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Cultivating Scientific Integrity

By Tim Verslycke, Ph.D., and Dave Mayfield, M.S., DABT, BCES

As scientific research comes under increased scrutiny in today's hyper political world, it is imperative that scientists continue to pursue the highest levels of scientific integrity in their research.

Science and scientific research form a cornerstone of our society. Billions of research dollars are spent in ways that not only enhance our understanding of the natural world, but also boost economic growth and improve our health (NAS, 2017). Science is often assumed to be of the highest integrity; objective, honest, and transparent. Misconduct is supposed to be prevented through the peer review process (of research proposals and scientific journal publications) and independent replication of published findings. Yet, scientists are human and therefore fallible, and skepticism of scientists and scientific findings are as old as science itself. Still, something has changed. In 2016, in the context of a contentious political environment, Oxford Dictionaries chose "post-truth" as the international word of the year, which it defined as "relating to or denoting circumstances in which objective facts are less influential in shaping public opinion than appeals to emotion and personal belief." In this "post-truth" climate, there has been a growing concern that science is no longer insulated from interference, suppression, or manipulation.

In this "post-truth" climate, there has been a growing concern that science is no longer insulated from interference, suppression, or manipulation.

High-profile cases of research misconduct, including data fabrication, falsification, and plagiarism, put the topic of scientific integrity firmly in the spotlight. Unfortunately, such cases of flagrant research misconduct are not isolated

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I N S I D E

Letter from the Editors

September 2019

Dear Colleague,

In this issue of *Trends*, we pause from writing about a technical topic to address the increasingly challenged context within which scientists work. This issue will address scientific integrity.

The first article provides an overview of the importance of scientific integrity amidst rising public distrust, and outlines ways that integrity can be cultivated within the research and publication processes. The second article addresses tools intended to minimize bias in scientific research. Our final article explores the role that uncertainty plays in toxicology and risk assessment.

Gradient contributors to this issue include Drs. Tim Verslycke, Lisa Bailey, Teresa Bowers, Lorenz Rhomberg; and Dave Mayfield, M.S. Joining us for our guest editorial is Trevor Butterworth, Executive Director of Sense About Science USA, who will discuss the ongoing controversy regarding the reproducibility of scientific studies.

We hope that this issue of *Trends* will give you insight into the importance of integrity in scientific pursuits.

Yours truly,

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Cultivating Scientific Integrity

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incidents, with a meta-analysis of survey data finding close to 2% of scientists admitting to having fabricated, falsified, or modified data or results at least once (Fanelli, 2009). The prevalence of less severe research misconduct has been reported to be much higher, and includes plagiarism, duplicate publication, and conflicts of interest (Fanelli, 2009).

In response, various scientific institutions, professional organizations and governmental agencies have increased their focus on scientific integrity. For example, The National Academy of Sciences published a 2017 report on fostering integrity in research (NAS, 2017). Just recently, the U.S. Government Accountability Office (GAO) published scientific integrity policies that contain additional actions intended to strengthen the integrity of federal research (GAO, 2019).

There have been similar efforts in the environmental sciences field. For example, we co-authored a recent publication on scientific integrity issues in environmental toxicology and chemistry (Mebane *et al.*, 2019). This paper was the result of a tripartisan effort among academia, business, and government scientists. It describes scientific integrity as a set of norms similar to those taught from a young age (see figure).

The authors concluded with a number of actions that could be taken to maintain and improve a culture of scientific integrity, such as: scientific institutions should increase attention to quality management training; scientific journals should require that all supporting data of a published study be included and consider rejecting studies that lack such data; science users should be discouraged from judging science solely on the basis of its funder and should instead maintain an open-minded skepticism; and professional societies should help foster respectful evidence-based dialog during meetings and support scientific integrity training seminars.

Ultimately, the need to foster a culture of research integrity is a critical challenge faced by anyone that funds or conducts research. As environmental consultants, we are generators, interpreters, and communicators of scientific research and therefore have an important role to play. Whether in a journal publication, technical report, during a public meeting or during trial testimony, it is our role as scientists to educate and advocate for transparency and sound science.

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GAO. 2019. Report to the Ranking Member, Committee on Commerce, Science, and Transportation, U.S. Senate. SCIENTIFIC INTEGRITY POLICIES Additional Actions Could Strengthen Integrity of Federal Research.

