With glyphosate under fire, scientists look for alternatives to the most effective — and safest — weedkiller in the world. It’s not going well

Last March, Mexican President Lopez Obrador announced he was indefinitely postponing a scheduled April 1 ban of the herbicide glyphosate. It gravely disappointed advocacy environmentalists. They blamed pressure from the United States government doing the bidding of the agricultural industry.

Glyphosate will remain the herbicide of choice for Mexican farmers, the government said, until it can find a reasonably safe, “low toxicity” alternative.

If that’s the standard for a replacement weedkiller, it will be many years, and perhaps never, before glyphosate is withdrawn from Mexican farmers.

The ‘super weed’ case against glyphosate

The first synthetic herbicide, 2,4-dichlorophenoxyacetic acid (2,4-D), was introduced in the 1940s. It was used mainly to control weeds in cereal grains. About 10 years later, in 1956, the first evidence of resistant weeds (Daucus carota, or “Queen Anne’s Lace”) was reported in Canada.

Since its introduction in the 1970s, glyphosate has gradually become one of the most important weedkillers, praised for its effectiveness and broad-spectrum weed control capabilities. It fulfills many agricultural and regulatory requirements—it’s effective, relatively inexpensive, boosts crop yields, and is safe for humans as well as plants engineered to avoid its herbicidal functions.

However, the extensive and at times indiscriminate use of glyphosate led to significant agronomic challenges: the development of glyphosate-resistant weeds. The first weed resistant to glyphosate was reported in Australia in 1996. That was the first year that Monsanto’s trademarked version of glyphosate, “Roundup Ready,” was available, but only in soybeans. Shortly after, the resistant ryegrass weeds were discovered in a New South Wales orchard.

Glyphosate targets the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), which is essential for synthesizing aromatic amino acids in plants. By inhibiting this enzyme, glyphosate effectively kills a wide range of weed species. However, with repeated use, certain weed populations, such as Palmer amaranth, have evolved resistance.

The increased use of glyphosate tied to herbicide-resistant GMO crops gradually emerged as a proxy used by advocacy groups to turn the public against the crop biotechnology revolution. When some farmers did not rotate herbicides as part of an Integrated Weed Management program, activists raised a storm as weed problems escalated.
But as Michigan State University’s AgBioResearch department noted, this phenomenon is not unique to glyphosate; exclusive use of almost any herbicide can result in herbicide-resistant weeds.

The new difficulties in weeds, pests, and biodiversity encountered in modern agriculture don’t stem directly from the use of GMO crops, but rather from treating the crops’ traits as a final solution to weed and pest management issues. Treating GMO crops as one among many tools in a management plan will help limit the spread of superweeds and secondary pests, as well as preserve landscape biodiversity.

Resistant strains of weeds have continued to gain speed over herbicide development, and that’s partly driven by the enormous success of glyphosate.

Now, more glyphosate-resistant weeds have been recorded, including weeds found in farms with “Roundup-Ready” soybeans. According to a report from Iowa State University, these include:

- Rigid ryegrass in a wheat production system in Australia and in California
- Italian ryegrass in Chile
- Goosegrass in Malaysia
- Horseweed (marestail) in the eastern, midwestern, and southeastern United States.

Iowa State noted that the biochemical mechanisms for all, but goosegrass remain unknown. And now, according to the International Herbicide-Resistance Weed Database, more than 50 weed species are resistant to glyphosate.

But the solution, as MSU wrote, lies not in taking agriculture back to the 19th century, but in developing new herbicides that overcome—or sidestep—resistance.

**Effective alternatives to glyphosate?**

Not knowing the mechanisms of resistance is one of the several factors that make herbicide development difficult. To evade (or at least postpone) resistance, a new herbicide needs a new mechanism of action. But in the last 40 years, only one herbicide with a new mechanism has been introduced.

A 2012 paper by Steve Duke at the University of Mississippi showed US patents for new herbicides totaled 432 in 1997. By 2009, that number dropped to 65. Some of this decline was attributed to the popularity of glyphosate—Why compete with success?

Another challenge is the cost and time needed to develop a new product. Currently, a new agricultural chemical involves screening 100,000 compounds, a process that runs more than $200 million and can take 8 to 10 years.

Without a viable alternative to glyphosate, scientists must identify new modes of action. According to the Herbicide Resistance Action Committee, there are 25 herbicidal modes of action, usually involving the direct inactivation of an enzyme key to a plant’s growth and/or function. These include nucleic acid inhibitors, inhibition of internal microtubule assembly, or fatty acid synthesis inhibitors, for example.
Unfortunately, only one new mode of action was discovered since 1984.

