TOXICOLOGY

Science Only One Part Of Arsenic Standards

When the Bush Administration decided last week to withdraw new standards that require lower arsenic levels in U.S. drinking water, it brandished scientific uncertainty as a shield against environmental protesters.

Ruled out. EPA's Christine Todd Whitman cited scientific "uncertainties" in dropping new standards for arsenic in drinking water.

But the reality is that setting safe levels of very small amounts of toxicants such as arsenic is not a question that science alone can answer. It's a judgment call, and that means a role for politics.

Rocks and soils are the main source of inorganic arsenic in groundwater, although mining and other humanmade sources also contribute. People who drink water from tainted sources can eventually develop bladder and other cancers. In 1999, a National Research Council (NRC) reviewed the evidence on arsenic and concluded that the current acceptable level of 50 parts per billion (ppb) should be lowered "as promptly as possible." Although the NRC did not recommend a specific level, on 22 January the outgoing Clinton Administration issued a final rule that would have dropped the safe level to 10 ppb.

Western officials and industry objected, estimating that they would need to spend billions of dollars on treatment equipment to meet the new standard. On 20 March, EPA Administrator Christine Todd Whitman sided with them, saying that she agreed with the NRC but that the Clinton plan was based on "unclear" science. "An independent review … will help clear up the uncertainties," she added.

But scientists say the evidence won't become clear anytime soon. The lack of a good animal model, until recently, has forced scientists to rely on human evidence—in particular, studies of cancer in Taiwanese villagers exposed to arsenic from wells from the 1920s to 1960s. But those arsenic levels were relatively high—200 ppb or more. To estimate risks at levels below 50 ppb, experts have used a linear relationship to extrapolate the data. But if there is a level of exposure below which arsenic-laced water is harmless, that statistical technique could overestimate the risk. "The lower you go, the greater the uncertainty is," says Robert Goyer, a retired pathologist who chaired the NRC panel. As a result, Goyer says, setting a standard "depends on a subjective judgment" that must also weigh costs.

As the EPA takes another look, one new study may bolster the 10 ppb standard. In the 1 March issue of the *American Journal of Epidemiology*, a Taiwanese research team examined cases of urinary tract cancer in villagers exposed to arsenic levels as low as 10 to 50 ppb. The study, the first of its kind, found that cancer risk rose with arsenic levels even at these low exposures. "On the face of it, I think [the new study] might be quite important," says Kenneth Brown, a statistician and consultant in Chapel Hill, North Carolina.

–JOCELYN KAISER

PEER REVIEW

NSF Scores Low on Using Own Criteria

Scientists seem to have no trouble giving their opinions on the scientific merit of a grant proposal. But ask them to rate its potential social impact, and they tend to clam up. And that poses a problem for the National Science Foundation (NSF).

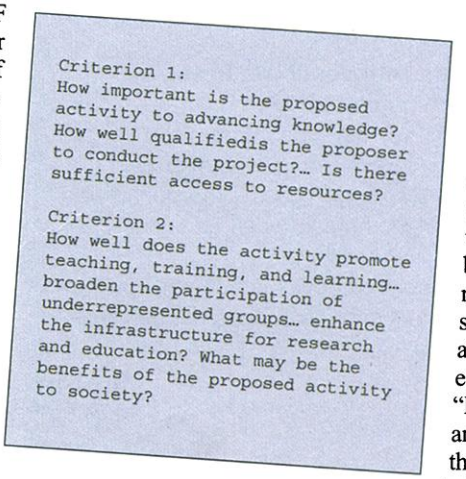
Three years ago, NSF changed the criteria for rating the quality of grant proposals it receives. Instead of asking reviewers to judge them on four factors—the research's merit, its relevance, the investigator's ability to do the work, and the work's impact on the scientific enterprise—NSF asked for ratings on just two: scientific quality and social impact. The change was intended to give social impact —defined to include issues such as education and training, diversity, and addressing of national priorities—a more prominent role in assessments. But a new report from a panel of management experts says that most reviewers don't even bother to rate proposals on their potential social impact, and it chides NSF for not doing more to get scientists on board.

