Welcome to the RSESS Winter Newsletter. I want to thank the members of RSESS for electing me to this position. It is a great honor and I hope I will serve the SS well in the coming year.

Our SS had another great year at the SOT Annual Meeting in San Diego. The meeting was a needed break from winter, filled with more activities than any of us could possibly attend. The RSESS reception at the SOT Annual Meeting was very well attended and the food was great. Our Great Debate entitled “Peer-reviewed Literature Can Be Used to Formulate Regulatory Policy,” was a big success.

Thanks to our debaters, David Jacobson-Kram and Ray York, and our moderator, Vice President Michael Dourson, for a spirited and entertaining debate with a lot of audience participation. We are beginning to plan for next year’s Great Debate and am hoping that some of you can suggest an equally provocative topic.

On Tuesday of the SOT Meeting, RSESS sponsored a luncheon with Dr. Beatriz Silva Lima, Former Chair of the Safety Working Party of the European Medicines Agency, who gave a presentation on EU nonclinical pharmaceutical development. The luncheon was also very successful. Thanks to Annette Koerner and Hilary Sheevers for their hard work in arranging both the speaker and obtaining financial support from Roche. This is the RSESS’s first annual “Global Regulatory Toxicology Luncheon,” at which a non-US regulator is invited to SOT by RSESS to present perspectives. We will have more information soon about next year’s Global Regulatory Event.

And thanks also to Senthil Kuppusamy who coordinated the review of the many high-quality applications that we had for travel awards to SOT.

Two new outstanding people have been added to the RSESS Executive Board as a result of our elections. Dr. Ed Ohanian from EPA is now our Vice President-Elect, and Dr. Amy Roe from Procter & Gamble is our new Councilor.

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Planning is already underway for the 2016 SOT Annual Meeting in New Orleans. Once again, we had numerous requests for sponsorship of programs for this meeting. All of the proposed submissions were of very high quality, and several were given tentative approval. We are fortunate to have an exceptional program committee who gave very serious consideration to each of the proposals. The program committee was chaired Marie Fortin and included Matt Bogdanffy, Bob Budinsky, Susan Emeigh Hart, Mark Powley, and Tao Wang. These folks have done a wonderful job did the initial vetting for us – tireless work, but a system that RSESS has employed for several years and one that drives high quality into the selection process. We are also exploring the concept of sponsoring informative webinars throughout the year. Please be on the lookout for our upcoming webinar announcements.

Please consider getting more involved with this SS. It is a very rewarding experience both from a professional and from a personal one. Have a relaxing holiday season.

Suzy

RSESS Global Regulations Breakfast - Next stop: China

**Topic:** Regulatory landscape in China

**Speaker:** Dr. Qing-li Wang, Executive Director, Pharmacology & Toxicology, Center for Drug Evaluation, China Food and Drug Administration.

**Abstract:** Dr. Wang’s talk will provide an overview on the regulatory landscape in China, giving insights into the organizational structure of cFDA, focusing on the approval processes for pharmaceuticals, and briefly looking into how traditional medicines, food, dietary supplements/herbal products are regulated. The talk will touch as well on new guidelines and regulatory requirements currently being drafted by cFDA, and the similarities and differences to US FDA including new policies for pharmaceutical development in China.
Global Regulation - First Stop Europe!
What a great session on European Regulation of Pharmaceutical during SOT 2015.

By Annette Koernern, PhD

This year at the SOT Annual Meeting in San Diego the RSESS Council piloted a new lecture series about global regulation by starting with a first stop in Europe. It was a great pleasure to welcome Dr. Beatriz Silva Lima who came all the way from Portugal to talk in the RSESS luncheon session about European Regulation for Pharmaceutical Drug Development. She gave us a deep insight into the complex regulatory environment in Europe looking back on over 20 years of personal experience as an expert in non-clinical and regulatory science at Infarmed, Portugal and EMEA, UK and as a member of the Committee of Human Medicines (CHMP), Committee of Advanced Therapies (CAT) and the Scientific Advice Working Party (SAWP) until recently. For those who could not join us in person in San Diego her presentation is uploaded to the RSESS website. The over 50 participants in the room joint a lively discussion during and after the session raising very specific questions on how to best approach tricky drug development discussion with the European regulatory bodies and understanding of the interconnectivity of the different procedures and committees. The similarities and differences with especially FDA practice and how European and US agencies start interacting more and more directly was a focus area as well. ‘It was extremely helpful to get first-hand information from Beatriz with her deep experience in European Regulation’ said one of the participants and another one added ‘Hearing that regulatory cross-talk is intensified is excellent as we sometimes struggle with greatly different advice for our global programs’. This high interest was nicely reflected as well in the overly positive questionnaire feedback received, highly appreciating the topic being discussed broadly. On top of this you gave us very valuable advice with regard to future set-up, duration and integration of the talk in the general SOT program, that we aim to incorporated in the future setting.