Mebane, C.A., J.P. Sumpter, A. Fairbrother, T.P. Augspurger, T.J. Canfield, W.L. Goodfellow, P.D. Guiney, A. LeHuray, L. Maltby, D.B. Mayfield, M.J. McLaughlin, L.S. Ortego, T. Schlekat, R.P. Scroggins, T.A.Verslycke. 2019. Scientific integrity issues in Environmental Toxicology and Chemistry: Improving research reproducibility, credibility, and transparency. *Integr. Environ. Assess. Manag.* 15(3): 320-344.

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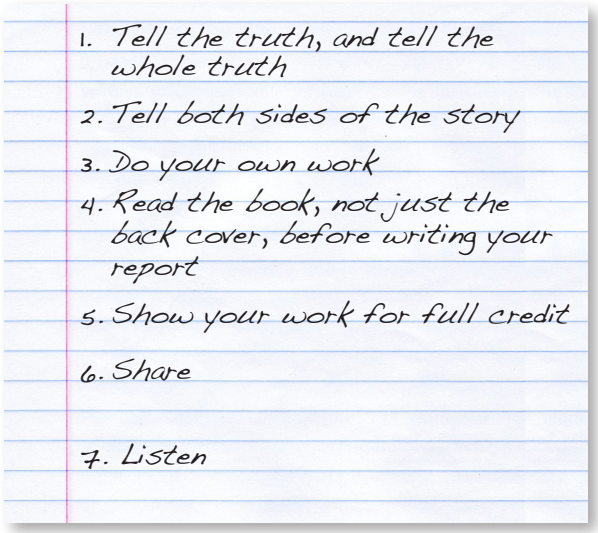
SCIENTIFIC INTEGRITY AS A SET OF NORMS SIMILAR TO THOSE TAUGHT FROM A YOUNG AGE



1. No data sanitizing, no selective reporting, and all conflicts reported
2. Avoid bias
3. No plagiarism
4. Properly research and cite primary sources
5. Transparency
6. Publish your work and data in peer-reviewed outlets for collective learning
7. Listen with humility and collegial fraternity to observations and suggestions of others

Tools for Minimizing Scientific Bias

By Lisa Bailey, Ph.D., and Teresa S. Bowers, Ph.D.

The systematic review and peer review processes – when done properly – can be powerful tools for minimizing bias.

The vast majority of scientists do not operate from a position of overt bias, and yet it is important to both employ and acknowledge techniques to minimize subjectivity and bias in scientific work. There are (at least) two junctures where tools can be used in this regard: by the scientist themselves during the analytical process, and by other scientists in the form of review of work before or after publication.

An in-depth toxicological evaluation, of the type typically required for substances where the data do not clearly point in one direction or the other, often requires identifying and synthesizing large amounts of scientific information. Since it is critical that these analyses be carried out in an objective and transparent manner, scientists have developed tools that can be employed during the analytical process to organize, evaluate, and communicate scientific information. The process of applying these tools to address a specific scientific question has been referred to as "systematic review and evidence integration" (see figure).

…the potential for bias comes with every funding source, whether it be corporate research or governmental grants…

Systematic review requires study identification and study quality evaluation, the aim of which is to provide a consistent and objective system for bringing study strengths and weaknesses to bear on the question of potential toxicological effects. Study quality evaluation frameworks have been developed that include specific criteria intended to help researchers determine how best to weight each study within the evaluation. For example, "risk of bias" – the concern for possible sources of systematic or directional error (as opposed to imprecision) – needs careful consideration for a toxicological evaluation, and is a key feature of most study quality evaluation frameworks. Funding sources and conflict of interest statements are also necessary criteria to provide transparency, but by themselves should not weigh heavily toward study quality.

Scientists have also developed frameworks for evidence integration that provide a methodology to synthesize scientific information within and across lines of evidence (see figure) so that each line of evidence can help inform interpretation of the others, and the overall confidence in the body of evidence can be determined and applied to decisions around particular toxicology and health effects questions. Therefore, study quality and evidence integration frameworks are critical tools that allow the researcher to communicate the soundness of scientific methods and confidence in overall scientific conclusions in a way that is clear and transparent to reviewers and readers.

