropes” by progressing from vice-president-elect to vice-president last year, and now to president. As vice-president-elect I got my one year to sit back and watch Jim Lamb and Brian Short organize meetings, decide how best to keep RSESS running smoothly, and think hard about ways to continuously improve RSESS.

Last year, as vice-president, I helped Brian and the RSESS leadership team initiate our by-laws review, coordinate the student travel awards, and watch in awe as Jim Lamb pulled together a Great Debate on Capitol Hill that had to be the best one yet. We are sorry to see Jim go out to pasture and Brian recede in his role, but I’m sure they will both keep a hand in RSESS. Now, as president of RSESS, I feel the weight of office compelling me to sustain and improve the largest specialty section in SOT.

What I learned is that RSESS does at least five things on behalf of the membership. I’ll list them here and at the end of each area ask what you can do on behalf of RSESS:

- **Enlist the next crop of officers:** We welcome our vice-president elect, Daland Juberg (Dow AgroSciences) to our succession in leadership. We thank Cindy Afshari (Amgen) for her diligent work as secretary/treasurer and welcome former councilor Nancy Beck (Office of Management and Budget) into this important role. Succeeding Nancy as councilor is David Ackley (Pfizer). We also thank former student representative Tom Simones (University of Montana) who is succeeded by post-doctoral representative Michael Boyle (NIH) and graduate student representative Marcy MacNamara (University of Connecticut). If you would **like to serve in one of the RSESS roles, please let us know!** OK, the pay isn’t great ($0/hour), but being engaged in the leadership of a specialty section and, indeed, in the governance of SOT is personally rewarding and a professional feather in your cap. (Continued on page 2)
RSESS MISSION

The mission of the Regulatory and Safety Evaluation Specialty Section (RSESS) of SOT is to promote the development of sound governmental policies and regulations based on contemporary scientific knowledge arising from the disciplines encompassed by toxicology. RSESS provides a forum for the interaction of SOT members to discuss the impact of regulations, guidelines, and guidelines on the practice of toxicology and the safety evaluation of food additives, nutraceuticals, therapeutic drug products and environmental, industrial and household chemicals, and other products of concern.

President’s Message (cont’d from page 1)

- **Sponsor the annual meeting at the SOT (including the Great Debate):** This is a chance for members to network, see the student and post-doc travel awardees, enjoy food and drink, and watch the Great Debate. In this summer’s edition of the RSESS newsletter you will find a stirring synopsis by Michael Boyle of the outstanding Great Debate held at the 2011 SOT meeting. *We are looking for good ideas for next year’s Great Debate, so if you have ideas, let us know!* Don’t be bashful about popping an email to any of us (look for our email addresses in the sidebar).

- **Select student and post-doctoral travel funds awardees.** Each year the RSESS awards approximately six checks to post-docs and students for travel to the SOT. This $1500 award is very competitive and the awardees come from over two dozen applicants. However, I’m not sure everyone knows about this generous award, and if they are, where to find the forms to apply. *Please take a moment and let others know about RSESS’s offering of travel funds.* Perhaps you might consider sending a note to your graduate program. Maybe you know of specific graduate students or post-docs who could benefit from RSESS’s generosity. In any case, let’s see if we can publicize our award as broadly as possible. Please see the SOT awards page (http://www.toxicology.org/ai/af/awards.aspx) and the RSESS awards page (http://www.toxicology.org/ISOT/SS/regulatorysafety/Awards.asp) for more information.

- **Identify proposals for the next year’s SOT that are worthy of RSESS support:** Each year, right after the SOT meeting, the RSESS leadership team convenes to consider which proposals to support for next year’s meetings. The proposals may be for a symposium, workshop, roundtable, or update. This is an arduous task made easier by the long-suffering work of Susan Hart (Intrexon Corporation) who organizes the proposals and provides the leadership team with a head start on selecting proposals to support. This is a very important part of the SOT governance process. Many proposals are received by SOT, but there is limited room on the SOT meeting agenda. Therefore, each specialty section is asked to go through the proposals and rank their willingness to sponsor. I was not aware of this multi-step process to get a proposal accepted until I became an officer in RSESS. Now that I know, I feel the need to let you know that *if you have a good idea for a symposium, workshop, or other session at SOT, please approach an RSESS officer and ask how best to get that idea accepted.*

(continued on page 3)
President’s Message (cont’d from page 2)

- **Communicate to the membership via these newsletters:** In the digital, sound-bite age, perhaps these newsletters are a bit archaic. On the other hand, these periodic updates serve a purpose to let you know, in one place, what’s going on in RSESS. You can see the list of officers in the sidebar, you can get an update on RSESS activities, and we try and spice up the content with some late-breaking news. You’ll find all that in this edition because of the hard work and dedication of the leadership team. We hope you find this newsletter useful and enjoyable. If you have any suggestions on improving the RSESS newsletter, please let us know.

