GRADIENT
TRENDS
Risk Science & Application

Pharmaceuticals in the Environment – 15 Years Later

By Tamara Lunsman, Ph.D. and Tim Verslycke, Ph.D.

Research on pharmaceuticals in the environment has made great strides, but more work remains to better understand potential human and ecological health risks and to develop effective regulations.

In the 15 years since a widely publicized study by the U.S. Geological Survey (USGS; Kolpin *et al.*, 2002) found widespread occurrence of pharmaceuticals in U.S. streams, research on pharmaceuticals in the environment (PIE) has seen exponential growth (see figure). In this article, we describe key developments related to environmental effects, exposure, and regulation of pharmaceuticals.

…there are no regulatory water quality standards for pharmaceuticals in the U.S. or the EU.

Initial concerns over PIE were primarily focused on the potential effects of estrogenic drugs detected in sewage effluent and receiving waters. These concerns were driven by observations of feminized fish in rivers receiving sewage effluents containing trace amounts of estrogens (ng/L, equivalent to approximately one grain of salt in an Olympic-sized pool). A widely cited study (Kidd *et al.*, 2004) reported the collapse of a wild fish population following chronic exposure to low levels (5-6 ng/L) of a synthetic estrogen used in birth control pills. However, a recent follow-up study demonstrated that the fish population recovered after the exposure ended

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Letter from the Editors

January 2018

Dear Colleague,

In this issue of *Trends*, we discuss the potential adverse environmental and human health effects associated with pharmaceuticals.

The first *Trends* article looks back to a pivotal 15-year-old study documenting pharmaceuticals in U.S. surface waters and describes the significant advances in the measurement, assessment, and regulation of pharmaceuticals in the environment since then. The second article describes how "pharmacoepidemiology," an emerging field bridging clinical pharmacology and epidemiology, is used to enhance drug safety evaluations. The third article describes new advances in computational programs for predicting toxic effects that are improving their capabilities for screening and prioritizing the potential risks that pharmaceutical impurities, or unwanted chemicals associated with the drug development process, can pose.

Gradient contributors to this issue include Drs. Tim Verslycke, Tamara Lunsman, Kirsten Zu, Julie E. Goodman, Joel Cohen, and Tom Lewandowski. Joining us with a guest editorial are Erin M. Bosman and Julie Y. Park from the law firm Morrison & Foerster providing legal perspective on the rise of digital health.

We hope that this issue of *Trends* gives you insight into some of the current hot topics related to pharmaceuticals.

Yours truly,

Chris Long, Sc.D., DABT and Kurt Herman, M.Eng., P.G.
clong@gradientcorp.com kherman@gradientcorp.com

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Pharmaceuticals in the Environment – 15 Years Later

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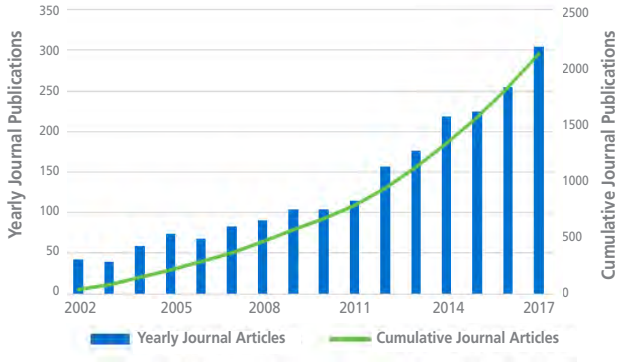
(Blanchfield *et al.,* 2015). While environmental effect studies of endocrine-active drugs remain an area of active research, studies on antibiotics are rapidly increasing. Environmental release of antibiotics can cause antibiotic resistance, which the World Health Organization identified as one of today's biggest threats to global health, food security, and development.

A key development in PIE exposure studies is the ongoing advance in analytical technology that now makes it possible to detect trace quantities of pharmaceuticals, in the sub-ng/L range. While using better analytical methods has provided increasingly detailed information, it remains unclear whether overall environmental exposures to pharmaceuticals have increased. For example, a 2017 follow-up to the 2002 USGS study found higher detection frequencies, but also relied on more sensitive detection limits, making it difficult to elucidate temporal trends (Bradley *et al.*, 2016). The potential importance of sources other than those associated with societal usage was highlighted by a series of studies that found high emissions of pharmaceuticals (in the mg/L range) associated with bulk drug manufacturing in India (*e.g.*, Larsson, 2014). This indicates the need to expand monitoring studies beyond releases from societal uses.