Why does it matter? If NSF doesn't convince legislators that the peer review system provides fair, comprehensive reviews, Congress has suggested it may try to apply its own remedy.

NSF made the changes partly to address complaints from federal legislators that the grants process is an "old boys network" biased against first-time applicants and less prestigious institutions. Indeed, barely a week after the new criteria were promulgated, a Senate spending panel asked NSF to hire the National Academy of Public Administration (NAPA) to study the impact of the new criteria "on the types of research the agency supports." Although NSF thought the suggestion premature, it agreed to a limited review. But when the Senate repeated its request the following year, NSF contracted with NAPA for a $250,000 study.

That report, delivered last month, concludes that the reviewers are mostly ignoring social impact. Some 73% "disregard criterion 2 [social relevance] altogether or simply merge it into scientific merit," it notes, while others "parrot the language without making any actual evaluation on the basis of it." Most reviewers, it says, "use criterion 1 [scientific merit] as a cutoff and then apply criterion 2 to evaluate any remaining proposals." The report says NSF bears some of the blame. It notes that the agency gave reviewers broad discretion on how to apply each criterion, a decision that "essentially gives reviewers license to not apply [the social impact criterion] at all."

"We're not achieving our goal," admits Nate Pitts, head of NSF's Office of Integrative Activities, which collects data on NSF's peer review process. Some members of the National Science Board, NSF's oversight body, seem to agree. At the board's meeting last month, they asked some sharp questions about the office's latest annual report. "How many proposals are sent back because they don't address criterion 2?" asked mathematician Pam Fergu-



Keeping score. NSF wants reviewers to pay more attention to the second criterion.

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son of Grinnell College in Iowa. "If we want to implement something, we have to make it bite by affecting funding decisions," added fellow board member Richard Tapia of Rice University in Houston.

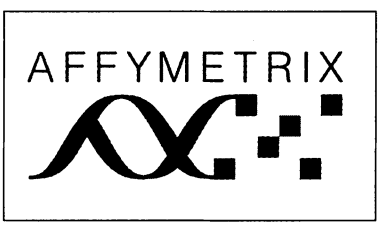
NSF isn't ready for such drastic steps. "It takes time to get everybody to understand that this is important," explains Deputy Director Joseph Bordogna. "But that's not an excuse to delay." Rejecting proposals or reviews "might be an appropriate step to take after we've tried all the other methods," notes board chair Eamon Kelly. "But remember, you're asking for a real cultural change."

Congress may not wait. A Senate aide says that peer review at NSF "is one of the top priorities" for the spending panel and that the subject could be addressed in a report later this year that accompanies the agency's 2002 budget. "We want to hear NSF's response to the NAPA report," says the aide, "and see if it goes far enough." **–JEFFREY MERVIS**

DNA ARRAYS

Affymetrix Settles Suit, Fixes Mouse Chips

A leading maker of DNA arrays, Affymetrix Inc. of Santa Clara, California, last week made peace with a rival British firm, Oxford Gene Technology (OGT), in a patent fight over fundamental DNA array technology. The settlement ends a bruising transatlantic battle that pitted Affymetrix's patents against similar patents in Europe filed by University of Oxford biochemist Ed Southern. The companies have agreed to withdraw a string of lawsuits in the United States and Europe, and OGT is dropping an appeal it had planned to take to the House of Lords.



The settlement provided welcome relief for Affymetrix, which is contending with an embarrassing, but unrelated, problem: Some of its arrays have contained scrambled mouse-DNA data. Both developments will be expensive, however. According to an Affymetrix notice posted on 26 March, the company is spending $19 million on the patent settlement and an unspecified "smaller" amount for legal fees. And replacing the scrambled chips could cost up to $4 million.

"Basically the litigation between us and OGT is over—it's done," says Rob Lipschutz, vice president of corporate development at Affymetrix. "We are very pleased because this lets us go back to providing tools for our customers." Southern issued a statement on behalf of OGT saying he felt it was "essential for genomic research" to resolve the dispute, because his company and others could now devote their energies to developing and licensing the technology.

