Is Risk Assessment Conservative?

Among regulators and the regulated, the dogma is that the risk assessment procedures typically used by the Environmental Protection Agency (EPA) and other federal agencies are conservative—that is, they overestimate the risk a chemical poses, often by a substantial amount. EPA officials have made such assertions repeatedly in the past few weeks in the debate over the pesticide Alar.

The bias is intentional. Risk assessment is so uncertain, based as it is on extrapolation from animal data to humans and from high doses to low, that federal regulators decided to err on the side of safety to protect the public health. That approach has nonetheless been roundly criticized by those who say it carries protection to the extreme, usually at the expense of industry.

Now a study challenges that dogma. It concludes that the cancer risk assessment model typically used to estimate effects at low doses—known as the "one-hit" model—in most cases is not conservative at all. Moreover, in a small number of cases, it substantially underestimates risk. The paper, by John Bailar, Edmund Crouch, Rashid Shaikh, and Donna Spiegelman, was published in the December issue of *Risk Analysis*.

What tipped off the investigators was vinyl chloride. Unlike most chemicals, there is an abundance of experimental data on the cancer-causing effects of vinyl chloride at a wide range of doses. This allowed them to see how well the model predictions stack up against actual experimental data. The answer, in this case, is not well.

Most chemicals have been tested at just two or three doses: at close to the maximum tolerated dose, at about half the maximum tolerated dose, and at zero. Risk analysts then rely on a model, often the one-hit model, to estimate the effects at the very low doses to which humans are likely to be exposed. Both the one-hit model and EPA's linearized multistage model, which the investigators lump in the same category, assume that there is no threshold below which a carcinogen does not act and that the relationship between dose and response is approximately linear at low doses.

Bailar, Crouch, and their colleagues tried the standard risk assessment procedure on vinyl chloride, for which the actual dose-response curve is known: it rises sharply at low doses and then flattens out near the high doses. They looked at how many tumors arose from the high and moderate doses, plugged those data into a computer, and came up with a "cancer potency factor," an estimate of the number of tumors likely to arise from a given dose. When they repeated the procedure, this time using low-dose data, the analysis yielded a cancer potency factor nine times higher than the first analysis. Thus, the model would substantially underestimate the actual cancer risk.

Is the one-hit model this misleading for other chemicals? To find out, they analyzed data from 1212 bioassays of 308 different chemicals. They fitted the one-hit model to the zero and high doses and then looked at how well it predicted the observed cancer incidence at the mid-dose range.

In a small but significant number of cases—more often than would be expected by chance—the model underestimates risk, they found. This underestimation occurs in about 2.5 to 4% of the cases. The model also overestimates risk in about 5 to 7% of the cases. The upshot, says Crouch of Harvard University, is that "in some fraction of cases we may be making a substantial underestimate of the risk, and we have no idea how big that underestimate is."

Nor is it clear when this will occur, adds Bailar of McGill University and the U.S. Department of Health and Human Services. "There is no good way to tell when there are overestimates or serious underestimates of the risk. If we could tell, we would fix the risk assessments."

Crouch adds a couple of caveats. First, the findings are for the mid-dose range, and not for the extremely low doses that regulators are typically interested in. Nonetheless, the authors conclude that "there is no reason to assume that the underestimation is any less frequent at doses much closer to zero." Nor does the study address the nagging question of whether it makes sense to extrapolate linearly to low doses. But if you are going to use that model, says Crouch, "the paper says here are some things to watch out for."

"The message to regulators is they should modify what they say when they talk about risk. I think they should be much less certain in their language than they are now."

Bailar hopes the paper will halt efforts to make risk assessment procedures less conservative, as some people are advocating. "I would prefer to see a move in the other direction, or at least, to hold the current line." Granted, he adds, there is conservatism built into other risk assessment steps, but there is "anticonservatism" as well. "We just do not have evidence that our risk assessments for chemical hazards are substantially conservative."

■ LESLIE ROBERTS

Pulsar, Pulsar, Where Art Thou, Pulsar?

It has been 2 months now since an international team of astronomers announced their detection of a furiously rotating pulsar at the heart of Supernova 1987A—and no one has seen it since. Supernova watchers are left feeling as skeptical as they are intrigued.

On the one hand, the original observations have held up well under outside scrutiny. "It really looks like a signal," says Robert Kirshner of the Harvard-Smithsonian Center for Astrophysics. "There's no 'if' about it." Extensive computer analysis of the data shows that, on the night of 18 January, the supernova was flickering ever so faintly at 1968.629 times per second, or more than twice as fast as any other pulsar ever seen. Equally astonishing, the rate gently rose and fell as though the pulsar were being tugged back and forth by the gravity of some kind of companion object. Indeed, the most recent analyses show that the frequency shifts are beautifully explained by assuming that the companion is in a slightly elliptical orbit following classical Newtonian mechanics—not the sort of behavior one would expect from an observational artifact.

Against all this, however, one has to balance the fact that nobody has seen the pulsar since 18 January. Presumably, of course, the pulsar is sitting in the middle of a rapidly expanding shell of debris from the original explosion. So perhaps it was shining through a thin spot on 18 January, and has been lost behind the clouds again ever since. But 2 months? "There will be fewer excuses as time goes by," says Kirshner.

Be that as it may, the theorists have lost no time in speculating about the implications of the pulsar if it is real. For example, its rotation rate puts it on the ragged edge of flying apart, so its very existence would force theorists to reevaluate their ideas of how nuclear matter behaves under such extreme conditions. Meanwhile, Stanford Woosley of the University of California, Santa Cruz, and Roger Chevalier of the University of Virginia have pointed out that, if some of the explosion debris were to fall back on the newborn pulsar, then the pulsar could have plausibly acquired its incredible spin rate by conservation of angular momentum. Some of the infalling material may also have condensed to form the mysterious companion. Unless, of course, the object is not rotating at all, but pulsating in and out. Stay tuned.

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