Predictive Toxicology for 21st Century Risk Assessment

By Daniella M. Pizzurro, Ph.D.

New regulatory mandates to consider non-animal testing methods in assessing chemical risks have brought predictive toxicology methods and tools to the forefront.

The current international chemical regulatory landscape requires greater substance toxicity evaluation and characterization than ever before. Simultaneously, regulatory bodies across the globe are calling for reduced animal testing and preferential use of emerging, alternative technologies. This includes the United States (U.S.) under the recently amended Toxic Substances Control Act (TSCA), which contains a mandate to consider non-animal alternatives in meeting data requirements for the assessment of new and existing chemicals in the marketplace. This directive has opened the door to both new opportunities and challenges for chemical hazard and risk assessment, including issues related to regulatory acceptance of such methods across different agencies and contexts; how to best validate test results; and their applicability to complex chemicals, such as substances of unknown or variable composition, complex reaction products, or biological materials (referred to as UVCBs).

> *...regulatory bodies across the globe are calling for reduced animal testing and preferential use of emerging, alternative technologies.*

Even with many remaining challenges, the development, use, and acceptance of so-called predictive toxicology methods is on the rise. Predictive toxicology describes a multidisciplinary approach to chemical toxicity evaluation that uses a suite of non-

INSIDE

Letter from the Editors

September 2017

Dear Colleague,

In this issue of *Trends*, we discuss the new Toxic Substances Control Act (TSCA) rules. On par with international regulatory trends, the new TSCA rules promote the use of alternatives to animal testing, which has opened the doors for various predictive toxicology tools while highlighting their potential challenges.

The first *Trends* article discusses risk assessment using predictive toxicology, a multidisciplinary approach that employs various predictive tools to forecast the effects of a chemical on biological systems. The second article discusses the phrase "all conditions of use" and how comprehensive exposure assessment will be a key component under the new TSCA regulations. The third article looks more broadly at TSCA as one aspect of the interconnected international, legislative, and consumer-driven market trend towards intrinsically safer products.

Gradient contributors to this issue include Drs. Daniella Pizzurro, Lisa Bailey, and Jessie Kneeland. Our guest editor is Kristie Sullivan, M.P.H. from the Physicians Committee for Responsible Medicine.

We hope that this issue of *Trends* introduces you to the challenges and opportunities associated with TSCA.

Yours truly,

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animal testing methods to forecast the effects of a chemical on biological systems. Tools used for this purpose include:

- Iterative read-across strategies: Identification and evaluation of physicochemical and toxicologically similar substances to a chemical of interest (*i.e.*, one that preserves features like reactive functional groups, bioavailability, and general metabolism).

- High-throughput *in vitro* toxicity data: Evaluation and interpretation of such data generated by national or international agencies (*e.g.*, the U.S. EPA's Tox21 and ToxCast).

- *In silico* computational toxicology programs: Application of computational programs that model physical and biological properties of chemicals. These include quantitative structure activity relationship (QSAR) and predictive software programs, such as Derek Nexus.

- Adverse outcome pathway (AOP) evaluation: Interpretation and application of pathway-based toxicology for predicting unknown chemical toxicity based on perturbations to early cellular and molecular events in the mechanism leading to the health effect of interest.

These tools are gaining increased usage under various regulatory programs around the world, including in the U.S. (see figure). For example, the cosmetics, personal care products, and fragrance industries, while not regulated in the U.S. under TSCA, have already been relying on non-animal testing methods in order to meet international regulations restricting or completely banning the use of animal testing for their products. Use of read-across data, in particular, was used in over 80% of published fragrance safety assessments put out by the Research Institute for Fragrance Materials (RIFM) and in approximately 75% of the dossiers submitted to the European Chemicals Agency (ECHA) under the REACH regulation (Ball *et al.*, 2016).

In practice, however, regulatory acceptance of testing data generated with alternative testing methods differs across jurisdictions and specific endpoints, and these data have typically required extensive justification or other lines of supporting evidence prior to being accepted as adequate basis for hazard determinations. As a consequence, they often do not, by themselves, obviate the need for reliance on animal testing data. Further validation of certain methodologies (*e.g.*, *in vitro* assays) and clear guidance from regulatory agencies on the use of these tools are needed in order to successfully implement predictive toxicology into chemical assessment and compliance activities.