Peer review, the process by which other scientists with similar or overlapping expertise evaluate a piece of work prior to publication, serves as the current gate-keeper of the scientific publication system. Peer review is meant to identify which science is ready for publication, and which is not, on the basis of its scientific merits alone. For a toxicological evaluation, this process should consider whether it has followed a scientifically sound systematic review and evidence integration process. It should be recognized that the potential for bias comes with every funding source, whether it be corporate research or governmental grants, but allegations that science from specific funding sources is inferior and should not be published is an insult to the peer

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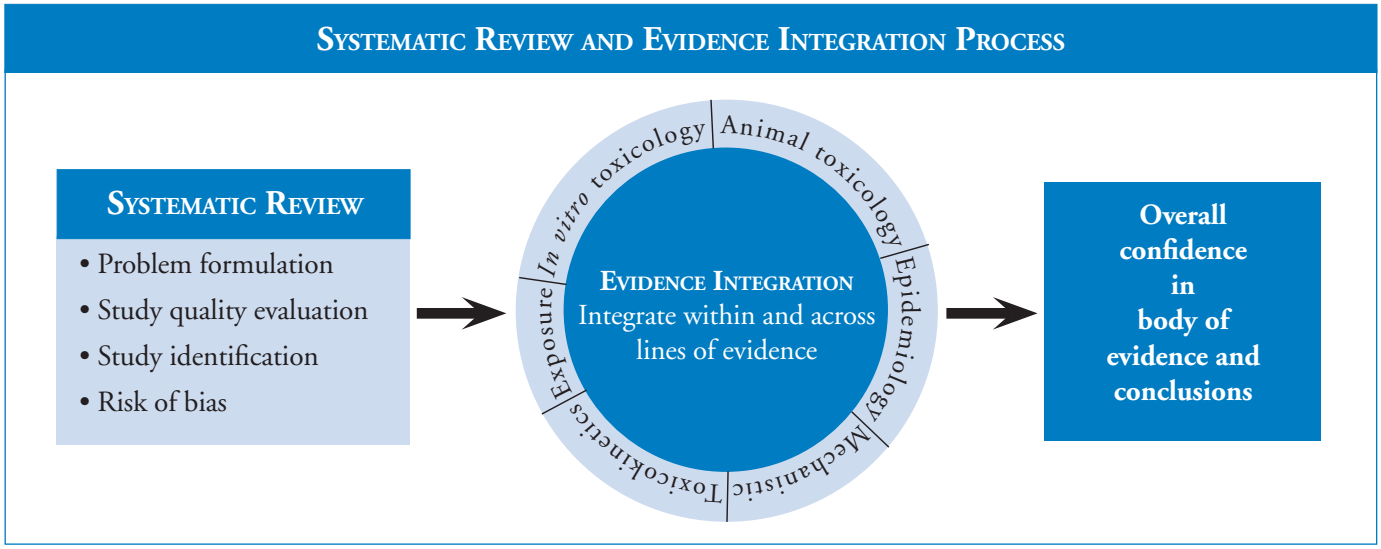
Systematic Review and Evidence Integration Process



Probing Uncertainty Is What Makes it Science

By Lorenz Rhomberg, Ph.D., ATS

Debating the uncertainties of science and uncovering different interpretations of the data ultimately creates strong, reliable, and actionable science.

One sometimes sees in the criticism of scientific commentary on risk assessments that the commenters are merely trying to "manufacture doubt" in an attempt to delegitimize regulatory actions. It is implied that the actual truth is evident, and the probing of scientific issues is merely self-serving attempts to obscure the facts. This view profoundly misunderstands the nature of scientific evidence and of its application to regulatory analysis.

…the explorations of the limits of scientific certainty are a means not for creating doubt, but for reducing it.

First off, some scientific uncertainty is always there; it's not a matter of creating it but rather of examining it and working through the implications. Science does this through the examination of tentative hypothetical explanations for the observed phenomena (and for their generalizability to apply to the assessment's target risk question). Alternative tentative explanations are vetted against the data at hand – not just the experimental results but also our deeper knowledge of underlying biology, species differences, dose-dependency patterns, and so on. Good, dependable scientific explanations are those that stand up to such skeptical attempts at finding alternative possible interpretations. In short, the explorations of the limits of scientific certainty are a means not for creating doubt, but for reducing it. We scope out the span of supportable inferences by challenging each specific hypothesis against the array of data, thereby eliminating some and placing limits on those that remain.