I have learned a lot about RSESS in the past two years: it is orderly and it clearly serves as a rallying point for those of us interested in issues regarding regulatory safety. I am very pleased and honored to be president of RSESS for 2011-2012 and will strive along with an outstanding leadership team to make sure your specialty section functions in a way that works for you. Please let us know ways to make it even better.

**PAST PRESIDENT’S MESSAGE**

By Brian Short, DVM, PhD, DACVP

I am looking forward to my next phase as ‘out to pasture’ President of the Regulatory and Safety Evaluation Specialty Section. I am pleased to see that membership has elected a very strong team; you all are in capable hands with Dr. Tim Pastoor as President. I am sure you agree it was a memorable 50th Anniversary SOT meeting for all, especially the RSESS Reception and meeting Monday March 7th on Capitol Hill featuring the Great Debate (see article on page 4). Although not attended by Senator Johnny Isakson (R-GA) and congressional staffers, this did not detract one iota from the historical venue, excellent speakers, and stimulating topic that was spearheaded by Former RSESS President Dr. Jim Lamb and attended by many including SOT executive officers.

Last summer Dr. Lamb reflected on the strength of our scientific session and the importance of the RSESS Program Chair and Committee in reviewing the numerous session proposals. RSESS Program Chair Dr. Susan Hart and her capable committee volunteered to help out during those busy weeks. Dr. Lamb suggested that the Program Chair be recognized by the RSESS as an official member of our Executive Committee. I am working on helping revise By-Laws for your vote to do just that, and you should be receiving an email to vote for this important change to our By-Laws later this year. Just as importantly, I am helping to revise our By-Laws to recognize Student and Postdoctoral members of the Executive Committee. This year we welcomed our new Student (Marcy McNamara) and Postdoctoral (Michael Boyle) Representatives to our group and will hopefully formalize the selection and responsibilities of these positions in the same By-Laws ballot.

Thanks again to your support for a great experience in leading RSESS the past year. I’m happy our group is getting stronger and confident that our Executive Committee will build upon the success that we enjoyed the past year.
March 2011 RSESS Great Debate: "Hazard information provides an adequate basis for restricting chemical use"

by Mike Boyle, DVM DACVP

On the beautiful afternoon of March 7th, 2011, busloads of eager SOT 50th Anniversary Meeting attendees descended upon the Russell Senate Office building for the annual Regulatory and Safety Evaluation Specialty Section Great Debate. The attendees filed through the marble and limestone entrance of the first US Senate Office Building, which finished construction in 1909, and ascended the grand staircases to the Kennedy Caucus Room with the beautiful rotunda roof overhead.

Attendees and participants alike gave heartfelt thanks to Senator Johnny Isakson (R-GA), George Corcoran, head of the SOT Congressional Task Force, as well as our own Dr. James Lamb, for making this landmark event a reality. Sen. Isakson was the SOT Congressional Science Leadership Award recipient, and he and his staff graciously hosted this historic event.

The Debate attendees were fortunate this year to be entertained by such eloquent, clever, and passionate debaters: Drs. Lorenz Rhomberg of Gradient Corporation and George Gray of George Washington University. Referencing other famous investigations and caucuses that had taken place in the Kennedy Caucus room, including Watergate, Teapot Dome, and McCarthy, Dr. Lamb quipped: "My guess is, they are going to add Lorenz Rhomberg and George Gray to this list, because what you're going to hear is scandalous!" Dr. Lamb's comment was certainly tongue-in-cheek, and set the stage for the very entertaining yet informative debate that followed. As you will learn, Drs. Gray and Rhomberg had the audience alternately engaged in policy postulations one moment and roaring with laughter the next.