In addition to understanding the advantages and limitations to these predictive toxicology tools, clear guidance is needed

ADVANTAGES, LIMITATIONS, AND REGULATORY CONSIDERATION OF VARIOUS PREDICTIVE TOXICOLOGY TOOLS

Tool	Advantages	Limitations	Regulatory Consideration
Read-across	• "Human touch" with expert input • Uses existing, high-quality data • Can handle some complex substances	• Requires expert judgment, extensive justification • Dependent on availability of data-rich analogues	EU; Australia; U.S.
QSAR	• Rapid testing for multiple chemicals and endpoints • Fairly simple to use some tools • Several free available trainings	• Some tools have steep learning curves • Limited capability for complex substances • Results require expert interpretation • Sophistication and reliability varies greatly by endpoint	EU; Australia; U.S.; Canada
In vitro testing	• Rapid simultaneous testing for multiple chemicals and endpoints • Useful for hazard screening of large number of chemicals	• Results require expert interpretation • Simplified models of human disease may have limited relevance for risk assessment	EU; Australia; U.S.; Canada
AOP	• Can identify earlier stage responses for testing (*e.g.*, molecular and cellular changes) that occur prior to disease development	• Limited established pathways and endpoints • Limited acceptance for risk assessment	Limited acceptance; considered in mechanistic discussions

Acronyms: Adverse Outcome Pathway (AOP); European Union (EU); Quantitative Structure-Activity Relationship Program (QSAR); United States (U.S.)

New Exposure Assessment Strategies Under TSCA

By Lisa Bailey, Ph.D.

Exposure modeling for "all conditions of use" will play a critical role in prioritizing chemicals that could pose a threat to human health.
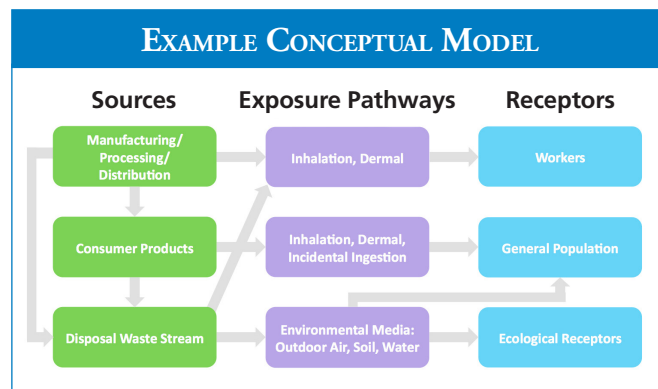
Exposure information will be a key component of chemical prioritization and risk evaluation under the Lautenberg Chemical Safety Act amendments to the Toxic Substances Control Act (TSCA). For example, since these amendments call for evaluation of all known, intended, or reasonably foreseen chemical uses, the risk evaluation rule released by the U.S. Environmental Protection Agency (EPA) in June 2017 states that the EPA will consider "all conditions of use" as part of the full life-cycle of a chemical; *i.e.*, exposures from manufacturing, processing, distribution, consumer uses, and chemical disposal, including worker exposures. This more extensive use evaluation component of the new TSCA requirements is a substantial change from the 1976 version of the law.

> *…chemical use information is lacking for many chemicals in commerce today…*

For each chemical that will undergo risk evaluation under the new requirements, the EPA is required to publish a scoping document that includes chemical hazard and use information, an initial conceptual model that describes each exposure pathway, and a description of potentially susceptible subpopulations that the EPA expects to consider. As part of the scoping process, the EPA will request use and exposure information from manufacturers and other interested parties. To that end, the EPA reopened the dockets for the first 10 chemicals – asbestos, 1-bromopropane, carbon tetrachloride, 1,4-dioxame, cyclic aliphatic bromide cluster, methylene chloride, N-methylpyrolidone, perchloroethylene, pigment violet 29, trichloroethylene – that will undergo risk evaluation under the new TSCA rules so that stakeholders can provide additional use and exposure information (by September 19, 2017) to inform the Agency's problem formulation. The problem formulation documents will be released for public comment in December 2017.

For the exposure portion of the risk evaluation, measurements are preferable over modeling since exposure models are often conservative and tend to overestimate exposures and risks. Further, as described in the risk evaluation rule, unreasonable risks will be managed with use restrictions. Exposure measurements may not be possible, however, for some exposure pathways, and exposure modeling will be required.

