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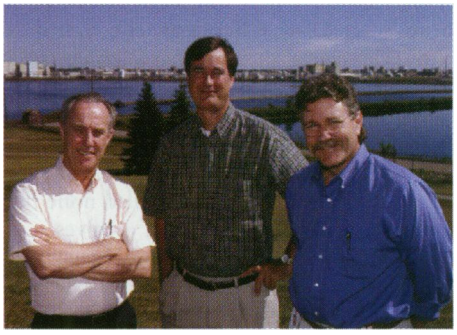
Toxicology: Judge Data or Dollars?

Research should be judged on the basis of scientific merit, without regard for funding source or where the studies are conducted...

[Society of Toxicology. SOT Principles for Research Priorities in Toxicology. Available: http://www.toxicology.org/AboutSOT/about.html (1999).]



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The knowledge gained by our work as toxicologic scientists ranges from molecular mechanisms to clinical signs of toxicity, from physiologically based pharmacokinetics to tumor counts. Any of this research, from any source, may be translated into regulatory action in order to protect the public and the environment; thus, society is best served by the best science from every source. The challenge is to find the criteria to accurately and, increasingly, quickly judge which studies are valid and appropriate to affect regulation. Cynics make these quick judgments based on funding sources; traditionalists trust the proven, but slow, peer-review process; regulatory agencies want to see raw data from industry, but have implicitly trusted and exempted academia from this scrutiny. Needs for confidentiality place limits on disclosure, but they do not preclude a more even and open approach to data from all sources. Greater disclosure will result in a scientific process that is faster, better, and more trustworthy—"trust" is the key word here. But, as a former U.S. president said near the end of the Cold War, "Trust but verify."

Verification was the apparent goal of a few lines buried deep in the voluminous 1999 Omnibus Spending Bill (*1*). It states

> That the Director of OMB amends section _.36 of OMB Circular A-110 to require Federal awarding agencies to ensure that all data produced under an award will be made available to the public through the procedures established under the Freedom of Information Act.

This new law has provoked, according to one editorial, "...howls of protest from scientists, their institutions, and the federal agencies that fund scientific research" (*2*). However, major scientific societies, including the American Chemical Society, the Council for Chemical Research, and the American Association for the Advancement of Science, all support, in principle, the need to assess the validity of such research results (*3*). Recently, it has again been made clear that the issues of quality and reliability of toxicology data and its reasoned interpretation for regulatory purposes are critical (*4*); the question is how best to accomplish that end.

The tried and true way, the unfettered peer-review process, is and will continue to be the keystone of scientific progress. However, it rarely depends on the scrutiny of raw data; rather, the peer-review process ultimately depends on the independent replication of important findings. Thus, it is slow, sometimes painfully so. Democracy is a similarly empirical endeavor. Like science, the process is generally ponderous and tentative, and our laws are often badly out of synchronization with science, a condition regularly exacerbated by swells of public concern. Fueled by a willing press, the public perception of a crisis can rapidly propel new regulations that may never gain a scientific foundation, nor are they repealed when science catches up. Rational or not, an alarmed public, or more often issue advocacy groups, call for immediate action well before any reasoned assessment of what action, if any, is called for. The scientific community is left unprepared. Poor decisions follow, which may have unintended consequences, levy unnecessary expense on taxpayers, and provide no demonstrable benefit for public health or the environment.

Unfortunately, as a preventative for bad regulation based on unvalidated or preliminary science, the new amendment to Circular A-110 is a crude vaccine that will cause more problems than it could possibly cure. The apparent intent of the law is laudable, but its shortcomings are serious: It lacks adequate protection for intellectual property, patient privacy, and against legal abuse by those who might be tempted to harass researchers with unreasonable

demands. Work in progress is not protected. Nevertheless, we believe that the raw data of all scientific studies, regardless of source—government, academia, or commercial enterprise—should be made available for rigorous outside examination before the conclusions may be used to justify any law or regulation. A scientist's intent or lack of intent to influence government is irrelevant; what must invoke data disclosure is the government's intent to use the conclusions. And without such scrutiny, lawmakers and regulators should not be allowed to take advice from the study.

Formulating a better law, or amending the requirements of A-110 by OMB, necessitates thoughtful deliberation and sensitivity. Such action must consider the attributes and complex relationships of academia, funding institutions, private enterprise, and other stakeholders, as well as the speedy verification necessary in the age of information. It will require that all parties acknowledge what still works and what should be improved. It will require that we embrace reasonable change as we face the dissolution of yet another comfortable status quo.

Like bitter medicine that is good for you, 20 years of regulatory oversight has been good for the integrity and credibility of industrial research. In the mid-1970s, the U.S. Environmental Protection Agency (EPA) and Food and Drug Administration defined stringent and detailed standards for conducting sound laboratory science in response to a widely publicized case of fraud in a contract toxicology laboratory. Good Laboratory Practices (GLP) were adopted and have been applied to studies submitted for regulatory consideration since 1979 (*5*). GLP requirements include, for example, retaining raw data for 10 years or for the life of the product. This requirement is routinely exceeded. In our toxicology laboratory at Dow Chemical, the Standard Operating Procedure (SOP) manual dictates that durable specimens such as paraffin tissue blocks, glass slides, and all original data are saved for their useful life or 75 years, whichever is longer. Thus, no material of potential use to reconstruct a study has been discarded for many years. In this respect, Dow is apparently typical; an informal polling of other industrial labs revealed none that had discarded potentially useful raw data from their archives.