As an introduction to the scandal, the topic for debate this year was "Hazard information provides an adequate basis for restricting chemical use". This topic was certainly timely, as restricting chemicals based on hazard is a topic of discussion in the United States Congress, which is considering amending the Toxic Substances Control Act. Within weeks of the RSESS Great Debate, the French National Assembly, based entirely on hazard information in an act that defies the European Union-wide chemical control regulation (REACH), banned an entire chemical class, including phthalates, parabens, and alkylphenols.

As is always the case with the RSESS Great Debate, a flip of the coin decides on which side of the contentious issue the expert debater finds themselves. This year, Dr. Gray defended the notion that hazard information provides an adequate basis for restricting chemical use, while Dr. Rhomberg promoted relative risk-based and risk assessment evaluation-based approaches, in addition to hazard information, for imposing restrictions.

Dr. Lamb began the debate with a plea for peace, and the statement "Nothing that they say can or should be used against them". He then gave a grave warning should either speaker exceed their allotted time and with that, he gave the podium over to the first debater, Dr. Gray. (story cont’d. on page 12)
The Standard for the Exchange of Nonclinical Data (SEND)

by Lorrence A Buckley, PhD, DABT

The contents of this article are derived from a draft manuscript authored by Lou Ann Kramer (Eli Lilly & Company) and Fred Wood (Octagon Research Solutions).

SUMMARY: A new standard for electronic formatting of nonclinical data, SEND Version 3.0, was released by the CDISC/SEND team on 17 June 2011. It is anticipated that FDA CDER will provide additional information yet this year, about the submission of nonclinical study data, especially for general toxicology and carcinogenicity studies.

IMPACT: The SEND project is designed to promote more efficient, higher-quality regulatory submissions through the establishment of one standard for electronic submission of nonclinical data.

- SEND-formatted datasets will be submitted instead of (or in combination with) PDF files
- FDA will be able to review and evaluate SEND formatted datasets instead of PDF files and will be able to replicate a sponsor’s tables and graphs and view or subset any data
- SEND should reduce regulatory review time, increase reviewer efficiency, and enable more precise communications between sponsors and FDA reviewers
- SEND supports FDA’s efforts to develop a repository for all data, both clinical and nonclinical but will also allow effective data mining for sponsors and CROs making possible virtual studies to predict outcomes based on historical data and facilitating collaborative inter-industry efforts to interrogate information across boundaries

BACKGROUND: In the early 2000s, a new standard for electronic formatting of clinical data developed by CDISC (Clinical Data Interchange Standards Consortium) was emerging, and work began to model nonclinical domains from the FDA Guidance (1) to be consistent with the clinical data standard. In early 2003, a SEND Team was formed consisting of more than fifty volunteers from the pharmaceutical industry, vendors, and CROs. The submission of nonclinical data in an electronic format had not been widespread with the exception of the tumor.xpt Tumor Analysis dataset for carcinogenicity studies. The idea of submitting data in electronic format on a regular basis was new (and maybe even scary) to more than a few people at the time.

For the initial FDA Pilot Project, the SEND model contained domains for data collected in repeated dose toxicity studies and carcinogenicity studies. A small subteam then worked to model safety pharmacology data domains. The main focus of this subteam - to determine how easily data modeled according to the SDTM could be utilized for statistical analysis – was a success (2).

Subsequent efforts were made to improve consistency with the Implementation Guide for Human Clinical Trials. For example, there was a need to address more complicated trial designs for safety-pharmacology (e.g., Latin square) and reproductive toxicity studies (e.g. to incorporate staggered timing of the phases of gestation and weaning within treatment groups and maintenance of parent-offspring relationships through multiple generations). Specifications were developed for a regulatory (live submission) pilot which involved eight sponsor companies who submitted nonclinical data to an IND or NDA in both the current PDF format as well as the electronic SEND format.

Based on the collaborative efforts of the SEND Team and FDA and learning from the regulatory submission pilot, the SEND Implementation Guide is now released (3). It is anticipated that SEND will begin to be used in regulatory submissions as early as 4Q2011.

References:

What's new at the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)?

by Paul Brown, PhD

Plenty!

The ICH M3(R2) document provides invaluable guidance for anyone working in the area of toxicology in support of pharmaceutical development. Since this revised version of the guidance was published in the Federal Register in January of 2010, a variety of questions have arisen related to its implementation. The implementation working group for this guidance has been crafting answers to a number of questions related to areas such as testing of drug metabolites, the use of limit doses in toxicity studies, the assessment of combination drug products and the nonclinical studies necessary to support early exploratory clinical trials. The working group finalized several sets of questions and answers at the ICH meeting in June 2011 and these should be posted to the ICH website soon. More topics will be discussed over the next year.