Environmental risks associated with pharmaceutical use have been regulated for decades. In both the U.S. and the EU, environmental assessments are required for drug approval and are regulated by the U.S. Food and Drug Administration (U.S. FDA) and the European Medicines Agency (EMA), respectively. Both the U.S. FDA (FR/Vol. 81, No. 44, p. 11811) and EMA (EMA/CHMP/SWP/44609/2010 Rev.1) published supplementary environmental assessment guidance in 2016 on a range of topics, including ionizable drugs and endocrine active compounds. New environmental assessment guidance is also expected to be released by Health Canada in the near future. At the present time, there are no regulatory water quality standards for pharmaceuticals in the U.S. or the EU. However, in the EU, several pharmaceuticals (including estrogens and antibiotics) have been identified as potentially posing a risk to the aquatic environment and have been added to a regulatory watch list (EU Decision 2015/495). Similarly, under its endocrine disruption screening program, the U.S. EPA released a list of chemicals to be screened, which includes some pharmaceuticals (FR/Vol. 78, No. 115, p. 35922).

So, what are the next big questions related to PIE? Several years ago, experts from academia, government, and industry identified 20 key questions regarding human and ecological health effects of pharmaceuticals (Boxall *et al.*, 2012). These questions fall into seven categories: 1) research prioritization strategies; 2) pathways of exposure; 3) bioavailability and uptake; 4) effects characterization; 5) risk and relative risk; 6) antibiotic resistance; and 7) risk management. Research on these topics is already ongoing and will continue to push our understanding of PIE forward. In particular, we foresee further improvements in pharmaceutical exposure modeling. For instance, the iSTREEM® model can estimate surface water concentrations from societal use of pharmaceuticals using information from approximately 228,000 U.S. river segments, covering over 243,000 U.S. river miles. In the area of pharmaceutical effects assessment, the adverse outcome pathway framework (OECD Guideline 184) will provide opportunities to link mechanistic information at the molecular level to key adverse outcomes at the population level. Finally, further environmental regulations, such as the development of water quality standards or changes to the regulatory approval process of some classes of drugs, such as antibiotics and endocrine-active drugs, seem likely.

Journal Articles on Pharmaceuticals in the Environment Over the Last 15 Years



An article citation search using ScienceDirect shows the dramatic rise of published articles between 2002 and 2017 that contain "pharmaceuticals in the environment" in title, abstract, or keywords.

The authors can be reached at tlunsman@gradientcorp.com and tverslycke@gradientcorp.com.

References:

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Boxall, A.B., M.A. Rudd, B.W. Brooks, *et al.* 2012. Pharmaceuticals and personal care products in the environment: What are the big questions? *Environ. Health Perspect.* 120(9):1221-1229.

Bradley, P.M., C.A. Journey, D.T. Button, D.M. Carlisle, J.M. Clark, B.J. Mahler, N. Nakagaki, S.L. Qi, I.R. Waite, P.C. VanMetre. 2016. Metformin and other pharmaceuticals widespread in wadeable streams of the southeastern United States. *Environ. Sci. Technol. Lett.* 3(6):243-249. DOI:10.1021/acs.estlett.6b00170.

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Pitfalls in Evaluating Adverse Drug Effects

By Kirsten Zu, Ph.D., Sc.D., M.P.H. and Julie E. Goodman, Ph.D., DABT, FACE, ATS

While pharmacoepidemiology is a valuable new tool for tracking the effects of drug use in large populations, researchers must be aware of several issues that can affect data interpretation.

Before a drug can go to market, its safety must be evaluated in clinical trials. However, the small number of participants and relatively short durations of clinical trials mean that they may not capture all potential adverse effects, particularly chronic disease outcomes. Thus, post-market studies are critical to evaluate drug safety.

"Pharmacoepidemiology," an emerging field bridging clinical pharmacology and epidemiology, is the study of the use and effects of drugs in large numbers of people. This relatively new discipline has been primarily used for post-market drug surveillance. With the widespread digitalization of the healthcare system, pharmacoepidemiology studies have increasingly relied on administrative databases of health records to evaluate potential adverse effects of therapeutics. In these studies, information on filled prescriptions is obtained from databases of pharmacies or insurance claims, and researchers determine whether prescriptions are statistically linked to subsequent adverse health outcomes identified from databases of medical records or insurance claims. Pharmacoepidemiology studies can detect drug use-related adverse events that would have been extremely difficult, if not impossible, to identify in pre-market research.