Other details saved in GLP study records include the curriculum vitae and signature samples of all study personnel; analyses of test material for identity, purity, homogeneity, and stability in the carrier; the record of randomization by weight of incoming test animals and their daily observations throughout the study; any amendments to the signed study protocol; and the location of all archived materials. We are assisted in compliance by Dow's Quality Assurance Unit (QAU), a group under separate line management (also a GLP requirement) whose job it is to ensure that each action specified by our SOP manual and study protocol is, in fact, carried out. Deficiencies are reported by the QAU to laboratory management—they tell your boss. So, when EPA inspectors show up unannounced (as they can and do) to inspect our facilities, personnel records, and raw data, we are always ready. The integrity of the study file and research process speaks for itself and gives us and regulators, and ultimately the public, confidence in our results.

We are not advocating that academic research be performed under the yoke of GLP law; that would be an unnecessary, counterproductive encumbrance that would impede scientific creativity if applied as a blanket regulation. Those encumbrances are why mechanistic and other nonguideline studies, even in industry, are often not designed to meet every GLP requirement. On the other hand, understanding and always applying principles of good record keeping to a practical extent prepares any scientist for outside scrutiny—scrutiny we believe is justified for science that may impact regulation. The GLPs were meant to counteract the bias generated by profit motives, but no objective analysis would conclude that this is the only bias industrial scientists live with, nor that industrial scientists are the only ones who live with potentially confounding influences.

There are a number of significant sources of bias that frame the way toxic risks and hazards are communicated. Perhaps the most important, but least obvious, is the bias of purpose. Both academic and industrial scientists are interested in hazard identification (learning what effects a chemical has at toxic doses) and in understanding the mechanisms of the effects. However, industrial and governmental scientists have a special need to answer the more practical question: At what dose is there no significant effect? Establishing a no-observed-effect level in a wide variety of studies provides the most vital information for determining safe exposure levels. This is not glamorous research, but it is GLP research, and it is reliable.

Cultural biases also loom large. For academics, publication is a primary product; sharing knowledge is perhaps the central satisfaction of university culture. For industrial toxicologists the product is the saleable product, and publications support products. The majority of our work is directed toward licensing new chemicals for commerce; companies are understandably protective of this valuable intellectual property. These reports and reams of supporting data are reviewed by the agencies, but are seldom submitted to peer-reviewed journals. However, much similar work concerns established drugs and chemicals, and much of that work never reaches the journals either. More of this research could be subjected to the rigors of the peer-review process, which would increase the credibility of industrial toxicology, improve communications, and benefit all parties. Toxicology could also benefit from more editorial and review articles from our quarter. Publication needs to become a more central part of our culture, but another source of bias should be acknowledged.

Journals have their biases; the most overt in toxicology is the preference for "positive results," and guideline studies often produce few toxic or novel effects, especially at relevant doses. However, a study with positive findings performed by an unnatural route of administration—for example, intraperitoneal injection of a material metabolized by the liver and found in minute concentrations in the diet—while of dubious value for risk assessment (*6*), may be more likely to find its way into the literature than a more relevant dietary study showing negative results with the same material. This bias against the dull, although understandable and perhaps defensible from a journal marketing perspective, needs to be more widely and deeply appreciated. Negative findings from realistic studies make a positive contribution to the shape of a dose–response curve and, more importantly, provide context for positive studies; thus, they are vital for unbiased judgment.

In part because of the GLP rules, the cynical belief that profit motives must bias the data of industrial scientists toward minimizing findings on safety studies is not generally shared by the regulatory scientists who receive our reports and verify our conduct. Long experience has taught the chemical industry that cooperation is key and that safety and good science are the friends of profit. This is because, GLPs and simple scruples aside, the consequences for industry of either under- or overinterpreting data can be extremely expensive—expensive because a good, safe product might never be made or expensive because an unsafe product might hurt people or the environment and generate lawsuits. These are strong but often unappreciated, mutually neutralizing biases that together favor an honest assessment of the data. This is why the assumption of a simple profit-driven bias that pollutes the

publications of industrial scientists is wrong. Nevertheless, this misperception is common enough that the Society of Toxicology (*6,7*) issued this policy statement:

> Research should be judged on the basis of scientific merit, without regard for funding source or where the studies are conducted (e.g., academia, government or industry).

This call for fairness was not inspired solely by unwarranted cynicism directed at industry, but by the too-common dismissal of unwelcome findings from any source perceived to have a bias different from one's own.

There are other significant financial interests that can affect bias, and they are relatively unmitigated and often favor alarmist interpretations. These include the way mass media profit from the insatiable public appetite for sensation and conflict, the highly competitive academic grant process that sometimes favors overstatement of toxic threats, the hyperbolic fund-raising pleas of some activist organizations, and even within big corporations, the conservative way legal departments assess risks of litigation.

There is no simple way to eliminate all of these biases. Perhaps the best solution is to recognize them collectively as a form of diversity and embrace them as alternative points of view that ultimately strengthen our collective understanding. But, to avoid the postmodern pitfall that says truth is relative, that reality bends to assertion, we can only fall back on our common training as scientists: We can ask to see the data.

As scientists, our bias should be toward universal candor in the scientific process, and we should recognize this stance as identical with the ideals of the democratic process. We need a carefully crafted, more focused law, one written to ensure that all research impacting on regulatory decisions is examined and verified while protecting the legitimate concerns of the whole scientific community. Such a law may slow the wheels of science a little, but they will spin far less as we all progress more surely toward the truths that exist quite independent of our limited perceptions and opinions. When we stand on less uneven ground in this age of disclosure, the credibility of all toxicologists will rise. When the diamonds of truth are brought fully into the light, with every facet seen clearly, the question of funding sources will seem dull indeed.

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