**Ommics revolution**

What could help identify new modes of action that could lead to new herbicides? The rapidly growing field of “multiomics” is promising [This research area](#) includes familiar lines of discovery in genomics and proteomics, but also involves a wide range of cell functions, including “transcriptomics” (the study of mRNA) and “metabolomics” (molecules involved in cellular energy production and consumption). These “omics” areas (which are difficult to define, and many other “omics” are popping up every few months), already used in pharmaceutical development, could result in unique new herbicide modes of action to fend off resistance.

Such a “multiomics” approach could diversify the ways that herbicides function, as well as more easily satisfy the other requirements of a new agricultural chemical—that it be safe and relatively easy to use, doesn’t harm the environment and is cost-effective.

One problem with traditional herbicide development has been its single mode of action, reacting to “target-site based resistance,” or TSR. This type of resistance involves a point mutation, single codon deletion, or target gene overexpression. Building a chemical to counteract these singular events can initially be effective, but eventually fall victim to resistance.

More powerful resistance comes from what’s known as “non-target site-based resistance” (NTSR), which involves changes in metabolism, reduced uptake of herbicide, and an ability to adapt to oxygen radicals (often used to kill plants).

Modern high-throughput technologies based on the various “omics” could help us understand the complexity of resistant weeds and therefore develop new modes of action. And because these modes are more integrated, it’s more difficult for weeds to develop resistance. But genomics alone won’t develop more modes of action. For example, gene expression can remain constant, while metabolism levels can vary widely at the same time.

A research team from [Czechia](#) recently published a review in *Frontiers in Plant Science* admitted that “inadequate initiatives have been taken to integrated multiple omics-based studies to elucidate the mechanisms of herbicide resistance in economically significant weeds.” Even in their review, they limited their search to transcriptomics and metabolics. “High-resolution genomic analyses of weedy plants will be needed in the future,” they added.

While no single herbicide matches the broad-spectrum effectiveness and cost-efficiency of glyphosate, several alternatives and integrated approaches can be substitutes, although without its effectiveness or safety profile. Glusofinate, dicamba, 2,4-D, and paraquat cannot fill glyphosate’s shoes.
While development of fungicides and insecticides has also been lagging over the past few decades, herbicides present an even more unique and formidable challenge—requiring solutions to plant complexity. Plants have evolved very intricate chemical defenses (including resistance to other chemicals) for a very good reason—they can’t run, and they can’t hide.

**Glyphosate analysis**

Are there any non-chemical alternatives? Mechanical weeding does work but it’s very inefficient and results in the release of carbon from the soil, exacerbating climate change instability. The value of cover crops and biological controls is limited. The only strategy that currently works, now and for the foreseeable future, involves Integrated Weed Management. And that requires the best and safest pesticide available: glyphosate.

The sad irony is that a sizable faction of the environmental movement, in defiance of the scientific consensus, remains steadfast in its opposition to all agricultural chemicals, including glyphosate. Chemophobia has been part of our culture for decades, but it accelerated after a disputed evaluation of glyphosate issued by the controversial International Agency for Research on Cancer, which evaluates what’s known as a “hazard”. In 2015, it issued a monograph based on three dozen studies out of more than three thousand available concluding that glyphosate was a possible carcinogen to applicators; it did not hold that micro-traces in food posed any known harm.

It’s safe to say that no independent chemical oversight or regulatory risk agency, most reviewing hundreds and in some cases thousands of studies, agrees with that assessment. Their findings are illustrated in this infographic. [Click here for a downloadable pdf version]
The 19 regulatory and research agencies—all independent—including the 2023 report from the European Food Safety Authority, have unanimously concluded that there is no convincing evidence that glyphosate can be linked to cancer. EFSA “did not identify critical areas of concern”. The consensus is more universal than the belief that humans are a critical driver of climate change.

How have the organic movement and anti-biotech environmental non-governmental organizations (NGOs) such as the Environmental Working Group, Greenpeace, and the Sierra Club, responded to these findings? The reaction to Mexico’s decision to indefinitely suspend its planned glyphosate ban is illustrative.

“US taxpayer-funded officials [are] entwined with the interests of big agrochemical companies, such as Chinese-owned Syngenta and Germany’s Bayer AG, wrote Carey Gillam, an online opinion page, The New Lede. It’s hosted by the Environmental Working Group and funded by the organic industry and tort lawyers who use her columns as legal gruel to sue agribusinesses over alleged health issues caused by glyphosate and other crop chemicals.

Gillam echoes the anti-biotech activist claim, presented without evidence, that there is an active conspiracy among the US Department of Agriculture, the Environmental Protection Agency, and the lobby group Crop Life America to promote “cancer-causing pesticides” like glyphosate.

The agricultural and science communities have a different, almost unanimous view: not one regulatory chemical advisory agency in the world concludes that glyphosate causes cancer in food or when used by applicators. But courtroom victories are not evidence.

“No pesticide regulatory authority in the world currently considers glyphosate to be a cancer risk to humans at the levels at which humans are currently exposed,” Health Canada wrote in its assessment.

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