Work has begun on a few new ICH guidances that will also be of interest to pharmaceutical toxicologists. A working group has been formed to gather information, discuss and begin drafting a guidance on the photosafety evaluation of pharmaceuticals (S10). The US FDA and the EU currently have separate guidance in this area. The ICH M3(R2) and S9 guidances also have sections that address photosafety testing. However, some ICH parties are seeking further harmonization and more specific guidance in this area. The working group will be examining data to assess the utility of different photosafety testing paradigms that include photochemical methods and in vitro and in vivo assays.

Work on two other ICH guidances related to drug impurities has also been initiated. The ICH M7 guidance will focus on the assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk. A variety of topics will be discussed as this guidance is developed such as the role of QSAR evaluations and the use of a threshold of toxicological concern (TTC). Another guidance (Q3D) will assess the available safety data to set permitted daily exposure levels for metal impurities in drug products. Other ICH impurity guidances do not specifically address metals. The Q3D working group will evaluate available toxicity data for various metals and derive acceptable limits for pharmaceutical products.

The ICH S6 guidance provides advice on the nonclinical safety evaluation of biotechnology-derived pharmaceuticals. A number of questions about this guidance were raised over the years since it was approved in 1997. An expert working group has written an addendum to ICH S6 which clarifies a number of the topics covered in this guidance. The working group has agreed on final wording for the addendum and it is expected to be published shortly.

There are always topics being considered under the ICH process that can have significant impact on the practice of toxicology in pharmaceutical development. Stay tuned for more developments! See the ICH website for information (http://www.ich.org/home.html).
Principles on Emerging Technologies and Nanotechnologies

by Nancy B. Beck, PhD, DABT

It has been a busy year for the Emerging Technologies Interagency Policy Coordination Committee (ETIPC). Created jointly by White House Office of Science and Technology Policy (OSTP), the Office of Management and Budget’s Office of Information and Regulatory Affairs (OIRA), and the Office of the United States Trade Representative (USTR), the ETIPC consists of assistant secretary-level representatives from about 20 Federal agencies.

On March 11, 2011 the ETIPC chairs released a memorandum to the heads of executive departments and agencies outlining broad principles to guide the development and implementation of policies for oversight of emerging technologies at the agency level (see: http://www.whitehouse.gov/sites/default/files/microsites/ostp/etipc-memo-3-11-2011.pdf). The Principles reflect the Committee’s goal of striking a balance in which novel technologies are subject to oversight that is adequate to protect public health and the environment but not so daunting as to unduly slow innovation or the development of those new technologies. To advance this goal, the memorandum lays out principles in the following categories:

- Scientific Integrity
- Public Participation
- Communication
- Benefits and costs
- Flexibility
- Risk Assessment and Risk Management
- Coordination
- International Cooperation
- Regulation

To assist in realizing the full potential of nanotechnology, a set of principles specific to the regulation and oversight of nanotechnologies was released on June 9, 2011 (see: http://www.whitehouse.gov/sites/default/files/omb/inforeg/for-agencies/nanotechnology-regulation-and-oversight-principles.pdf). These principles also reflect recommendations from a report on nanotechnology by the President’s Council of Advisors on Science and Technology (see: http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-nni-report.pdf). The report encourages Federal support for the commercialization of nanotech products and calls for the development of rational, science- and risk-based regulatory approaches that would be based on the full array of a material’s properties and their plausible risks and not simply on the basis of size alone.

Among the goals of all of these documents is the achievement of consistent approaches across different emerging technologies and to ensure the protection of public health and the environment while avoiding unjustifiably inhibiting innovation, stigmatizing new technologies, or creating trade barriers.

Federal agencies have started to release draft policies and guidelines aimed at providing greater regulatory certainty around nanotechnology. For instance, FDA, released draft guidance relating to considering when an FDA-regulated product involves the application of nanotechnology and EPA recently proposed, for public comment, a policy on nanoscale materials in pesticide products. More information on these actions is available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm258377.htm and http://yosemite.epa.gov/opa/admpress.nsf/o/05ff063e9205eb3e852578aa005aa0f8?OpenDocument.
SOT CCT Meetings Eligible for Seed Money and Profit Sharing

SOT Sponsors two types of meetings outside of the SOT Annual Meeting: Contemporary Concepts in Toxicology (CCT) and Non-SOT meetings. CCT meetings are one- to two-day focused, open registration, scientific meetings in contemporary and rapidly progressing areas of toxicological sciences. Non-SOT meetings are sponsored by other not-for-profit organizations and SOT will either endorse or provide sponsorship money to toxicology-related meetings.