So the train is already moving again and the organization team around Annette Körner, Hilary Sheevers and Amy Roe is making arrangements for the next Stop on Global Regulation… we’ll keep you posted.
Drinking Water Health Advisories for Harmful Algal Blooms (HABs) 
Cyanobacteria and Cyanotoxins in the United States*

By Edward V. Ohanian PhD

Algae are a natural component of aquatic ecosystems; however, when present in large quantities as “blooms,” they can pose a significant potential threat to human and ecological health. These harmful algal blooms (HABs) are often composed of microorganisms known as cyanobacteria, some of which with the potential to produce toxins that can cause adverse health effects in humans and animals through the contamination of waterways used for recreational purposes and as drinking water supplies. Freshwater cyanobacterial blooms may be dominated by a single-species or composed of a variety of toxic and non-toxic strains. Cyanotoxins are produced and contained within the actively growing cyanobacterial cells (i.e., intracellular toxins). The release of these toxins in an algal bloom into the surrounding water as dissolved (extracellular) toxins occurs mostly during cell death and lysis as opposed to the continuous excretion from the cells.

Cyanobacterial blooms in the United States have been associated with the death of wildlife and domestic animals. They may pose a risk to human health through the exposure to contaminated freshwater, the ingestion of contaminated drinking water, or the consumption of contaminated fish or shellfish. Additionally, cyanobacteria pose a potential risk to aquatic ecosystems when present in large quantities as their decomposition causes excessive oxygen consumption, which leads to an increased mortality rate in local populations due to hypoxia.

The most common exposures to cyanobacteria and their toxins are believed to occur during recreational activities via oral, dermal, and inhalation routes. Oral exposure may occur from accidental or deliberate ingestion of contaminated water. Dermal exposure may occur by direct contact of exposed parts of the body to water containing cyanobacteria cells. Inhalation may occur through the aspiration of water containing cyanobacteria cells and their toxins.

The Safe Drinking Water Act (SDWA) requires the U.S. Environmental Protection Agency (EPA) to publish a list of unregulated contaminants that are known or expected to occur in public water systems in the U.S. that occur at a frequency and at levels of public health concern and where there is a meaningful opportunity for health risk reduction. This list is known as the Contaminant Candidate List (CCL). The EPA’s Office of Water has listed cyanobacteria and cyanotoxins on the three drinking water CCLs.

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Under the SDWA, EPA may publish Health Advisories (HAs) for contaminants that are not subject to any national primary drinking water regulation. EPA develops HAs to provide information on the chemical and physical properties, occurrence and exposure, health effects, quantification of toxicological effects, other regulatory standards, analytical methods, and treatment technology for drinking water contaminants. HAs describe concentrations of drinking water contaminants at which adverse health effects are not anticipated to occur over specific exposure durations (e.g., one-day, ten-days, several years, and a lifetime). HAs also contain a margin of safety to address database uncertainties. HAs serve as informal technical guidance to assist federal, state and local officials, as well as managers of public or community water systems in protecting public health when emergency spills or contamination situations occur. HAs are not regulations and should not be construed as legally enforceable federal standards. HAs may revised as new information becomes available.

On June 17, 2015, EPA posted drinking water health advisories for the cyanobacterial toxins, microcystins and cylindrospermopsin. The advisories describe concentrations of the two algal toxins in drinking water at or below which adverse human health effects are not anticipated to occur over a ten-day exposure period. Specifically, EPA developed health advisories for the cyanobacterial toxins microcystins and cylindrospermopsin. EPA’s HAs provide states, drinking water utilities and the public with information on health effects of microcystins and cylindrospermopsin, analytical methods to test for cyanotoxins in water samples, and treatment technologies to remove cyanobacterial toxins in drinking water. EPA recommends HA levels at or below 0.3 micrograms per liter for microcystins and 0.7 micrograms per liter for cylindrospermopsin in drinking water for children pre-school age and younger (less than six years old). For school-age children through adults, the recommended HA levels for drinking water are at or below 1.6 micrograms per liter for microcystins and 3.0 micrograms per liter for cylindrospermopsin.

EPA also released Health Effects Support Documents (HESDs) for three cyanobacterial toxins of concern: microcystins, cylindrospermopsin, and anatoxin-a. These three cyanotoxins were identified on EPA’s most recent CCL for potential regulation in drinking water. HESDs describe the health effects basis for the development of HAs. Based on the reported occurrence, toxicology, and epidemiology data, EPA found there are adequate data to develop HAs for microcystins and cylindrospermopsin, but inadequate data to develop an HA for anatoxin-a.