In toxicology, for instance, we examine effects at high exposures in experimental animals to make inferences about possible effects from low and variable exposures in humans. Different studies may contradict one another, and many examples exist where human risks are not found for agents that cause high-dose effects in animals. Extrapolations and generalizations are made as the regulatory analysis applies these facts to infer possible (but not directly observed) effects that might occur at low exposures in the human population, as well as to help determine exposure limits that can be expected to be protective. Seeing how well such inferences stand up to scientific skepticism is the means for narrowing the range of tenable interpretations, while also recognizing that some questions cannot be fully and unambiguously answered.

The misunderstanding about the application of science to regulatory evaluation is the failure to recognize how it copes with making decisions in the face of some unavoidable uncertainty. Definitive and unassailable knowledge is not needed to act, but to avoid being arbitrary, it is important to assess the consequences of the limits to knowledge. And to do this, one needs to characterize those limits. How much certainty is needed to justify which actions is not itself a scientific question, but a risk management policy decision.

It is sometimes said that decisions should be "precautionary" and guard against any exposure that cannot definitively be deemed without risk. But all substances – natural as well as artificial – pose some toxicity concerns at sufficiently high exposures, and so the question of how this information informs low-exposure risk potential is not avoided. These decisions can be made if a forthright exploration of the uncertainties in the characterization of risk or safety has been made, and its soundness debated in the scientific community.

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review system, and denigrates the scientists who give their time as peer reviewers. The gate-keeping role of the peer review system is why scientific journals that publish peer reviewed articles carry distinction over publications carrying non-peer reviewed materials.

Of course, the peer review system is not perfect, and that is why the opportunity for published comment/response is also important. It has been said that the real peer review process begins when a piece of scientific work is published. The published comment/response cycle is an important part of the vetting process in science, and can point to new required avenues of analysis, or to fatal flaws. And finally, it is a truism that if everyone agrees with what you're doing, you're not on the cutting edge of science.

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What's New at Gradient

Awards and Announcements

Joel 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.

Joel Cohen was invited to serve on the EPA's All Ages Lead Model (AALM) Scientific Advisory Board (SAB) Review Panel.

Joel Cohen has been appointed to the Secretary position for Society of Toxicology's Computational Toxicology Specialty Section.

Julie Lemay has been reelected to the Belmont, MA Board of Health.

Publications

Johnson, K., **S.R. Boomhower,** M.C. Newland. 2019. Behavioral effects of chronic WIN 55,212-2 administration during adolescence and adulthood in mice. *Exp. Clin. Psychopharmacol.* doi:10.1037/pha0000271.

Pizzurro, D.M., M. Seeley, **L.E. Kerper, B.D. Beck**. 2019. Interspecies Differences in Perfluoroalkyl Substances (PFAS) Toxicokinetics and Application to Health-Based Criteria. *Regul. Toxicol. Pharmacol.* 106:239-250. doi:10.1016/j.yrtph.2019.05.008.

Yamada, T., K. Asano, K. Miyata, **L.R. Rhomberg,** J.K. Haseman, P. Greaves, H. Greim, C. Berry, S.M. Cohen. 2019. Toxicological evaluation of carcinogenicity of the pyrethroid imiprothrin in rats and mice. *Regul. Toxicol. Pharmacol.* 105:1-14. doi:10.1016/j.yrtph.2019.03.012.

Upcoming Presentations

Columbus, OH. September 10-12, 2019. Product Stewardship 2019.

- **"From 60 Day Notice to Compliance: Navigating Prop 65 Testing and Exposure Assessment Challenges."** K. Reid, R. Mattuck, C. Kagel, A. Lewis.
- **"Polymers: Global Product Stewardship Approaches."** J. Kneeland, J. Zhang, G. Becker.

Philadelphia, PA. October 7-10, 2019. MGP Conference 2019.

- **"Developing and Implementing an MGP Site Prioritization Framework."** J. Rice, K. Herman.
- **"Source Allocation Modeling: Checking Under the Hood."** C. Tuit.

Phoenix, AZ. November 17-20, 2019. American College of Toxicology 2019 Annual Meeting.

- **"Safety Evaluation of High Potency Mutagenic Impurities: A Timely Case Study."** J. Cohen, W. Liu, M. Jordi.
- **"Evaluation of Silicone Rubber as a Potential Impurity in a Drug Product."** T. Lewandowski, S. Pacheco-Shubin, I. Mohar.
- **"A Comparison of Environmental Assessment Requirements of New Human Drugs in the U.S. and the EU."** I. Mohar, T. Lunsman, T. Verslycke.