The Society will underwrite all the liabilities of the CCT meeting with the expectation that the meeting will at least break even financially. The goal of providing $25,000 seed funds is to stimulate the creation of CCT meeting proposals.

For more information about CCT meetings, please visit the SOT Web site.
2011 RSESS Student and Postdoctoral Travel Awardees

by Paul Brown, PhD

Six awardees were each given $1500 by the RSESS to defray costs to this year's Annual meeting in Washington, D.C. RSESS president, Dr. Tim Pastoor presented the monetary awards along with commemorative plaques to the recipients during the RSESS annual meeting which was held in the historic Kennedy Caucus Room of the Russell Senate Building on Capitol Hill.

The RSESS executive council selected three graduate students and three post-docs as recipients. The application process was highly competitive and the winners were selected based on the quality of research, relevance to the RSESS, the applicant's description of their work and letters of support.

The RSESS leadership looks forward to reviewing another slate of highly qualified candidates for the 2012 awards and encourages candidates to check the SOT website for application information. Please see the SOT awards page (http://www.toxicology.org/ai/af/awards.aspx) and the RSESS awards page (http://www.toxicology.org/ISOT/SS/regulatorysafety/Awards.asp) for more information.

Postdoctoral Fellow Travel Awardees:

Anna Grosberg, PhD: “Novel In Vitro Approach For Assessing Cardiac Contractile Liabilities Using Micropatterned Muscular Thin Films” Harvard University, WYSS & SEAS. Research Summary: We present a novel in vitro approach to assessing the affect of drugs and toxins on the contractile properties of cardiac muscle. In this new technology we utilize micropatterning, providing the cardiomyocytes with in vivo like microenvironments on a tissue scale. The tools we are developing in the lab will be applicable for use with both primary neonatal cells and iPS derived myocytes, which will let pharmaceutical companies screen for cardiac toxicity in human myocytes.

Kyung-Jin Jang, PhD: “Kidney Proximal Tubule-on-a-Chip for Drug Transporter Studies and Nephrotoxicity Assessment” Harvard University, WYSS Institute. Research Summary: Using our renal tubule-like microfluidic device, we can analyze renal drug transporter expression, specific markers of proximal tubule function, and effects of known nephrotoxic compounds. Furthermore, our novel system may provide a useful and cost-effective tool for studying biotransformation profiles, renal pharmacology, renal drug transport and toxicity relevant to the human kidney, and hence help to facilitate the drug development process.

Jie Zhang, MD, PhD: “Acute oral toxicity studies of a new pesticide-AMTS18 in mice”. Mayo Clinic, Molecular Pharmacology and Experimental Therapeutics. Research Summary: Soybean and green peach aphids are devastating pests to the North America. For example, in 2003 aphid populations exceeded 3,000 aphids per plant in many fields of Iowa. During this year, Iowa soybean yields averaged 32 bushels per acre—a 16 bushel per acre (or a 32%) reduction from 2002. Minnesotan farmers have planted >6,300,000 acres for soybean in 2007. Controlling soybean aphids in the huge soybean field requires pesticides at quantities toxic to mammals, while green peach aphids are resistant to current pesticides. There is an urgent need for a human-safe pesticide that is so effective that a tiny amount of the new pesticide is effective enough to incapacitate soybean and green peach aphids. Conceptually, this need can be met by developing an irreversible inhibitor that specifically acts on a unique and conserved molecular target in aphids. A recent paper from our laboratories (Pang Y-P, PLoS ONE 4(2): e4349, 2009) reported a newly developed methanethiosulfonate-compound, AMTS18 that could selectively and irreversibly inhibit insect acetylcholinesterase (AChE). Therefore, the purpose of our study is to determine whether methanethio-sulfonates in general should be expected to exhibit unacceptable non-specific toxicity in mammals, and our study shows that AMTS18 exerts no detectable toxicity even at the high dose of 300mg/kg delivered by the gavage route and it is worth exploring equally selective but more potent methanethiosulfonates as insect-targeting pesticides with reduced risk to mammals. (awardee’s cont’d on page 10)
Graduate Student Travel Awardees

