The Challenge: Bias is creeping into the science behind risk assessments and undermining its use and credibility.

Increasing concerns about conflicts of interest and bias in chemical risk assessment are leading to initiatives and calls for action that are sometimes more confrontational than they should be and will not necessarily lead to more scientifically sound decisions. On the other hand, most assessors continue to accept published results without due diligence to detect bias. The most widely publicized issues of bias relate to studies funded by industry, due to a perception of conflict of interest. But there are also potential biases from academic research that relate to career and funding pressures, and there has been an increasing number of retractions of work from internationally renowned journals such as Nature and Science. Government and regulatory science can also be suspected of bias for political pressures. Ideally, the scientific method should work independently of all of these issues and deficiencies and lead to unbiased scientific conclusions. Unfortunately, this is not guaranteed either for guideline studies conducted under good laboratory practice but is subject to the peer-review process. This means that science does not always self-correct, at least immediately. The present Perspectives column assesses the challenges for the science of risk assessment in the regulatory arena and offers a series of suggestions, from different perspectives, for how they can be addressed.

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In Response: We are all biased, but the scientific process recognizes that and delivers despite it; still, it can do a better job—A perspective from academia

There is not much reason to believe that scientists as individuals do not suffer from the same cognitive biases and use the same heuristics (rules of thumb in solving problems) as people in general [1,2]. There is a persuasive argument that evolution shaped our rapid, intuitive responses to problem-solving based on a need to survive in an ancestral environment that is not necessarily in tune with our current needs for problem-solving in a technological age [3]. This is 1 reason why our preconceived ideas about likely adverse effects from risk agents or about the causes of observed adverse effects in people and ecosystems often turn out to be wrong.

Science, the process, recognizes these fundamental biases and has delivered knowledge that has worked to improve health, communication, transport, and a host of other benefits. There are 2 important features of the scientific process. First, all preconceived ideas seeking to explain anything are assessed using evidence from carefully controlled conditions (the experimental ideal); second, this should be carried out in a way that is acceptable to the community of scientists through peer review and publication. So science is supposed to be self-correcting.

Yet an increasing body of evidence begins to call into question the ability of science to self-correct. This includes evidence of funding bias in risk assessments [4] and, more broadly, evidence of increasing retraction rates in the primary literature that are predominantly the result of fraud [5], as well as concerns about ability to reproduce results from work in both the social [6] and natural [7] sciences. The implications are that the evidence is being collected sloppily and that factors other than those based on evidence are influencing the conclusions drawn from the scientific work.

Developments such as these seem to be increasing as the opportunities to publish increase—for example, through various online venues—and as the pressures to publish for recognition, career development, funding requirements also increase. This raises deep and difficult questions for which there is unlikely to be a silver bullet solution. Yet there can be no doubt that a process of knowledge acquisition that is based on evidence is likely to lead to better conclusions for risk assessment, and environmental policy in general, than one based on intuition and negotiation. So the imperative is to improve on the science process to deliver more effectively. An important aspect of
this will surely come from increased transparency afforded by the Internet itself. This will provide a more powerful basis for allowing more effective scrutiny of the evidence base of scientific findings to the satisfaction of the community of scientists than has been possible with traditional approaches based on paper publications. Already it is possible to publish detailed methodologies and databases online as supplementary materials. There are calls for hypotheses and study designs to be published in advance of the work being done and even to publish workbook writings in real time [8]. Peer review can be published in advance of the work being done and even to detailed methodologies and databases online as supplementary based on paper publications. Already it is possible to publish scientists than has been possible with traditional approaches applications is the ultimate test of reliability. The rest falls by the wayside.

In our view, all these opportunities should be embraced as a way of developing an even more credible science basis for risk assessment and policy advice. We all depend on science that works; indeed, that science can work in real-world applications is the ultimate test of reliability. The rest falls by the wayside.

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In Response: Bias in the science that supports environmental assessments—A perspective from regulatory assessment

Concerns about actual and perceived biases in environmental assessments and their consequences for public trust and environmental quality led us to publish articles on bias in data and bias in the performance of assessments [1,2]. These articles describe the problems, summarize the evidence that the problems are important, and present some potential solutions.