Pharmacoepidemiology studies can detect drug use-related adverse events that would have been extremely difficult, if not impossible, to identify in pre-market research.

Because of the observational nature of these studies (researchers have no control over who gets treatment *vs.* clinical trials, where treatment is assigned) and the use of databases for information on treatment and outcomes, there are several common pitfalls that can impact the findings of pharmacoepidemiology studies. One common issue for pharmacoepidemiology studies is that not all of the participants have the particular diseases (*i.e.*, the indications) for which the drug under study is approved to treat. If a study includes people with off-label drug use, it is difficult to tease out the source of any observed adverse events because it may be related to the condition being treated. For example, to evaluate whether methylphenidate, a prescription drug used to treat attention-deficit/hyperactivity disorder and narcolepsy, increases the risk of suicide attempts, a study needs to exclude patients who received methylphenidate to treat depression (*i.e.*, an off-label use).

Also, study participants often have other coexisting health conditions, and may take medications to treat or control these conditions. If a study does not account for these comorbidities and medications, it may not produce reliable results. For instance, if a study aims to assess whether a drug impacts the risk of adverse cardiovascular events, it is important to account for comorbidities such as diabetes and high blood cholesterol, and the use of medications such as aspirin in the study participants, because these factors independently affect cardiovascular risk regardless of the drug under study.

In addition, many studies determine drug use based on whether participants filled prescriptions for the drug. But in reality, some people may not have initiated the treatment even if they filled the prescription, and others may have not used the drug for the full prescription period. This results in errors in assessing drug use, which in turn undermine the statistical associations between drug use and health outcomes. If a drug has multiple routes of administration (*e.g.*, oral, topical, injections), it may be more desirable to select a route less likely to be self-administered (*e.g.*, intramuscular or intravenous injections) to reduce errors in assessing drug use.

In summary, observational pharmacoepidemiology studies are powerful tools for post-market drug surveillance, particularly for chronic adverse outcomes. However, when interpreting the results of these studies and attempting to infer whether a drug causes a particular adverse event, it is critical to consider the methodological strengths and limitations of these studies, and how they impact the interpretation of the results.

The authors can be reached at kzu@gradientcorp.com and jgoodman@gradientcorp.com.

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Kidd, K., A. Salki, M. Paterson, D. Findlay, K. Mills, P. Blanchfield. 2004. Responses of a freshwater food web to whole-lake additions of a potent estrogen. Presented at the Society of Environmental Toxicology and Chemistry (SETAC) Annual Meeting. 1p.

Kolpin, D.W., E.T. Furlong, M.T. Meyer, E.M. Thurman, S.D. Zaugg, L.B. Barber, H.T. Buxton. 2002. Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999-2000: A national reconnaissance. *Environ. Sci. Technol.* 36(6):1202-1211. Accessed at http://pubs.acs.org/doi/pdf/10.1021/es011055j.

Larsson, D.G. 2014. Pollution from drug manufacturing: Review and perspectives. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 369(1656):20130571. DOI:10.1098/rstb.2013.0571.

Predictive Toxicology: Are We There Yet?

By Joel M. Cohen, Sc.D. and Tom Lewandowski, Ph.D., DABT, ERT, ATS

Computational toxicology is now making major contributions to streamlining chemical evaluations.

Chemical impurities can be present in drugs (*e.g.*, as a process residual), but many of these chemical impurities lack toxicological testing data. The non-clinical safety assessment of these chemical impurities lacking toxicological testing data can pose a significant challenge for pharmaceutical safety specialists. Although *in silico* models for toxicology (*i.e.*, use of computers to predict toxicity) have been developed for at least the past 30 years, recent advancements in computational programs that predict toxic effects based solely on chemical structure are finally becoming commonplace for screening and prioritizing potential chemicals of concern.

The reliability and validity of in silico assessments can vary greatly depending on the health effect of interest.