The EPA's ExpoBox (https://www.epa.gov/expobox) contains 700+ exposure modeling tools that the EPA may consider using for TSCA risk evaluations. These models generally fall into two categories: 1) far-field models that estimate concentrations in outdoor air, water, and soil, and from food possibly contaminated by these media; and 2) near-field models that estimate concentrations in indoor air and consumer products. Recent modeling studies conducted by researchers at the EPA's National Center for Computational Toxicology (NCCT) and National Exposure Research Laboratory (NERL) (*e.g.*, Wambaugh *et al.*, 2013) predicted that near-field sources contribute more than far-field sources to human exposures, and suggested that better near-field models are needed to predict exposures from consumer products. NCCT and NERL are in the process of developing such models.

The EPA is also developing high-throughput (HT) exposure models that could be used for chemical prioritization under the new TSCA requirements. These include models within the EPA's ExpoCast (HT Exposure Forecasting), which is complementary

EXAMPLE CONCEPTUAL MODEL

Sources	Exposure Pathways	Receptors
Manufacturing/ Processing/ Distribution	Inhalation, Dermal	Workers
Consumer Products	Inhalation, Dermal, Incidental Ingestion	General Population
Disposal Waste Stream	Environmental Media: Outdoor Air, Soil, Water	Ecological Receptors

to the EPA's ToxCast (HT Toxicity Forecaster). ExpoCast predicts exposures for almost 8,000 chemicals. Since chemical use information is lacking for many chemicals in commerce today, and accurate use information is important for exposure predictions, the EPA is also developing HT models that predict chemical uses based on structural similarities to other chemicals with known uses. Since the ultimate goal is to predict human health risk, the EPA is also developing HT models that will make predictions about how much chemical exposure would be needed to cause the observed chemical toxicity within the EPA's ToxCast. These exposures could then be compared to known exposures in the population to predict whether a chemical should be considered high priority for risk evaluation. The EPA is also developing

TSCA in a Global Context

By Jessie M. Kneeland, Ph.D.

TSCA is just one part of a global regulatory and corporate response to consumer demand for safer products with fewer harmful chemicals.

TSCA reform was, in large part, a response to public concern about chemical safety. Consumers around the world want safer chemicals in the products they buy and use, and many companies have responded by offering products with

> *The market pressures for safer chemicals will continue to reward companies that proactively evaluate the safety of their products and substitute harmful ingredients with safer alternatives.*

fewer chemicals, for example by removing artificial dyes and fragrances. Many of these voluntary efforts are coordinated by organizations like the Sustainability Accounting Standards Board (SASB) or programs such as the U.S. Environmental Protection Agency's (EPA) Safer Choice. Regulators around the world are reworking chemical safety laws to restrict harmful chemicals. In addition to the regulatory and market pressures for "greener" products, companies are also motivated by the potential for lawsuits alleging health effects and environmental damage from chemical exposure.

Most of the new TSCA changes were designed to give the public greater confidence that chemicals in U.S. commerce are not unreasonably hazardous by granting the EPA more authority to evaluate and manage chemical risks. Many Asia-Pacific countries are increasing data requirements and stepping up chemical safety reviews, which raises the global regulatory burden of manufacturing and selling chemicals. In contrast, reforms underway to Australia's National Industrial Chemicals Notification and Assessment Scheme (NICNAS) program are aimed at reducing the overall regulatory burden by shifting the focus of chemical evaluation and restriction to the most harmful chemicals. TSCA's chemical prioritization requirement should also focus attention on chemicals expected to pose the greatest risk, but the EPA will continue to need additional data to complete the prioritization and subsequent risk evaluations for high-priority chemicals.

To evaluate risk, the EPA needs sufficient information on a chemical's toxicity, and they need to know how the chemical will be used, which impacts how workers, consumers, and the environment could be exposed. In contrast to EU's REACH, TSCA specifically does not set a minimum required data set

of chemical toxicity information. This gives the EPA and chemical manufacturers greater flexibility to collect only the data that is most clearly needed for each chemical, but it means greater uncertainty – companies cannot know ahead of the EPA's evaluation how much toxicity testing will be enough. Some global efficiency is possible if the EPA (and companies) take advantage of data gathered to satisfy other regulatory requirements. For example, substantial chemical dossiers are available through EU's REACH program, but many of those studies are not freely available for non-REACH uses. Using data collected by REACH consortia may require securing permission from many consortia members. Unlike REACH, TSCA does not strictly require companies to coordinate on new toxicity testing, though it encourages cooperation. The new TSCA requires the EPA to consider all foreseeable conditions of use, which will require more exposure information. As part of the first 10 chemical risk evaluations under the new TSCA requirements, the EPA has recently reopened the dockets to request further information on how these chemicals are used. The EPA also continues to develop and employ exposure models that fill gaps where exposure measurements are not adequate.