Corie Ellison*: “Construction and validation of a human PBPK/PD model for dermal chlorpyrifos exposure utilizing human biomarker data”. The State University of New York at Buffalo, Pharmacology and Toxicology. Research Summary: Chlorpyrifos (CPF) is a widely used organophosphorus pesticide (OP) that is metabolized to chlorpyrifos-oxon, a potent cholinesterase (ChE) inhibitor, and trichloro-2-pyridinol (TCPy). Urinary TCPy is often used as a biomarker for CPF exposure while blood ChE activity is considered an indicator of CPF toxicity. Daily urine samples and weekly blood samples were collected from pesticide workers in Egypt’s Menoufia Governorate (n=37) before, during and after 9-17 consecutive days of CPF application to cotton fields. Blood butyrylcholinesterase (BuChE) and acetylcholinesterase (AChE) activities were compared with the respective urinary TCPy concentrations in each worker. Our findings are the first to demonstrate a dose-effect relationship between urinary TCPy and both plasma BuChE and RBC AChE in humans exposed occupationally to CPF. Additionally, by utilizing the human exposure and effect biomarker data, a human PBPK/PD model for dermal CPF exposure was developed which is able to accurately simulate a human dermal exposure to CPF. These findings will contribute to future risk assessment efforts for CPF exposure.

* The award to Mr. Ellison was jointly awarded from the International Society of Regulatory Toxicology and Pathology (ISRTP) and RSESS.

Senthilkumar Perumal Kuppusamy: “Telomere dysfunction and telomerase reactivation in human skin keratinocytes: a possible new mechanism of PCB carcinogenesis” The University of Iowa, Human Toxicology. Research Summary: This study was designed to test the hypothesis that PCBs modulate telomerase activity and telomeres via interference in telomerase gene regulation and generation of reactive oxygen species resulting in the deregulation of cell growth. This study adds a new pathway of toxicity of PCBs which will help the scientific community to better understand the mechanisms of carcinogenesis and to establish appropriate safety evaluation studies and risk assessment not only for this class of compounds but possibly also for many other structurally and mechanistically related environmental contaminants.

Liying Zhang: “Quantitative Structure-Activity Relationship (QSAR) Modeling of Estrogen Receptor (ER) Binding Affinity and Virtual Screening for Potential Endocrine Disrupting Compounds (EDCs)”. University of North Carolina at Chapel Hill, Eshelman School of Pharmacy. Research Summary: The endocrine disruptions by environmental chemicals have caused serious public concerns due to the adverse effects to human and wildlife. However, the animal testing of endocrine disrupting compounds (EDCs) is substantial and costly. In order to reduce the cost of experiments, computational approaches are more and more widely used as alternative methods to assess the safety and risk of environmental chemicals. In this work, the largest publicly available chemical library of Estrogen Receptor (ER) ligands was compiled and analyzed. By applying up-to-date cheminformatics approaches, in silico predictors of ER binding affinity were successfully developed. The resulted models were used to prioritize and select approximately 3,000 out of 40,000 environmental chemicals as potential EDCs for in vivo endocrine disruption tests.
Ever-Changing Paradigms in Safety Evaluation – Going Back to Our Roots in Toxicology

by Jyotigna M. Mehta, PhD, DIC, IDT* and Daland R. Juberg, PhD

Paracelsus (1493-1541): “All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy”.

This is one of the first principles taught to all aspiring toxicologists and still holds true today! As toxicologists and risk assessors, we are united in being ethically bound by the principle of the 3R’s (reduction, refinement, replacement) in our quest to differentiate a “poison” from a “remedy”. New and developing technologies offer exciting opportunities to further improve the current toxicity testing paradigms across all sectors to further our goal of providing better solutions for society without animal testing.

However, a key toxicological principle seems to get forgotten in the regulatory world and it is essential that we go back to our roots in Paracelsus and consider “The right dose differentiates a poison and a remedy”. Many global data requirements seem to focus on hazard assessment, and often regulatory decisions do not take account of true exposure scenarios following intentional use of “remedies” (be they medicinal, agrochemical, chemical, etc.).