Arlington, VA. December 8-12, 2019. 2019 Society for Risk Analysis Annual Meeting.

- **"Assessing Exposure Using an Image-based Land Cover Classification Model."** M. Mayo, C. Marsh.
- **"Water Quality Simulation to Inform Design of a Disinfectant-Free Floating Pool in New York City."** A. Dale, J. Lemay, H. Lynch, T. Bowers.

Guest Editorial: The Importance of Scientific Reproducibility

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Ioannidis, J.P.A. 2017. The Reproducibility Wars: Successful, Unsuccessful, Uninterpretable, Exact, Conceptual, Triangulated, Contested Replication. *Clinical Chemistry.* 63 (5), pp. 943-945.

Marcus, A., I. Oransky. 2018. Meet the 'data thugs' out to expose shoddy and questionable research. *Science.*

By The Way...

A premier U.S. university has settled for $112 million over claims of falsified data.

Source: *The Washington Post.*

Guest Editorial: The Importance of Scientific Reproducibility

By Trevor Butterworth, M.S.

The reproducibility of results is a cornerstone of sound science.

In his article,"The Reproducibility Wars," John Ioannidis outlined what could be thought of as replication's equivalent of David Kessler and Elisabeth Kübler-Ross's five stages of grief (Ioannidis, 2017). First, there are accusations of replicator incompetence, they just didn't do the replications right; second, the replicators are engaging in unconscionable shaming or even methodological terrorism, tarnishing the work of great scientists in the process; third, the replicators are thwarting scientific discovery and the ability to do critical translation work; and fourth, through "conceptual triangulation," it doesn't really matter if there is exact replication as long as there is a consistent story across various similar-ish studies.

The "reproducibility wars"…won't end without many more high profile defeats for the rhetorically strong but methodologically weak.

The "reproducibility wars" have been a long time coming. One could date the beginning of the revolution to Doug Altman's lacerating 1994 editorial in the *BMJ*, "The scandal of poor medical research." As Altman noted, "When I tell friends outside medicine that many papers published in medical journals are misleading because of methodological weaknesses they are rightly shocked."

Revolution, however, requires a grassroots movement to will editorials into cultural change; and while readers of Altman's editorial rated it, in a 2015 poll, as the most important paper the *BMJ* had published in the previous 20 years, Altman had to launch initiatives to do something about these problems. There wasn't a ready-made community of revolutionaries waiting to take action back in 1994.

Almost a quarter century later, speaking at the first American Statistical Association (ASA) Symposium on Statistical Inference in 2017, the Dutch mathematical psychologist E.J. Wagenmakers echoed Altman's complaint: if the public really knew how science was made, with all its conveniences and expediencies, they'd be shocked.

But amid such righteous anger, there was a critical difference: the grassroots movement for reform now existed. The ASA had convened the symposium (where Wagenmakers spoke) and its goal was to bring an end to the tyranny of misapplied p-values and significance testing. Reproducibility was now a part of a much wider reform movement in science – one focusing on openness, transparency, and methodological rigor.

You will have noticed that I omitted the fifth stage of reproducibility grief – acceptance. The "reproducibility wars" will not be over anytime soon, and it's clear that they won't end without many more high profile defeats for the rhetorically strong but methodologically weak. At some point the benefits of publication and media coverage will be weighed against the risks of methodological critique and retraction; "data thugs" and methodology bloggers represent a new kind of highly public peer review (Marcus, 2018).

There are also innovative efforts underway to see if new tools, including artificial intelligence, can be used to assess, at least in part, scientific research methodologies, data, and outcomes. Progress in natural language processing over the past decade has been startling and, in reality, beyond what many people realize. If successful, the "reproducibility wars" will rapidly end because journal editors will have evaluative superweapons and will be pressured to use them. Either way, scientific culture is changing; the question is which side of the "reproducibility wars" are you going to fight on?

Trevor Butterworth is the Executive Director of Sense About Science USA. He can be reached at trevor@sensci.org.

References:

Altman, D. 1994. The scandal of poor medical research. *BMJ*. 308.

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The next issue will focus on:
New Frontiers in Risk Assessment

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