The EPA's chemical risk evaluations depend on accurate information, and new information will often be needed. Manufacturers and stakeholders can help ensure the EPA comes to well-grounded conclusions by providing necessary data, but they will want to cooperate to minimize unnecessary testing. Consumers will benefit by gaining access to chemical information compiled during the EPA's evaluations. However, the market pressures for safer chemicals will continue to reward companies that proactively evaluate the safety of their products and substitute harmful ingredients with safer alternatives. This is the case throughout the world, no matter the chemical safety regulations.

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By The Way...

The Dutch are leading by example in the face of climate change-induced sea level rise.

Source: http://www.npr.org/templates/story/story.php?storyId=18229027.

What's New at Gradient

Awards and Announcements

Gradient is collaborating with the Humane Society U.S. to promote animal welfare objectives under the Toxic Substances Control Act (TSCA).

Barbara D. Beck has been recertified with the UK Register of Toxicologists and was appointed to the Society of Toxicology Task Force on the Impact of Toxicology on Public Health along with the Task Force on Low-Level Arsenic Exposure.

Joel M. Cohen has been reappointed as a Visiting Scientist in the Molecular and Integrative Physiological Sciences Program at the Harvard T.H. Chan School of Public Health.

Publications

Bailey, L.A. and **B.D. Beck.** 2017. Comment on Environmental exposure to manganese in air: Associations with tremor and motor function by Bowler, *et al.* (2016). *Sci. Total Environ.* 595:839-841. DOI:10.1016/j.scitoenv.2017.03.277.

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DeLoid, G.M., **J.M. Cohen,** G. Pyrgiotakis, and P. Demokritou. 2017. Preparation, characterization, and *in vitro* dosimetry of dispersed, engineered nanomaterials. *Nat. Protoc.* 12(2):355-371. DOI:10.1038/nprot.2016.172.

Gasper, M.A., A.C. Hesseling, **I. Mohar,** L. Myer, T. Azenkot, J.S. Passmore, W. Hanekom, M.F. Cotton, I.N. Crispe, D.L. Sodora, and H.B. Jaspan. 2017. BCG vaccination induces HIV target cell activation in HIV-exposed infants in a randomized trial. *JCI Insight.* 2(7):e91963. DOI:10.1172/jci.insight.91963.

Goodman, J.E., C.T. Loftus, **X. Liu**, and **K. Zu**. 2017. Impact of respiratory infections, outdoor pollen, and socioeconomic status on associations between air pollutants and pediatric asthma hospital admissions. *PLoS ONE.* 12(7). DOI:10.1371/journal.pone.0180522.

Goodman, J.E., M.K. Peterson, M.L. Hixon, and **S.P. Shubin**. 2017. Derivation of an Oral Maximum Allowable Dose Level for Bisphenol A. *Regul. Toxicol. Pharmacol.* 86:312-318. DOI:10.1016/j.yrtph.2017.03.024.

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under the new TSCA requirements. To this end, the new TSCA rules directed the EPA to develop a strategic plan regarding the development and implementation of alternative testing methods by June of 2018.

There are a number of existing resources established in the U.S. and abroad which the EPA can rely upon that can provide useful models and insights regarding best practices and challenges associated with non-animal testing methods. The U.S.-based Interagency Coordination Committee on the Validation of Alternative Methods (ICCVAM), for example, combines representatives from 16 U.S. federal regulatory and research agencies committed to establishing guidelines and recommendations that promote the regulatory acceptance of alternative testing methods. Guidance put forth by other agencies, such as the Read-Across Assessment Framework (RAFF) from the ECHA in the EU, should also be considered in this effort.

Decreased reliance on animal testing not only has ethical implications, but also the potential to improve company performance by reducing testing costs and time to regulatory approval of new substances. For regulators under the new TSCA requirements, these tools appear promising for chemical prioritization and screening efforts needed to address the large number of chemicals in and entering commerce without placing undue burden on chemical manufacturers. With the aid of global collaborations and well-constructed regulation, the future looks bright for the role of predictive toxicology in modern day risk assessment.

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Ball, N., M.T.D. Cronin, J. Shen, *et al.* 2016. Toward Good Read-Across Practice (GRAP) guidance. Accessed at https://www.ncbi.nlm.nih.gov/pubmed/26863606.

