Transgenic mice validated as faster, less expensive cancer test

A recently completed study of mice genetically altered to be more susceptible to cancer than other mice suggests that these "transgenic" mice can detect most types of carcinogens as accurately as, if not more accurately than, standard rodent bioassays and are less time-consuming and costly. Results of the National Institute of Environmental Health Sciences (NIEHS) study of two different strains of mice were presented in December at a National Academy of Sciences colloquium on advances in toxicology, held in Washington. D.C.

There was 81% agreement on the results of 22 chemicals tested in standard rodents and the Tg.AC transgenic mouse model developed by Philip and Aya Leder of Harvard University. For eight chemicals tested on the other animal model, the p53-deficient mouse developed by Larry Donehower and Alan Bradley of the Baylor College of Medicine in Houston, there was complete agreement on results. Both transgenic tests were completed in just six months, in contrast to the two-year period needed for standard rodent cancer tests, and the transgenics required only about one-quarter of the number of animals as did the standard tests. Transgenic tests cost about one-tenth as much as those of standard rodent cancer bioassays.

The encouraging results from the NIEHS study suggest the p53-deficient or the Tg.AC mouse model could substitute for one of the two standard two-year rodent species assays commonly required to determine the cancer-causing potential of chemicals. The U.S. Food and Drug Administration has already considered results from tests done on such animals, and several pharmaceutical companies are incorporating them in their testing procedures. EPA's Office of Pesticides and Toxic Substances has not yet agreed to allow tests on transgenic animals to substitute for the standard two-year tests in rodents, but if such data are provided by industry, the agency is willing to consider it.

In addition to being speedy indicators of carcinogenicity, transgenic rodents may be more reliable at detecting rodent carcinogens that are also likely to be hazardous to human health, because the NIEHS study found they were particularly sensitive to chemicals that cause cancer in more than one animal species. A chemical that causes cancer in only one rodent species is not usually thought to pose a significant cancer risk to humans. Because the Tg.AC and p53-deficient mice are prone to the same genetic damage that causes cancers in humans, tumors triggered by a carcinogen in the transgenic animals are also likely to be triggered by the chemical in people.

The p53-deficient mouse apparently cannot detect chemicals that are tumor promoters rather than tumor initiators. This limitation of the model is also an asset, however, because it provides valuable information for toxicologists struggling to ascertain how a particular chemical causes cancer in a rodent and whether the pathway is likely to be found in humans. Such mechanistic information plays a starring role in EPA's new cancer risk assessment guidelines. "The sooner we can introduce mechanistic considerations into the bioassay, the sooner we can get an answer in regards to a chemical's potential human health risk," said John French, who conducted the NIEHS tests on the transgenic animals along with Raymond Tennant and Judson Spalding at the institute's Laboratory of Environmental Carcinogenesis and Mutagenesis.

The NIEHS results suggest that both the Tg.AC and the p53-deficient models may miss certain carcinogens, such as those that act at highly specific sites. In addition, the Tg.AC model occasionally tested positive for chemicals that are not carcinogens. Because of their limitations, the transgenic models probably will not be sufficient carcinogen-screening tools on their own; but, for some of the chemicals tested, they will have to be combined or used along with the standard two-year tests on rodents.

"Yes, these transgenic assays have limitations," noted geneticist Vicki Dellarco of EPA's Office of Water, "but the standard two-year rodent assay has limitations as well. It's a matter of trying to use all the tools that we can to get the best understanding of chemicals. Even if we have to use two transgenic models, it's still cheaper than doing the traditional bioassay by an order of magnitude."

More important to Dellarco is the time saved by using the transgenic models. Her office has the daunting task of assessing the cancer-causing potential of more than 600 drinking water disinfection byproducts before 2002, when the second phase of the drinking water regulations comes into play. "Right now we couldn't begin putting chemicals through the conventional bioassay and still meet our regulatory deadlines," she said. She is collaborating with the NIEHS team in a study aimed at as-

Carcinogenicity tests with this p53-deficient mouse were completed in just six months, one-quarter of the time required for standard rodent bioassays. (Courtesy National Institute of Environmental Health Sciences)

sessing whether the transgenic assays generate the same results on drinking water disinfection byproducts as those generated by the standard two-year rodent cancer bioassay. If there is a high degree of concordance, her office will probably use the assays to screen such byproducts.