As for the scrambled mouse DNA, Affymetrix first disclosed the problem in a 7 March notice to the U.S. Securities and Exchange Commission (SEC). To assemble these chips, Affymetrix used information from a public database maintained by the National Center for Biotechnology Information (NCBI) in Bethesda, Maryland. Affymetrix told the SEC it was having trouble "because of the rapidly evolving nature of the public domain sequence databases," noting that "sequence errors may not be found prior to the commercial release of a product." Lipshutz made clear last week, however, that the glitch occurred when company employees processed the data. "There can be conflicting data in the database," he said. "It becomes quite a challenge to deal with potential ambiguities. ... We just didn't sort it out as well as we would have liked."

The mix-up involved the "Unigene U74" collection of mouse genes and expressed sequence tags (ESTs), Affymetrix executive Thane Kreiner explained. When company researchers began to annotate genes and ESTs that had already been placed on chips, they discovered that most appeared to be reproduced correctly, but some were reversed. A company review found that all three of the chips in the U74 set had problems. Least affected was the most valuable "A" chip, which contains the best gene information, according to Kreiner. About 75% of the sequences were usable. The "B" chip had the same error rate, but the "C" chip was 60% defective, making it unusable.

NCBI director David Lipman confirms that "there has always been some ambiguity" in the directionality of genetic data submitted to NCBI. The information comes from many labs; they may use different methods of sequencing and report the results in different ways, he explains. It's up to the user to interpret the data with care, because differences are not always clearly flagged.

Affymetrix plans to have replacement chips ready for those who want them in a matter of weeks, says Lipshutz. He notes that a bigger improvement is on the way: The company plans to put the entire mouse genome sequence on chips, after the public-private consortium that's at work on this project finishes assembling the data (*Science*, 13 October 2000, p. 242). This consortium has placed more than 8 million bases of raw mouse genomic data in NCBI and other public repositories already. However, mouse researchers say the information is highly fragmented and difficult to use. Affymetrix, like every other group, would like to have a fully assembled mouse genome. Lipshutz says: "We're going to do the best assembly we can, but it's not going to have the depth or richness of the human sequence." And he adds, "I can't say when that will be." **–ELIOT MARSHALL**

BIOMEDICAL TRAINING

NIH Pledges Big Hike In Postdoc Stipends

Acknowledging that its stipends for graduate students and postdocs are too low, the National Institutes of Health (NIH) plans to raise them significantly over the next 5 years—and then keep them competitive. NIH is also throwing its weight behind efforts to curb the length of a postdoc's tenure.

The new policies are part of the agency's long-awaited response to a report last summer from the National Academy of Sciences calling for changes in how the federal government trains biomedical and behavioral scientists (*Science*, 8 September 2000, p. 1667). The report said that current Ph.D. production is "more than sufficient" to meet demand and that institutions should concentrate not on growth but on improving the quality of training. In particular, it proposed reducing the number of students supported on research grants and boosting training grants to universities and individual fellowships. It also said that stipends should be much higher and that a postdoc typically should not last longer than 5 years.

The NIH response, posted on 23 March, (grants.nih.gov/training/nas_report/NIHResponse.htm), pledges to raise its National Research Service Awards (NRSA) stipend levels by 10% to 12% a year, to a target of $25,000 for graduate students and $45,000 for beginning postdocs. (Current levels are $16,500 and $28,260, respectively.) In a break from current practice, NIH would also issue annual cost-of-living increases. Although NIH funds a minority of students, most universities tie their pay scales to the NRSA levels. It also said federal funding should not exceed 6 years for graduate students and 5 years for postdocs.

But NIH resisted the panel's suggestion to shift the balance toward training grants and away from research grants, saying it's unwise and unworkable. "Attempts to manipulate these mechanisms to control Ph.D. numbers would run counter to their primary purpose," it noted. **–JEFFREY MERVIS**