U.S. EPA. March 9, 2017. Models and tools developed by EPA to assess hazard under TSCA. Accessed at https://www.epa.gov/tsca-screening-tools/using-predictive-methods-assess-hazard-under-tsca#models.

Guest Editorial: Collaborative Approaches Advance Toxicology

By Kristie Sullivan, M.P.H.

The EPA has the opportunity to harness the collaborative power of government, industry, and NGOs to create global guidelines for predictive toxicology, which will reduce animal testing.

In 2007, the National Academy of Sciences released a seminal report outlining a vision for a more comprehensive, predictive, and efficient toxicological testing paradigm. Now, 10 years later, we are seeing significant scientific, regulatory, and political progress. Despite considerable issues facing legislators on Capitol Hill, their support for the development of more advanced test methods couldn't be more clear. The Fiscal Year 2018 Interior Appropriations bill and accompanying report – which funds the U.S. Environmental Protection Agency (EPA) – explicitly maintains funding levels for the EPA's predictive toxicology research program. This support for the EPA's predictive toxicology research comes at a time of significant cuts to other programs, and is consistent with the bipartisan support seen for the 2016 Lautenberg Chemical Safety Act, an update of the original TSCA. It includes strong directives to the EPA and the chemical industry to develop, require, and use test methods which reduce or replace vertebrate animal tests.

> *…support for the EPA's predictive toxicology research comes at a time of significant cuts to other programs…*

Provisions in the new TSCA rules requiring the consideration of non-animal testing have created new opportunities for scientific collaborations across non-governmental organizations (NGOs), government, and industry to advance the field of toxicology and decrease reliance on animal testing. Adverse outcome pathways (AOPs), for example, are a crucial concept to bridge the mechanistic knowledge generated by "new approach methodologies" with regulatory apical endpoints and to help facilitate the transition to predictive toxicology.

The Organisation for Economic Co-operation and Development (OECD) has facilitated a collaborative process for developing, reviewing, endorsing, and publishing AOPs. Within this transparent environment, AOP development and integration is being driven by successful partnerships between scientists in academic, government and non-profit institutions, and in industry. These AOPs are becoming the basis of new test guidelines and Integrated Approach to Testing and Assessment (IATA) guidance documents, which have the potential to change the chemical regulatory landscape by streamlining regulatory acceptance of *in vitro* and *in silico* test methods and strategies, especially those based on key events within an established AOP. OECD member countries are currently working to meld components of more flexible IATAs into "Defined Approaches," or combinations of methods or approaches following a fixed interpretation procedure, within harmonized test guidelines.

This innovative, harmonized process of discovering and cataloging toxicology knowledge across organizations and the globe, anchoring it to regulatory endpoints, and supporting the acceptance of new tools will be invaluable to the EPA as it authors the required strategic plan to reduce and replace vertebrate testing for industrial chemicals under the new TSCA requirements. But progress cannot be made by the EPA alone. Toxicologists – from industry, government, academia, NGOs, and beyond – must share the strategies and approaches they use with the EPA and others. In this way, we can continue to move towards a new, more efficient toxicological testing paradigm that is less reliant on traditional animal testing.

Kristie Sullivan, M.P.H., is the Vice President of Research Policy with the Physicians Committee for Responsible Medicine, a nationwide organization of physicians and laypersons that promotes preventive medicine, especially good nutrition, and addresses controversies in modern medicine, including ethical issues in research. She can be reached at ksullivan@pcrm.org.

New Exposure Assessment Strategies Under TSCA

HT models to predict distributions of exposure within the population in order to identify sensitive subpopulations that will need to be considered in the risk evaluation.

The EPA has not pointed to any specific use or exposure model within the new TSCA rules. Since many of the thousands of chemicals in commerce have little use/exposure information, models will play a potentially significant role in prioritizing these chemicals for future risk evaluation.

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What's New at Gradient

Hoffmann, S., R.B.M. de Vries, M.L. Stephens, N.B. Beck, H.A.A.M. Dirven, J.R. Fowle III, **J.E. Goodman**, T. Hartung, I. Kimber, M.M. Lalu, K. Thayer, P. Whaley, D. Wikoff, and K. Tsaioun. 2017. A Primer on Systematic Reviews in Toxicology. *Arch. Toxicol.* DOI:10.1007/s00204-017-1980-3.