EPA has also published a support document to accompany the release of the health advisories for microcystins and cylindrospermopsin. The document is designed to provide information and a framework that public water systems (PWSs) and others can consider using to inform their decisions on managing the risks from cyanotoxins to drinking water. It includes a potential stepwise approach PWSs could use to inform their decisions on whether and how to monitor, treat, and communicate with stakeholders.

For more information on the two cyanobacterial toxin health advisories, including the health effects support documents, visit EPA’s health advisory website: http://water.epa.gov/drink/standards/hascience.cfm.

* Adapted from EPA’s Health Advisory Material (June 17, 2015) to inform SOT/RSESS membership
The New York Attorney General’s Office Takes Aim at the Dietary Supplement Industry

By Amy Roe

On February 3, 2015, New York Attorney General (NY AG) Eric T. Schneiderman issued cease-and-desist letters to four major retailers (GNC, Walgreens, Walmart, and Target), demanding that they remove certain store-brand botanical dietary supplement products from stores in New York. The action was based on claims of adulterated product after the NY AG’s office tested several supplements using a DNA barcoding test method. Results from the testing reportedly found unlisted ingredients, or a complete lack of the labeled herbs’ DNA, in 79% of the tested products. The DNA barcoding results detected trace levels of plants not listed on the label and/or potential allergens such as rice and wheat. In a purported large number of tested products, there was no detectable plant DNA. This action by the NY AG’s office was the first time that a state law enforcement agency has taken direct action against major retailers of dietary supplements for alleged fraud.

DNA barcoding is the process of examining sequences of DNA from a standard region (gene) for species identification, and was initially introduced to identify animal species. This technology is appropriate for distinguishing fresh or living tissue obtained from distinct species (e.g. identifying tuna versus snapper), and has been validated by the FDA for this purpose. Although DNA barcoding has been used to identify major plant groups (e.g., grasses and pine trees), its use for specific identification of plants remains a topic of great debate in the academic community. The difficulty in using DNA barcoding to identify specific plant species in dietary supplements, in addition to the complexity of plant species, is based largely on the manufacturing process used to obtain plant extracts. DNA barcoding may be able to authenticate raw herbs (if appropriate genes are used); however, many finished herbal-containing dietary supplements have been highly processed (extracted), which typically removes or damages DNA-containing material. For this reason, the dietary supplement industry as a whole, in consultation with various academic and commercial experts, believes that the use of DNA barcoding is inappropriate for routine testing of botanical extracts and were used inappropriately in this case. In a response to an inquiry from Senators Hatch and Heinrich on the appropriateness of the NY AG’s use of DNA barcoding, the FDA has stated, “Currently, if FDA were to use DNA methods on botanical extracts, we would use them in combination with established chemical or other acceptable methods historically used to verify the identity of these products.”

Unfortunately, as the popular media has reported on the actions by the NY AG’s office on these dietary supplement companies, it is often erroneously stated that dietary supplements are not regulated by the FDA. Dietary supplements are not approved by FDA; however, manufacturers are responsible for ensuring that products are safe, claims are not false or misleading, and that products comply with the Federal Food, Drug, and Cosmetic Act and FDA regulations in all other respects.

FDA’s Center for Food Safety and Applied Nutrition (CFSAN) is responsible for the oversight of dietary supplements. The Dietary Supplement Health and Education Act (DSHEA) of 1994, which amended the Federal Food, Drug, and Cosmetic Act, created the regulatory framework for the safety and labeling of dietary supplements. In general, FDA’s role with dietary supplement products begins once the product enters the marketplace. Dietary supplement manufacturers must report to FDA any serious adverse events they receive from consumers or health care professionals; which FDA then monitors. FDA also reviews product labels and other information (e.g. package inserts, accompanying literature, internet promotion), and claims substantiation as resources permit. Dietary supplement advertising (e.g. radio and television ads), falls under the jurisdiction of the Federal Trade Commission.
All four companies implicated in the NY AG’s investigation readily complied with the NY AG’s office and removed product from stores in New York; and Target and Walgreens removed implicated supplements from stores across the nation. The NY AG’s office took further action against the original four companies by issuing subpoenas for any and all data supporting claims made by the retailer’s herbal products. In addition, four more dietary supplement manufacturers were asked to submit detailed information regarding their products. GNC quickly reached an agreement with the NY AG’s office, which included performing DNA barcoding on “active” plant ingredients used in its products, and testing for contamination with allergens. GNC’s position to stakeholders indicated that this agreement was completed to end a protracted battle. However, their quick decision has frustrated many in the dietary supplement industry; particularly as it relates to the use of DNA barcoding.