The reliability and validity of *in silico* assessments can vary greatly depending on the health effect of interest. Mutagenicity, for example, has a well-understood mechanism of toxicity, and a large database of robust and reliable toxicity data for chemicals evaluated *via* the standard bacterial Ames assay. Computer programs designed to identify key chemical structures most often associated with a positive Ames test result can offer a relatively fast and inexpensive alternative for evaluating the mutagenic potential of pharmaceutical impurities. For mutagenicity assessment, these alternative testing approaches have recently seen regulatory acceptance. For example, the International Conference on Harmonisation (ICH) guidance on mutagenicity testing for drugs (ICH M7) requires the use of two complementary *in silico* systems to screen the mutagenic potential of non-active drug ingredients: 1) an expert-rule based approach, and 2) a statistical based approach (U.S. FDA 2015 215-8523). *In silico* models for other health endpoints (*e.g.*, developmental toxicity) are less well accepted but are actively under development.

Currently Available Predictive Toxicology Programs

- Derek Nexus
- Leadscope
- OECD QSAR Toolbox
- Toxtree
- MultiCase
- EPA Toxicity Estimation Software Tool (TEST)

Expert Review of Computational Toxicology Predictions

Both expert-rule and statistical *in silico* approaches are gaining increasing usage across a range of health endpoints. Expert-rule based systems rely mainly on publicly available toxicity data to identify key structural features likely to be involved in a specific toxicological reaction. Chemicals flagged as having one of these structural alerts are predicted to be toxic based on knowledge of chemicals where the same structural feature and toxic effect have previously been seen and there is a clearly defined toxicity mechanism. In contrast, statistical *in silico* approaches rely mainly on large databases of oftentimes proprietary toxicity data for a wide variety of chemical structures. These programs then use statistical analysis to fit the chemical of interest within a probabilistic space ranging from 0-100% probability that the chemical exhibits the toxicity of interest. For mutagenicity, consistent predictions from both expert-rule and statistical approaches may constitute a well-justified hazard classification without the need for additional cellular or animal toxicity testing.

Both expert-rule and statistical *in silico* programs have limitations. Some highly complicated and unusual chemical structures (*e.g.*, metal-based compounds) may be so dissimilar from a program's training set that no valid prediction can be offered (an "out of domain" result). Program output should be reviewed by toxicologists with knowledge of the toxic effect of interest as a final check on model validity. This is particularly important when different *in silico* programs yield inconsistent results; a knowledgeable reviewer may be able to provide an explanation for the disparate results and support a more definitive conclusion. For example, toxicologists can use existing toxicity data (or in-domain *in silico* predictions) for similarly structured analog chemicals in a well-justified read-across assessment. If no suitable analog chemicals exist, a chemical impurity may require *in vitro* testing in the standard Ames assay.

It may be that computational toxicology will never replace actual chemical testing completely. Nonetheless, the field has

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What's New at Gradient

Awards and Announcements

Gradient recently became a Third-Party Profiler of the U.S. EPA's Safer Choice Program.

Gradient has opened a new office in Charlottesville, Virginia.

Gradient is teaming with the Mystic River Watershed Association and the MIT Center for Environmental Health Sciences to assess human health risks associated with boating on the Malden River.

Barbara D. Beck 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.

Michael Peterson was awarded the Society of Toxicology Domestic ToxScholar grant, which allowed him to present about the basics of toxicology to undergraduates at Lake Forest College, Illinois Wesleyan University, Bradley University, and Knox College.

Tim Verslycke was nominated to serve on the U.S. EPA's Board of Scientific Counselors' (BOSC) Safe and Sustainable Water Resources (SSWR) Subcommittee.

Christopher Long has been reappointed as Associate Editor for the Journal of Exposure Science and Environmental Epidemiology.

Publications

Boroumand, A., **G. Greenberg, K. Herman,** and **A. Lewis**. 2017. Incorporating green and sustainable remediation analysis in coal combustion residuals (CCR) surface impoundment closure decision making. *Remediation.* 27(4):29-38.

Cox, L.A., **X. Liu, L. Shi, K. Zu,** and **J.E. Goodman**. 2017. Applying Nonparametric Methods to Analyses of Short-term Fine Particulate Matter Exposure and Hospital Admissions for Cardiovascular Diseases among Older Adults. *Int. J. Environ. Res. Public Health.* 14(9):1051. DOI:10.3390/ijerph14091051.

Goodman, J.E., E.M. Kennedy, and **M.R. Seeley**. 2017. Do Individuals with Asthma Experience Airway Hyper-responsiveness After Exposure to Nitrogen Dioxide? *Regul. Toxicol. Pharmacol.* 89:279-287. DOI:10.1016/j.yrtph.2017.07.021.