We presented summaries of these articles at the SETAC 2015 North America Annual Meeting in 1 of 2 sessions that addressed issues of bias in environmental science. The other presentations and comments from the audience focused primarily on funding bias, which has prompted us to revisit the issue with a regulatory assessor’s perspective. Assessors at the USEPA that “Funding sources should be considered in the risk-of-bias assessment conducted for systematic reviews that are part of an IRIS [Integrated Risk Information System] assessment” [5]. The USEPA IRIS program has not determined how to implement that recommendation, but funding bias is assessed in the navigation guide systematic review methodology [6].

Another response to studies demonstrating that funding bias occurs is that industry scientists would not bias their results because it is not in their long-term interest. That is, incorrect results may be detected, and the results of detection would be embarrassing and costly. That argument would hold if there were not so many instances of scientists and organizations that risk their reputations for short-term benefit. The obvious current example is the defeat device on the Volkswagen “clean diesel” engines [7]. More mundane examples of scientists risking their reputations for short-term benefit can be found by perusing the thousands of cases of altered photos, plagiarism, and data manipulation documented by the website Retraction Watch.

In addition, this response implies that all biasing of data is deliberate, which it often is not.

A third response that we heard was, “it is not just industry-funded scientists.” That is certainly true. Anyone with an advocacy position or financial conflict of interest is prone to bias. Since most studies that generate data used in regulatory assessments are funded by industry, most of the conscious and subconscious pressures to bias results are industry pressures. However, some data are generated by agency contractors (notably for agency-led remedial investigations of Superfund sites), and the agency must be skeptical of the quality of those data as well. Although they are not motivated to bias results in one direction or another, agency contractors may take shortcuts or otherwise compromise the data. Finally, some environmental and health advocates have been found to bias their science. For example, the fraudulent assessments performed by Maest and Beltman on behalf of Ecuadorian villagers came to light while the USEPA’s Bristol Bay watershed assessment was being written [8–10]. As a result, conclusions based on 2 reports...
coauthored by Maest were deleted from the assessment, even though those reports had passed a peer review and were believed to be correct. The USEPA simply could not use the products of a scientist who had admitted to a lack of integrity.

A fourth response is, “everybody is biased.” This special case of the “everybody does it” excuse cannot satisfy a regulatory agency any more than it satisfied your mother. The strength of the motivation for bias and the opportunity to substantially bias the body of evidence for a chemical must be taken into account. The cognitive and heuristic biases that we all possess are not equivalent to the bias in favor of an employer’s or client’s product or in favor of an environmental advocacy group’s position.

Many of the statements of industry scientists were the opposite of “everyone is biased.” They stated or implied that they are good unbiased scientists, and we should not imply that they are not. Recognizing sources of bias does not imply conscious ill intent or submission to biasing management directives. Just the process of acculturation to a particular place of employment can bias perceptions and inclinations. G. Suter joined Oak Ridge National Laboratory with no particular feelings about nuclear energy; but after years of walking among reactors and interacting with nuclear scientists and engineers, he developed a bias in favor of nuclear energy, which has since subsided.

The most important response of regulatory agencies to the potential for biased science has been preemptive measures such as requirements for use of standard methods, good laboratory practices, training, chain of custody, inspections, and full documentation and disclosure of processes and results. When they apply, as in pesticide registration, these requirements reduce the opportunities for bias; but they are not sufficient. Agencies must check documentation, reanalyze the original data, and otherwise perform their due diligence. This quality-assurance process creates a bias in favor of industry-funded studies. Even when nonindustry studies are available for a chemical, they do not have the reassuring quality assurance that the industry studies have, and they often have unconventional methods and nonstandard results that make them harder to interpret. As desirable as they are, standardization and quality assurance cannot eliminate bias. In fact, they introduce a bias against nonstandard but potentially sensitive taxa and responses. Finally, no quality-assurance requirements can preclude deliberate falsification of results, including quality-assurance documentation. The most notorious case was Industrial Bio-Test Laboratories, which falsified thousands of tests [11].

The primary evidence of funding bias is differing results from studies with different funding sources; see a review of the Cochrane database [12] and other studies listed in Suter and Cormier [1]. However, with a few exceptions, such as atrazine, it has not been possible to clearly show a pattern in environmental toxicology and chemistry results because there are too few industry and nonindustry studies of a common chemical and endpoint. In most cases, assessors must attempt to detect bias in individual studies, not bodies of studies.