Schneiderman has also led the formation of a coalition of state AGs with the intent of further investigating the dietary supplement industry; at last count, there were 14 members. On April 2, 2015, Schneider and Indiana AG, Greg Zoeller called for a Congressional inquiry into the herbal supplements industry demanding, among other things, “a more robust oversight role for the U.S. Food and Drug Administration with respect to herbal supplements”. To date, no congressional inquiry has been established.

The dietary supplement industry, through various trade associations, has met with the NY AG’s office for what has been described as frank conversations. At least one quality control proposal was discussed in those meetings. Additionally, industry groups have made it clear that they support increased resources for the FDA to enhance its ability to enforce existing regulations. On May 11, 2015, the NY AG’s office acknowledged its shared goals with the Natural Products Association (NPA) to provide “authentic, pure,” and fully compliant herbal supplements for consumers. Schneiderman also acknowledged the industry’s criticism about using DNA barcoding as the only test method to authenticate herbal ingredients.

References:


FDA 101: Dietary Supplements
http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm050803.htm

Dietary Supplements http://www.fda.gov/aboutfda/transparency/basics/ucm193949.htm

AG Schneiderman and AG Zoeller lead bipartisan group of 14 attorneys general calling for congressional inquiry into herbal supplements industry. http://www.ag.ny.gov/press-release/ag-
As the Associate Director for Science with OW, Dr. Ohanian provides OW’s leadership with expert oversight for the development of risk assessments as required under both the Safe Drinking Water Act and Clean Water Act. Previously, he served as the Director of the Health and Ecological Criteria Division in OW. The Division was responsible for conducting human and ecological risk assessments as required under the National Water Program. As the Chairman of the USEPA Risk Assessment Forum, he has been instrumental in promoting Agency-wide consensus on priority human and ecological risk assessment issues and in ensuring that this consensus is incorporated into Agency risk assessment guidance documents and implemented across the Agency. Dr Ohanian has also served as Adjunct Associate Professor with the School of Public Health and Tropical Medicine at Tulane University Medical Center, and as Professorial Lecturer with the Department of Environmental and Occupational Health/School of Public Health and Health Services at George Washington University Medical Center. As the Co-Chairman of the Federal-State Toxicology and Risk Analysis Committee, he has fostered cooperation and consistency regarding improved risk assessment/management methodologies.

Dr. Ohanian has contributed more than 60 articles and chapters to scientific journals and books; and has been a member of editorial boards of scientific journals, including HERA. Dr. Ohanian was the co-editor of the book entitled “Toxicokinetics and Risk Assessment” (Taylor and Francis, October 2006). He was the past president of SOT’s Risk Assessment Specialty Section and the recipient of SOT 2010 Arnold J. Lehman Award for his contributions to risk assessment and regulation of chemical agents. In March 2015, Dr. Ohanian was elected Vice President-Elect of SOT’s Regulatory and Safety Evaluation Specialty Section.
Biosketches of New Councilors

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Amy Roe received her PhD in Toxicology from the University of Kentucky in 1997; and, completed a 2 year Post-Doctoral Fellowship at the University of Cincinnati Division of Environmental Genetics and Molecular Toxicology. In 1999, Dr. Roe joined Procter & Gamble (P&G) Pharmaceuticals to lead the metabolism group within the Drug Disposition Section. Dr. Roe has over twenty years of experience in studying drug/xenobiotic disposition, descriptive and regulatory toxicology, and risk assessment. Her current position is in Product Safety & Regulatory Affairs of the Personal Health Care division at P&G. In this position she is responsible for developing non-clinical safety programs and regulatory strategies in support of OTC drugs, medical devices, and dietary supplement products marketed globally. She is leading an industry-wide effort in collaboration with academia and government regulatory authorities, to develop a framework approach for assessing herb-drug and herb-herb interactions. Dr. Roe is a member of the Society of Toxicology (SOT) and a past-president of the Ohio Valley SOT. She serves on a number of expert committees including, Councilor of the Regulatory and Safety Evaluation Specialty Section of SOT, the Consumer Health Products Association, Dietary Supplements Committee, and the United States Pharmacopeia (USP) Dietary Supplement Expert Committee. Dr. Roe is a Diplomate of the American Board of Toxicology; and, currently serves on the Board of Directors of the American Board of Toxicology. In addition, she is an Adjunct Assistant Professor at the University of Cincinnati, Department of Environmental Health. Dr. Roe’s previous work experience includes the US FDA, where she was a staff scientist at the National Center for Toxicological Research (NCTR).

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 guidances 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.