Goodman, J.E., K. Zu, C.T. Loftus, **H.N. Lynch, R.L. Prueitt, I. Mohar, S. Pacheco Shubin,** and S.S. Sax. 2017. Short-term Ozone Exposure and Asthma Severity: Weight-of-Evidence Analysis. *Environ. Res.* 160:391-397. DOI:10.1016/j.envres.2017.10.018.

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Pedroso, F.E., F.A. Angriman, A. Endo, H. Dasenbrock, A. Storino, R. Castillo, A.A. Watkins, M. Castillo-Angeles, **J.E. Goodman,** and M.D. Zitzman. 2017. Weight Loss after Bariatric Surgery in Obese Adolescents: A Systematic Review and Meta-analysis. *Surg. Obes. Relat. Dis.* DOI:10.1016/j.soard.2017.10.003.

Peterson, M.K., J.C. Lemay, S. Pacheco Shubin, and **R.L. Prueitt**. 2018. Comprehensive multipathway risk assessment of chemicals associated with recycled ("crumb") rubber in synthetic turf fields. *Environ. Res.* 160:256-268. DOI:10.1016/j.envres.2017.09.019.

Prueitt, R.L., H.N. Lynch, K. Zu, L. Shi, and **J.E. Goodman**. 2017. Dermal exposure to toluene diisocyanate and respiratory cancer risk. *Environ. Int.* 109:181-192. DOI:10.1016/j.envint.2017.09.017.

Zu, K., D.M. Pizzurro, T.A. Lewandowski, and **J.E. Goodman**. 2017. Pharmacokinetic Data Reduce Uncertainty in the Acceptable Daily Intake for Benzoic Acid and Its Salts. *Regul. Toxicol. Pharmacol.* 89:83-94. DOI:10.1016/j.yrtph.2017.07.012.

Upcoming Presentations

San Antonio, TX. March 11-15, 2018. Society of Toxicology Annual Meeting.

- **"A Critical Analysis of the Toxicological Mode of Action of Automotive Brake Dust."** T. Cook, M. Peterson, B. Beck.

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Predictive Toxicology: Are We There Yet?

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evolved sufficiently that it is contributing substantially towards increasing the speed and efficiency of chemical evaluation.

And, as discussed in *Trends* 70, there is an ethical incentive for reducing our reliance on animal testing methods.

The authors can be reached at jcohen@gradientcorp.com and tlewandowski@gradientcorp.com.

Guest Editorial: Managing Product Liability at the Crossroads of Pharmaceuticals and Digital Health

By Erin M. Bosman and Julie Y. Park

High-quality digital health care services have the potential to improve patient health and safety while reducing pharmaceutical companies' liability risk.

It's no secret that digital health is the future of health care. With access to big data, portable wearable technology, and Internet-connected devices, health companies can put a world of data at a patient's fingertips. The rise of digital health may give pharmaceutical companies new opportunities to manage adverse side effects and product liability risk.

Digital health is the next tool for an industry that is already exploring creative pricing based on outcomes.

Consumers want to use digital services for health care. A digital patient survey showed that more than 75% of respondents would use high-quality digital health care services that meet respondents' needs. With advances in sensor technology, patients could monitor continuously any number of vitals from the comfort of their living rooms or while on the go: blood pressure, heart rate, muscle spasms, blood oxygen levels. Quality, easy-to-use technology would make patients want to monitor these metrics.

How can drug companies use this technology to their advantage? Digital health technology has the potential to assist drug companies measure real-time outcomes and side effects by combining digital diagnostics tools with mobile app technology. Digital health is the next tool for an industry that is already exploring creative pricing based on outcomes. Companies could use digital health to combine traditional pharmaceutical therapy with lifestyle changes, such as diet and exercise. In a world where pricing is tied to outcomes, digital health technology could motivate patients towards compliance both in dosing and in adopting healthier lifestyles.

Digital health could help manage side effects, too. Catching side effects early through continuous monitoring could improve patient outcomes. Product liability exposure might be reduced by using data and technology to optimize a patient's side-effect profile. At the same time, companies could collect data that would provide more insight into post-market safety and efficacy trends.