In the end, scientists at regulatory agencies, like all good scientists, must apply open-minded skepticism before accepting data. If they do not, they are failing to fulfill their legal obligations to the public and to the environment. Accepting scientific results at face value would be a dereliction of duty.

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In Response: Resolving the perception of bias in a discipline founded on objectivity—A perspective from industry

Science should be objective and should be evaluated based on its merit rather than its funding source. However, a perception exists among parts of society that research sponsored by industry is inherently biased, and perhaps more insidious is the notion that academics who collaborate with industry partners are therefore also biased by association. This misconception is not only unproductive but actually counterproductive as it devalues research based on funding source, detracts from the
collaborative SETAC tripartite paradigm (business, government, and academia), and corrodes the educational fabric from which all scientists are sewn.

Why is it that society assigns bias solely by affiliation post hoc? Most students enter college with an ambiguous, often fanciful, notion of a career path, which is dynamic and subject to change during the formative years of undergraduate studies but which does serve to inform field of discipline or interest. Moreover, at the conclusion of a graduate degree or postdoctoral appointment, a career path can still be frequently indeterminate, absent definitive commitment of figurative orientation toward any particular angle of the tripartite paradigm. The reality is that occupation is rarely predetermined but rather subject to opportunity and the nuances of the job market and availability. Moreover, mentors can have a disproportionate influence, either reinforcing bias by affiliation or encouraging students to explore all options when seeking the most appealing opportunity for employment. However, it is at this crucial juncture that society often ascribes bias by affiliation. This is a peculiar and seemingly illogical behavior given that employees in government, industry, and academia are all sourced from the same educational system, from the same academic institutions, and often from the same laboratories, mentors, and advisers, which instill commensurate scientific training, education, experience, integrity, morals, and ethics. Consequently, an insinuation of affiliation bias categorically ignores educational equality and job opportunity/availability and is therefore completely irrational. Ultimately, society would be better served by tripartite cooperation rather than tripartite segregation; and we, as members of the scientific community, and more importantly as members of society, have the capacity to effect this change.

Why does the public mistrust “industry-sponsored” research? Historical examples of naiveté and negligence fostering skepticism about the pesticide industry certainly exist. Regarding the latter, among the most egregious and notorious examples is Agent Orange [1], a tragic illustration of gross misconduct that can be neither tolerated nor defended. Regarding the former, perhaps the most prominent example is DDT. The initial discovery of DDT was hailed as a public health miracle in terms of controlling the vector-borne spread of malaria, though there were obvious unintended environmental consequences that were exposed by the seminal work of Rachel Carson [2]. However, it is important to keep in mind that this revelation led to the establishment of the US Environmental Protection Agency (USEPA) and effective regulation of the pesticide industry. Still, it is generally not understood that the pesticide industry is in fact intensively and stringently regulated; in the United States, this is done under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) [3]. In addition, the environmental and health scientists who work for industry have a moral obligation and ethical responsibility to inform their management of the risk of harm, a very important function supporting the development and use of the products a company produces. Much of the data generated by industry are submitted as confidential business information status under FIFRA statutes that protect its confidentiality (FIFRA Sections 10 and 3[c][1][F]; section 10 is trade secrets, and section 3[c][1][F] is data compensation), resulting in public suspicion and frustration, although the US Congress recognized this as a problem and implemented checks and balances that govern the standards by which scientific data are generated by industry. However, as described by Hon and Grunig [4], distrust is not the absence of trust, nor is trust the absence of distrust, though distrust is more salient than trust since negative information is considered to have a stronger effect on public perceptions than positive information [5]. In addition, distrust has 2 dimensions: lack of credibility and malevolence [4,5]. The former is resultant primarily from lack of transparency (i.e., data confidentiality) and lack of public understanding of the regulatory process, and the latter derives largely from the for-profit status of corporations. Although confidential business information and corporate profit are challenging perceptual hurdles to overcome, greater transparency, education, and credibility can be achieved through tripartite collaboration.