Because the NIEHS group has pioneered testing of transgenic models, its results have not yet been corroborated by other laboratories. Large-scale testing of the models is being done by the International Life Sciences Institute, but results are not expected until 2000. Those results will be the real "proof of the pudding," said Julian Preston, a science adviser to the Chemical Industry Institute of Toxicology, who finds French's initial findings "very promising." —MARGIE PATLAK

States pushing experiments with "performance-based" regulations

State regulators are increasingly finding flexibility within existing environmental regulations to innovate and focus programs on performance measures, according to several case studies presented at a recent symposium of state regulatory agency leaders. The symposium, hosted by the Environmental Council of States and the Minnesota Pollution Control Agency, explored ways to support state-level regulatory innovation.

Some states have streamlined their regulatory systems without bumping up against federal rules. States such as Florida, Indiana, Oklahoma, and New Jersey have implemented their own variations on performance-based measures of environmental results. By measuring their success in terms of actual environmental quality, as opposed to traditional counts of permits issued and enforcement actions taken, these states have found that they can do a better job of reducing pollution while providing companies greater operational flexibility.

Three years ago, Florida initiated environmental performance measures under Department of Environmental Protection Secretary Virginia B. Wetherell. Steve Adams, a senior management analyst, believes the performance measures, such as environmental indicators, have led to a different measure of success that has highlighted several problems.

For instance, whereas traditional measures of regulatory success showed a greater than 98% compliance rate with air emission permits, environmental indicators showed that nitrogen oxide emissions had grown by 1.6% since 1989. As a result, last October Wetherell directed the Division of Air to work with industry to reverse the upward trend.

"Environmental indicators inform our understanding of how well a state program is operating," said Adams. "People are beginning to understand that a higher order of information is necessary before you initiate regulatory innovation."

Indiana has also focused more closely on results as part of its Environmental Performance Partnership with EPA. In 1996, Indiana set a goal of sending 95% of its Resource Conservation and Recovery Act solid waste to landfills with synthetic liners and leachate collection systems by 2001. Bruce Palin, assistant commissioner of the Office of Solid and Hazardous Waste in Indiana's Department of Environmental Management, said that the state is now more than halfway toward reaching that goal. New state rules provided incentives for haulers to patronize state-of-the-art landfills, said Palin. "The concept is to start with the results and work backwards to figure out what administrative actions you need to take," he concluded.

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—Steve Adams, Florida Department of Environmental Protection

New Jersey's pilot facility-wide permitting program takes a multimedia approach that incorporates pollution prevention measures and sets limits for each process in a facility. Mike DiGiore, manager of facility-wide permitting, credits the new permits with reducing environmental risks and eliminating cross-media transfers of pollution. As a result of facility-wide permitting, Huntsman Polypropylene anticipates reducing its use of hazardous substances by 4300 tons per year and air and water emissions by 751 tons per year.

DiGiore noted, "Facility-wide permitting provides companies greater flexibility, because whole processes are permitted instead of each piece of equipment in the process. That means companies can switch products and notify the department after the change." All of these changes were accomplished, said DiGiore, "without requiring any special waivers from federal regulations or statutes."

Oklahoma's Simplified Uniform Program for Environmental Regulation improves agency performance by simplifying the permit process and reducing the time required to obtain a permit. According to Mark Coleman, executive director of the Oklahoma Department of Environmental Quality, before the program existed, "it took 12 years to process some permits and over 100 permits were in the agency's hands for over a year." It now requires 30–90 days to process a permit. Oklahoma achieved this efficiency by simplifying state rules and laws, and issuing general permits whenever possible.

Although state regulatory innovators at the symposium, held in Minneapolis last November, agreed that there is flexibility within current state rules, they predicted that federal waivers would be necessary as innovations grow more sophisticated. —JANET PELLEY