Digital health also holds promise of a future where patients could receive automated warnings for any number of litigation drivers. Take side effects, for example. A drug that causes high blood pressure might trigger an alert on a mobile app telling the patient to go visit their doctor, facilitating the type of preventive care that can cut off failure-to-warn claims. But alerts don't have to be limited to side effects. A mobile app could store data from the pharmacy and alert patients if their medications have expired or been recalled.

Despite these potential benefits, digital health should be approached cautiously. While collecting data might empower companies to manage risk more proactively, companies might come under increased obligations to warn based on access to information that reasonably could have put them on notice of a hazard.

Beneficial or not, one thing is clear about digital health: it is the future of health care. Recognizing this, the FDA recently issued a Digital Health Innovation Action Plan. Pharmaceutical companies should embrace this future and anticipate ways that improving patient safety through digital health can impact their product liability risk profile.

Erin Bosman is chair of, and Julie Park is a partner in, Morrison & Foerster's product liability practice. They defend pharmaceutical, medical devices, and consumer products clients against mass tort and class action claims. They also advise clients on product risk assessments and minimizing liability exposure. They can be reached at EBosman@mofo.com and JuliePark@mofo.com.

By The Way...

In November 2017, the U.S. FDA approved the first digital pill (Abilify MyCite) for the U.S. This pill, which is used to treat schizophrenia and bipolar episodes, includes a digital ingestion tracking system to record that the medication was taken.

Source: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm584933.htm

What's New at Gradient

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- "**An Analysis of Uncertainties in Minnesota's Reference Dose (RfD) and Health-based Value (HBV) Drinking Water Limits for PFOA and PFOS."** D. Pizzurro, M. Seeley, H. Lynch, L. Kerper, B. Beck.
- **"A Safety Analysis of an Energy Drink."** L. Beyer, M. Hixon, L. Kerper.
- **"Critical Evaluation of Thresholds for Respiratory Effects of Toluene Diisocyanate."** H. Lynch, R. Prueitt, I. Mohar, J. Goodman.
- **"Critical Review of the Evidence for a Causal Association Between Exposure to Asbestos and Esophageal Cancer."** M. Peterson, I. Mohar, T. Cook, A. Engel.
- **"Derivation of Maximum Allowable Dose Levels for Bisphenol A."** J. Goodman, M. Peterson, M. Hixon, S. Pacheco Shubin.
- **"Evaluation of Interspecies Differences in Susceptibility to Thyroid Perturbation."** T. Lewandowski.
- **"Evaluation of Respiratory Cancer Risk from Dermal Exposure to Toluene Diisocyanate."** R. Prueitt, H. Lynch, K. Zu, L. Shi, J. Goodman.
- **"Get the Lead Out: The Persistent Problem of Lead Exposure from Soil, Dust, and Water."** B. Beck, M. Seeley, R. Mattuck.
- **"Incorporating ToxCast Data into Naphthalene Human Health Risk Assessment."** L. Bailey, L. Rhomberg.
- **"Interspecies Comparison of Perfluorinated Chemical Pharmacokinetic Parameters."** M. Seeley, D. Pizzurro, B. Beck.
- **"Skin Sensitization Assessment for 1,796 Chemicals Extracted from Apparel Products."** I. Mohar, J. Cohen, S. Pacheco Shubin, T. Lewandowski.
- **"Systematic Review and Meta-analysis of Diazepam and Labor Duration."** X. Liu, K. Zu, J. Goodman.
- **"Use of Clinical Data to Inform Risk Assessments of Food Additives: A Case Study of Sodium Benzoate."** K. Zu, J. Goodman, D. Pizzurro, T. Lewandowski.

New Orleans, LA. March 18-22, 2018. American Chemical Society National Meeting.

- **"Chemical Safety Evaluation Challenges of the Lautenberg Chemical Safety Act."** T. Lewandowski, J. Rice.
- **"Does One Size Fit All? Tailoring Read-across Methodology Based on Endpoint-specific Criteria."** J. Rice, J. Cohen, T. Lewandowski.
- **"Evolving Chemical Hazard Evaluation Strategies to Address Compliance under the New Toxic Substances Control Act (TSCA)."** J. Rice, T. Lewandowski.
- **"Potential Health Risks of Cannabis Extracts."** T. Lewandowski, J. Rice.

Join Gradient's *Trends* authors for a live webinar for further discussion on this Pharmaceuticals issue.

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Gradient
Cambridge, MA
Seattle, WA
Charlottesville, VA
trends@gradientcorp.com
www.gradientcorp.com

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Climate Change Response

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