Furthermore, increasing the understanding of the process whereby industry-sponsored research is conducted and used by government agencies will aid in establishing and promoting trust. Industry is required to submit studies on the environmental fate and effects of their products under the good laboratory practice regulations [6]. These regulations, which have been in place for more than 25 yr, cover studies submitted to regulatory agencies worldwide on many types of substances (pesticides, drugs, industrial chemicals, etc.). Good laboratory practice encompasses many of the basic elements of conducting a sound scientific investigation, including having appropriately trained and qualified personnel, maintenance and calibration of equipment, handling of test and reference substances, written standard operating procedures, inspection by an independent quality assurance unit, detailed record-keeping to allow reconstruction of the study, and archiving of all data. Good laboratory practice compliance thereby promotes reliability. Nonetheless, good laboratory practice studies often do not see daylight in the peer-reviewed literature, and there are valid business reasons for this, including the preservation of compensability for the studies. (When a chemical’s patent protection expires, other companies may seek to develop products based on the intellectual property developed to support a particular technology. The company that owns the intellectual property is entitled to data compensation when another company uses this information for their product.) Companies may still be willing to publish results, but few high-impact journals are interested in the results of routine standard toxicity tests conducted in support of pesticide registration. However, another set of “checks and balances” is provided when the government regulatory agency conducts an independent review of the good laboratory practice study. These study reviews and summaries are usually available to the public under the Freedom of Information Act in the United States. Under FIFRA, for example, the USEPA issues “data-evaluation records,” which provide the agency’s review, analysis, and interpretation of the good laboratory practice study. The USEPA also routinely conducts inspections of performing laboratories to ensure good laboratory practice compliance.

Part of the “checks and balances” inherent in regulation not only in the United States but also in other regulatory jurisdictions, such as Canada and Europe, is the requirement of industry to report the adverse effects of their products. In the United States, these important laws are a part of FIFRA and the Toxics Substances Control Act legislation under sections 6(a)(2) and 8(e), respectively. These laws require a company to report any information that may impact a safety assessment and, in the United States, give very specific time frames by which the information must be reported. These laws are taken very seriously, as there are fines, civil penalties, and possible jail time for failure to comply; companies spend considerable resources in compliance with these laws.
As members of the greater scientific community, scientists in the business sector have important contributions to make, and these should not be perceptually devalued relative to other tripartite entities because of preconceived notions of bias. Clearly, misunderstanding exists regarding the roles and responsibilities of scientists in the business sector; however, increased education, collaboration, transparency, and public outreach can be instrumental in promoting better understanding of the roles and responsibilities of scientists from all sectors. Already, SETAC has embraced the ideology that we are stronger when working together; and it will take collective, concerted, and cooperative tripartite efforts to address the many daunting environmental and societal challenges looming on the horizon. As stated by Helen Keller, “alone we can do so little; together we can do so much.”

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In Response: Reporting recommendations to ensure reliability and reproducibility of ecotoxicity studies—A tripartite initiative

It is a great loss, both in terms of knowledge and resources and in terms of credibility of the scientific community, when peer-reviewed studies are of insufficient quality. Reliability evaluations of recently published ecotoxicity studies show incomplete and inadequate reporting, regarding both description of methodology and presentation of results [1,2]. For a reader of these publications, it can be difficult to determine whether the missing information is the result of insufficient reporting only or if it is the result of inadequate design and performance of the experiment. Regardless, this obstructs the evaluation process and decreases the chance that the studies are used in future research and for regulatory processes.

The medical journal Lancet recently presented a series on how to increase value and reduce waste in biomedical research and mentioned standards for reporting of studies in scientific journals as an important factor [3,4]. The editor of Toxicological Sciences recently stressed the problem of low reproducibility and pointed out 3 things that journals can do to improve the situation: promote proper reporting of studies, make sure statistical analyses are accurately described and appropriately used, and request disclosure of all potential conflicts of interest [5]. Until recently, word limits in peer-reviewed journals caused authors to focus on short and concise publications, discussing mainly their results and economizing on the description of methods. Because it is now possible to publish supporting information online, for which word limits do not apply, raw data can be provided and all aspects of a study can be described in sufficient detail [6].

In several research areas, systematic reporting recommendations have been developed to guide researchers, reviewers, and editors during the publication process. In the field of epidemiology, for example, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement is used to increase the quality of peer-reviewed publications [7]. So far, the statement has been endorsed by more than 100 biomedical journals, and it provides checklists for a variety of applications: cohort studies, case-control studies, cross-sectional studies, and conference abstracts. The National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) has developed the Animal Research: Reporting In Vivo Experiments (ARRIVE) guideline to improve the reporting of animal experiments. The guideline has been adopted by more than 300 journals and provides a checklist with 20 items, ranging from an ethical statement to sample size and funding [8]. Minimum Information About a Microarray Experiment (MIAME) is a reporting standard created by the Functional Genomics Data Society for microarray experiments. It specifies the information necessary to interpret results from experiments clearly and to potentially reproduce the experiment [9]. Currently, there are no generally accepted reporting guidelines for peer-reviewed ecotoxicity studies, but some journals have introduced a few specific requirements such as confirmation of exposure concentrations.