There are many on-going initiatives to address various factors integral to our testing paradigms (ACSA, Risk 21, Toxicity Testing in the 21st Century, to name a few), but it is imperative to make these programs more global in both participation and utilization, in order to reap the true benefits of smarter and integrated testing strategies. Leading global regulatory authorities should embrace their colleagues across the world in order to help them advance to a position of accepting new paradigms, based on (often innovative) science and realistic risk analysis.

Those involved in testing to meet regulatory requirements would be able to work more efficiently if there was only one global standard or requirement to meet. Preservation of risk assessment as the operating principle for regulatory decision making is essential to product stewardship. The conduct of risk assessments may differ and underlying data may differ depending upon the populations and their practices. However, how these data are used and how decisions are made should be more uniform. Harmonization attempts (e.g., NAFTA, EU, etc) with uniform data requirements and mutual recognition (work-sharing) have begun to tackle this, but do not go far enough to transform our risk assessment and management sciences to be globally accepted. Hazard and exposure have a global definition. However, their utility is too fragmented (e.g., GHS), and sometimes too political. How can we attempt to follow the 3R’s principles when required to conduct additional studies beyond core data packages to meet unrealistic needs or aims of specific nations (redundant testing)? How can society then have confidence in the data we generate (which regulators evaluate) if they see different requirements in different countries with different interpretations? How would we explain ourselves as scientists to Paracelsus, 500 years later?

To provide a concluding example, OECD test guidelines go a long way towards providing a basis for global harmonisation of testing for all varieties of chemicals and their intended use patterns. However, we still have national test guidelines – are these really adding value to the process of safety evaluation? Work needs to be done at all levels to help the world unify to protect our global populations. A more globally uniform process would allow us to better demonstrate to society that it is the “right dose” and, more importantly, a safe dose. Finally, toxicological testing and approaches that contribute to the safety evaluation process going forward should embrace a philosophical shift towards harmonized, integrated, tiered testing as advancements continue to come forward in the world of toxicology.

*J. Mehta is a Senior Regulatory Toxicologist at Dow AgroSciences European Development Centre She can be reached at jmehta@dow.com
The 2011 Great Debate (Cont’d. from page 4)

Dr. Gray enthusiastically began in defense of hazard information alone, as he put it: "When I think about hazard, I think about the bread and butter of toxicology." The premise of his defense of hazard identification was based on the history of risk assessment, stating: "Risk assessment and risk-based regulation is slow, and it causes harm". As an example, he related the well-known carcinogen benzene, whose path to regulation was fraught with roadblocks (see review by James Huff 5).

"Benzene has been a known a hazard for a very long time," he related. "Up to 490 workers got leukemia while we diddled around trying to figure out: Is it a risk, what do we do?" He noted that during the time the EPA was able to implement 200 hazard-based assessments, they only completed 6 risk-based assessments. "The EPA has been working on its assessment of dioxin for over 20 years," he noted. He added, "Congress got so aggravated by risk-based approaches that they put technology-based standards into the hazardous-based solutions of the clean air act." Dr. Gray wrapped up his opening salvo, and gave way to Dr. Rhomberg's approach.

Dr. Rhomberg did not dispute that hazard information is important, but that it is not sufficient to determine restrictions on chemical use. "We do need hazard information," he said. "It's a fundamental principle of toxicology that the dose makes the poison. Toxicity isn't an inherent property of compounds, it's a property of sufficient exposure". He continued, "It is understanding the quantitative properties of those [hazards] that shows us that those actions are reasonable and desirable." Dr. Rhomberg went on to explain that in using hazard information alone, what's being left out is dose-response analysis, how much exposure will cause problems, how much exposure there is, and for that matter, what kinds of risks are we exposed to by banning something." With concern he stressed that when we "ignore a key tool used to make sound decisions" we "undermine the scientific credibility of regulation." In defense of this concern, he noted, "The supreme court said in order to be not arbitrary and capricious, regulators have to show that there is a risk that is unacceptable with the way things are, and that regulations could reduce those risks." Attendees were certainly mesmerized by the interaction at this point, and seemed sympathetic to Dr. Rhomberg's argument. However, they didn't realize the debaters were just getting started.