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Zu, K., X. Liu, L. Shi, G. Tao, C.T. Loftus, S.S. Lange, and **J.E. Goodman**. 2017. Concentration-response of Short-term Ozone Exposure and Hospital Admissions for Asthma in Texas. *Environ. Int.* DOI:10.1016/j.envint.2017.04.006.

Upcoming Presentations

Tacoma, WA. September 19-20, 2017. Washington State Governor's Industrial Safety and Health Conference.

- **"Chemical Risk Communication Best Practices: A Case Study of Diacetyl."** M. Peterson, D. Dodge.
- **"Toxicology 101 for Occupational Safety and Health Professionals."** M. Peterson, D. Dodge.

Arlington, VA. September 25-27, 2017. Food Contact & Additives Conference.

- **"Safety Determination of Substances Added to Food *Via* U.S. FDA's Voluntary GRAS Notification Rule."** L. Beyer, R. Mattuck.

Denver, CO. September 27, 2017. Utilities Solid Waste Activities Group Decommissioning Workshop.

- **"Applications of Risk-Based Approaches to Remediate PCB's Impacts During Power Plant Decommissioning."** M. Sharma.

Pittsburgh, PA. September 27-28, 2017. Shale Insight.

- Panelist for the session **"Just the Facts: Public Health and the Shale Industry."** C. Long.

Amherst, MA. October 16-19, 2017. Association for Environmental Health and Sciences Annual International Conference on Soils, Sediments, Water, and Energy.

- **"PAH Source Apportionment and Weathering Effects."** C. Tuit, J. Rominger.

Spokane, WA. October 25-27, 2017. Northwest Occupational Health Conference.

- **"Emerging Evidence Addressing Occupational Health Risks of Diacetyl in Coffee Production Facilities."** D. Dodge.

Tampa, FL. November 2-4, 2017. Product Stewardship.

- **"Around the World with Your New Chemicals."** J. Kneeland.
- **"Hazard Assessment: Building Blocks of Compliance and Proactive Product Stewardship."** A. Lewis.
- **"How to Avoid Animal Testing in Your Chemical Registration."** J. Zhang.

Palm Springs, CA. November 5-8, 2017. American College of Toxicology 38th Annual Meeting.

- **"Evaluating *In Silico* and *In Vitro* Approaches for Identifying Developmental and Reproductive Toxicity in the Workplace."** T. Lewandowski, S. Pacheco Shubin, I. Mohar, J. Cohen.
- **"Expert Review of *In Silico* Predictions for Skin Sensitization Potency."** J. Cohen, T. Lewandowski.
- **"Use of Pharmacokinetic Data for Adjustment Factor Derivation for Benzoate Preservatives."** D. Pizzurro, K. Zu, T. Lewandowski, J. Goodman.

What's New at Gradient

Minneapolis, MN. November 12-16, 2017. Society of Environmental Toxicology and Chemistry North American 38th Annual Meeting.

- "**Environmental Statistical Software – Pros and Cons.**" I. Bamgbose.

Santa Clara, CA. November 15-16, 2017. IDTechEx Show.

- "**Will the Newest Wearable Device Leave You Itching for More?**" M. Dothage, T. Lewandowski.

Pittsburgh, PA. December 5-7, 2017. Brownfields.

- "**Building on Vapor Intrusion Sites – Recent Developments and Effects of the New Administration.**" L. Levy, W. Walsh, L. Siegel.

Arlington, VA. December 10-14, 2017. Society for Risk Analysis Annual Meeting.

- "**Benzo(a)pyrene Toxicity Value Updates: Implications for Human Health Risk Assessment.**" J. Chien, J. Lemay.

- "**Comprehensive Multipathway Risk Assessment of Chemicals Associated with Recycled Rubber in Synthetic Turf Fields: An Update.**" J. Lemay, M. Peterson, S. Shubin, R. Prueitt.

- "**Exposures to Styrene from Food Packaging under CA Proposition 65.**" R. Mattuck, X. Liu, G. Greenberg.

- "**Incorporating ToxCast and ExpoCast Data in Naphthalene Risk Assessment.**" L. Bailey, L. Rhomberg.

- "**Using GIS data and tools to assess the vulnerability of industrial facilities and natural resources to flooding events.**" M. Mayo, S. Ikeda, N. Briggs, C. Petito Boyce, D. Mayfield.

- "**YPLL: A Comprehensive Quantitative Tool to Evaluate Worker Risk Under Green and Sustainable Remediation.**" G. Greenberg, B.D. Beck.