As a response to the need for a more robust and complete reporting of ecotoxicity studies, reporting recommendations have been developed in a collaboration between the Dutch National Institute for Public Health and the Environment, the Swiss Centre for Applied Ecotoxicology, the Swiss Federal Institute of Aquatic Science and Technology, and Stockholm University [10]. To ensure reliability and reproducibility of studies, the recommendations are based on reporting requirements for Organisation for Economic Co-operation and Development test guidelines and reliability evaluation methods for ecotoxicity studies. By considering these recommendations, preferably already when designing experiments, researchers will ensure that crucial aspects of the methodology and results are reported and that others, within and outside academia, can use the study results.
To respond effectively to bias in risk assessment, it is essential to appreciate the social context surrounding regulatory science, which is one of intense conflict and suspicion among stakeholders [1]. In this context, effective solutions to bias need to be designed not only to promote scientific objectivity but also to promote the perceived legitimacy of research. Even if risk assessments are of high quality, they will still have limited effectiveness if they are not trusted by the public. Conversely, it is obviously inadequate to have risk assessments that are perceived to be of high quality but that are not based on good scientific practice.

Recent work by philosophers of science suggests 3 important criteria for evaluating the objectivity of scientific work: transparency, procedural consistency, and effective criticism [2–4]. The transparency, or public accessibility, of information is sometimes regarded as constitutive of objectivity itself, and it is a necessary condition for evaluating whether other criteria for objectivity have been met [3]. Procedural consistency refers to the extent to which “the same outcome is always produced, regardless of who is performing the process” [2]. Effective criticism is achieved when there are extensive opportunities for critically evaluating scientific work and when there are procedures for responding effectively to critical feedback [4]. Peer review is 1 approach for generating critical feedback, but criticism can also be provided through venues such as advisory boards, conferences, and collaborative research projects.

A number of strategies can potentially help risk assessments to meet these 3 criteria, but there are no “magic bullets.” Regulatory studies are typically performed in accordance with standardized protocols that contribute to procedural consistency, but these protocols can be difficult to revise and can thereby slow the implementation of new, cutting-edge study methodologies [5]. Moreover, despite efforts at standardization, judgment cannot be eliminated from the risk-assessment process [6]. Therefore, it is essential to develop appropriate procedures for making these judgments, along with the values that influence them, more transparent so that they can be subjected to effective criticism [7].

Unfortunately, it is difficult to achieve full transparency. Disclosure of financial conflicts of interest has become increasingly common in journal articles, but this alone does not ensure that studies are of high quality [8]. To achieve adequate transparency, greater public access to study data and methods—for academic, government, and industry studies—is needed; but concerns about product confidentiality and other legal issues make this difficult to achieve. There may be opportunities for risk assessors to draw lessons from the field of medical research, where a number of steps are being taken to promote the registration and reporting of clinical trial data [9].

Effective criticism can be promoted through the development of advisory boards, such as the Scientific Advisory Panel and Science Review Board that help to evaluate risk assessments under the Federal Insecticide, Fungicide, and Rodenticide Act [10]. Nevertheless, these boards often face significant time constraints that limit their oversight capacity. In some cases, collaborative research projects can generate high-quality research that takes multiple perspectives into account [11], but these projects can also come under fire if some partners are suspected of co-opting others.

In addition to exploring strategies for promoting transparency, procedural consistency, and effective criticism in the risk-assessment process, more work is needed to investigate how these strategies affect the perceived legitimacy of research. Surprisingly little work has been performed on this issue [12]. Preliminary work by researchers at Michigan State University suggests that industry involvement in research decreases its perceived legitimacy and that procedures designed to increase the objectivity of the research may do relatively little to alleviate this lack of perceived legitimacy. These results highlight the importance of pursuing further scholarship designed to identify conditions under which both the objectivity and perceived legitimacy of research can be maintained.

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REFERENCES


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