Dr. Rhomberg then seemingly turned his attention directly on the platform of his opponent, Dr. Gray. He described Dr. Gray's proposal as a "resolution to regulate on fear, rather than on scientific understanding," and added, "What we decide to list and what we don't decide to list is what we decide we're afraid of." He remarked that "Whenever you don't do something, you do something else", and cautioned that the substitute for the hazard-based ban may be a greater danger than the danger we know through risk-based assessments. Getting back to his opponent, he directly attacked Dr. Gray's reasoning by mentioning, "All compounds are hazards, calling some things hazards, and others not hazards, is artificial." He noted that water, salt, air, and oxygen all cause toxicity above certain dose levels. He then closed his opening statement by pronouncing, "We should rather bear the ills we know than flee to ills we know not of."

"I'm sorry you had to listen to that", was the first response by Dr. Gray to Dr. Rhomberg's attack. It was then that the audience observed the event escalate from a debate, past a conflict, to a confrontation. Dr. Gray tore right into Dr. Rhomberg: "I suggest my opponent might want to spend a little time in the absence of that highly-toxic oxygen stuff he was talking about." The attendees burst into laughter at this statement. He agreed that hazard information doesn't ipso facto dictate the banning of substances, and declared the argument of substituting one hazard for another greater hazard absurd. "We can take incremental actions," he answered in response to the worry of substitution. "This isn't a one-way street, we can continue to learn and continue to learn," he said. Maintaining we need to consider hazard information for a chemical, Dr. Gray stressed "If it is hazardous, if it is something that we can avoid, if it is something that we are being exposed to involuntarily," hazard information provides an adequate basis to restrict that chemical.

Dr. Rhomberg's rebuttal wasted no time in pointing out the ignorance of using hazard information alone. "We have no way of knowing whether we are making things worse, or making things better, whether the actions we take are worth it, or worthless." He then again went directly after his foil: (story cont’d. on page 13)
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"Formaldehyde is a known human carcinogen. We produce formaldehyde in our bodies in small amount, and we breathe it out when we talk, broadcasting a known human carcinogen out into the audience. With quantitative risk assessment, I can tell you this is a very tiny amount. My opponent, without that information, how is he to come up on the podium and open his mouth, and say anything, without deciding what he has to say is worth exposing you all to a known human carcinogen?" The audience exploded with laughter and applause at this pointed jab. Dr. Rhomberg wasted no time in delivering the final blow of his rebuttal, continuing on about Dr. Gray's statement and exposing the audience to his toxic arguments: "I don't know if it's worth it or not. I can make that decision for myself, but he can't."

Dr. Gray, recovering well from Dr. Rhomberg’s last volley, relayed the pleas of a woman affected by dioxin exposure: "If the chemical industry had taken all the money and scientists, and consultants, that they put into delays of the EPA dioxin process over the last 20 years, and had put all that money to stop dioxins, the world would be a much cleaner and safer place," he said. It was perhaps this emotional closer that garnered sympathy for Dr. Gray’s doomed argument in the upcoming vote.

Dr. Lamb wrestled the stage from the enlivened debaters, and proclaimed, “I want to hold a vote; this is not a vote on the debating skills of these two.” When asked how many were in favor of Dr. Gray’s proposal, that hazard information provides an adequate basis for restricting chemical use, the response was anemic, at best. Of the more than 75 attendees, only a handful raised their hands. When asked who opposed, or agreed with Dr. Rhomberg’s proposal that hazard information in addition to risk-based assessments were necessary for restricting chemical use, the response was robust and culminated in most attendees raising their hands. Dr. Lamb congratulated the preparation, vigor, and eloquence of the expert debaters to thunderous applause. When the battle was finally over, and the victor decided, the two gentlemen left the debate as they entered, as friends and colleagues.

Through their raucous applause, all in attendance echoed Dr. Short's closing comments that this Great Debate on the 50th anniversary of SOT was among the most memorable. Dr. Short described it as one of the “most spirited and lively debates that we’ve had.” He added with a smile, “Must be something to do with this room.” It certainly was a historic event, one fitting of the 50th Anniversary Meeting of the Society of Toxicology. All agreed with Dr. Short's sentiment when he said, "I hope I'm around another fifty years to enjoy it".

For more information on the Toxic Substances Control Act (TSCA), and what the SOT TSCA Task Force is doing to review and modernize it, please visit: http://www.toxicology.org/ai/pub/SP11/SP11_SOTTTF.asp.

Great Debate video footage can be seen at: http://www.toxicology.org/MI/MEET/AM2011/greatDebate.asp.

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1 http://www.senate.gov/RSOB/
2 http://www.epa.gov/regulations/laws/tsca.html
3 http://www.aperce.org/docs/pr_051311.pdf