

Weed Killer, Long Cleared, Is Doubted

By **Andrew Pollack**

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Thirty years ago, an Environmental Protection Agency committee determined that the popular weed killer Roundup might cause cancer. Six years later, in 1991, the agency reversed itself after re-evaluating the mouse study that had been the basis for the original conclusion.

Now the issue is back again, in an even bigger way. An agency of the World Health Organization has declared that glyphosate, the active ingredient in Roundup, “probably” causes cancer in people. One piece of evidence the agency cites is that same mouse study.

The declaration drew an angry response from Monsanto, the maker of Roundup, which has accused the agency of having an “agenda” and “cherry picking” the data to support its case.

The conclusion is “starkly at odds with every credible scientific body that has examined glyphosate safety,” Philip Miller, Monsanto’s vice president for global regulatory affairs, told reporters on Tuesday. That includes a recent review by German government regulators on behalf of the European Union.

The new controversy and the reversal by the E.P.A. decades ago demonstrate how the same data can be interpreted differently and how complicated and politically perilous such a decision can be. But the discrepancy between Monsanto and the health organization can be partly explained by the specific way its agency analyzes the data.

Officials at the agency, the International Agency for Research on Cancer, said they had no agenda other than to inform the World Health Organization. They said the conclusion was based on studies of people, laboratory animals and cells.

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“All three lines of evidence sort of said the same thing, which is we ought to be concerned about this,” said Aaron Blair, a retired epidemiologist from the National Cancer Institute who was chairman of the group of 17 reviewers from around the world; agreement on the classification was unanimous.

Glyphosate, introduced in the 1970s, is the most widely used herbicide in the world, sprayed on farms, in forests, on road sides and in gardens, and has a reputation for being benign, as pesticides go. It is now generic and used in many products, not only Roundup.

Use of glyphosate has soared in the last two decades because of Monsanto’s Roundup Ready crops, which account for most corn and soybeans grown in the United States. These crops are genetically engineered to withstand glyphosate, allowing farmers to spray their fields without harming the crops.

Monsanto executives said this week that they did not expect the agency's action to affect sales. But that could depend on whether regulators around the world impose restrictions on glyphosate use after the W.H.O. pronouncement. A spokesman for the California Office of Environmental Health Hazard Assessment said it was evaluating whether products containing glyphosate might have to be labeled as posing a cancer hazard under the state's Proposition 65.

Some consumer and environmental groups said on Friday that the findings strengthen the case for the labeling of genetically modified foods. They also called upon the E.P.A. to re-evaluate glyphosate and a newer weed killer from Dow Chemical that combines glyphosate and another herbicide, 2,4-D.

The E.P.A. said it would consider the W.H.O. agency's finding in its own review of glyphosate. The E.P.A. has maintained its classification of glyphosate as having "evidence of noncarcinogenicity for humans" since 1991, including through a review last year.

The International Agency for Research on Cancer looks at a very narrow question: whether a substance or behavior might cause cancer under some circumstances, even if those circumstances are unlikely to occur. It does not weigh the benefit versus the risks of a chemical, leaving that up to national regulators.

The agency classifies alcoholic beverages as human carcinogens, along with tobacco, arsenic and asbestos. Working the night shift or being a hairdresser are classified as probably cancer-causing, the same as glyphosate, because one job disrupts the body's circadian rhythms and the other involves exposure to dyes. Coffee is a "possible" carcinogen, a lower level.

Over all, the agency has reviewed 983 things like chemicals and occupations. About half could not be classified based on the evidence. Only one compound, caprolactam, which is used to make a type of nylon, had enough evidence in its favor to be judged "probably not" carcinogenic.

There are also differences in interpretation. Monsanto and some regulators say the preponderance of studies shows no cancer risk from glyphosate. But for the W.H.O. agency, a few positive findings can be enough to declare a hazard, even if there are negative studies as well.

Kathryn Z. Guyton, a senior toxicologist at the agency, said the reviews also considered only studies published in journals or government documents that were publicly available. That typically excludes many studies done by chemical companies to get regulatory approval.

She also said the reviewers did not include the German regulatory report because it has not been ratified by the European Food Safety Authority.

It is a bit difficult to judge how the W.H.O. agency reviewers arrived at their conclusion. Eventually, it will publish a detailed monograph. For now, there is only a brief paper published March 20 in *The Lancet Oncology*, a medical journal.

In that paper, the reviewers cited studies from the United States, Canada and Sweden suggesting that people exposed to glyphosate had a higher incidence of non-Hodgkin's lymphoma, even after correcting for exposure to other chemicals.

But a large and long study of pesticide applicators on American farms did not find any problems. Dr. Miller of Monsanto accused the agency of "disregarding" this study, though it is clearly mentioned in the *Lancet* article. Dr. Guyton said because of that study the reviewers concluded that there was only "limited" evidence from human studies that glyphosate could cause cancer.

The *Lancet* article cited several animal studies. As few as two are needed to establish carcinogenicity, Dr. Guyton said.

There are several ways to measure a possible effect. Are there more cancers in animals exposed to the chemical than in a control group? Do higher doses mean more cancers? Are the rates higher than expected based on historical data? In many studies, not all three measures are positive.

Take the mouse study at issue in the E.P.A. review 30 years ago and also cited by the W.H.O. agency. There were three cases of a rare type of kidney cancer in 50 male mice fed the highest dose. That type of tumor is rare, so it strengthens the case, Dr. Blair said. “They literally don’t occur, but they occurred when rodents were dosed with this stuff,” he said.

While the W.H.O. agency’s reviewers focused on the rise in cancer with dose, the E.P.A. reviewers in 1991 said the findings were not meaningful, in part because there was no statistically significant difference over all between the exposed mice and the control group.

Another finding cited by the W.H.O. agency was of an increased rate of hemangiosarcoma, a cancer of the blood vessels, in male mice, as discussed in a document issued by the W.H.O. and the Food and Agriculture Organization in 2004. The authors of that document dismissed the significance of the finding, and said that over all, the study had “produced no signs of carcinogenic potential at any dose.”

The 2004 document then discussed four rat studies that it said also showed no evidence of carcinogenicity. One of those studies was also cited by the W.H.O. agency reviewers as evidence of carcinogenicity. Dr. Guyton said the agency reviewers “don’t report the authors’ conclusion. They report their own conclusions on that data.”

Another sign of whether something can cause cancer is whether it causes mutations or chromosomal damage. Bacterial tests do not show that glyphosate causes mutations. But the reviewers said there was evidence of chromosomal damage in studies involving animal and human cells.

The agency assessment began about a year ago with a literature search and culminated this month, when the working group met in Lyon, France. Reviewers had no ties with the pesticide industry, Dr. Guyton said.