How Toxic is the World's Most Popular Herbicide Roundup?

Glyphosate, the active ingredient in Roundup, is designed to be toxic to plants, but scientists observe some untoward effects on animals in the lab.

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Glyphosate, the active ingredient in the world's most widely used herbicide, Roundup, is arguably also one of the most contentious. Mass protests erupted in Europe last November after the European Commission, following much discussion, granted a five-year extension for the license to use glyphosate in agriculture in the E.U.

Farmers have relied upon glyphosate-based herbicides to kill unwanted vegetation for more than four decades, but its use sparked hefty debate in 2015, when the World Health Organization's International Agency for Research on Cancer (IARC) concluded that it was "probably carcinogenic," adding it to a category that also contains red meat, for instance.

This followed previous conclusions by research agencies such as the European Food Safety Authority (EFSA) and the U.S. Environmental Protection Agency (EPA) that glyphosate is unlikely to pose a cancer risk to humans.

There's no question that the research around this small molecule has become highly politicized. Environmental activists have claimed that exposure is linked to everything from cancer to celiac disease to autism, while on the other hand, industry-backed reviews have insisted the pesticide has no untoward effects whatsoever.

So where does the science actually stand?

With an estimated 6.1 billion kilograms applied worldwide over the last decade, understanding its risk to farmworkers, consumers, and the environment is paramount.

Glyphosate's effects in the lab

Glyphosate is a small compound that has been sold as the active ingredient in herbicide formulations since 1974. It is marketed as having no effect in animals because it is designed to specifically inhibit an enzymatic pathway required for protein synthesis—and thereby, growth—unique to plants.

Danio rerio in the lab
RILEY BRANDT, UNIVERSITY OF CALGARY

Over the years, regulatory agencies have evaluated its potential effects on non-target organisms. However, recent assessments seem to be focused on carcinogenicity and genotoxicity of glyphosate, notes Deborah Kurrasch, a neuroscientist at the University of Calgary. Within the past decade, she says, evidence started to accumulate in the scientific literature that it might have other toxic effects. "There's a lot of systems beside cancer" that can be affected, she says.

Kurrasch, whose research is funded by the Natural Sciences and Engineering Research Council of Canada, began to look into glyphosate several years ago, and was surprised by how few studies there were in the literature. "There was very little for a chemical that we're all exposed to," she recounts, adding that there is still little known about its mechanism of action in model systems.

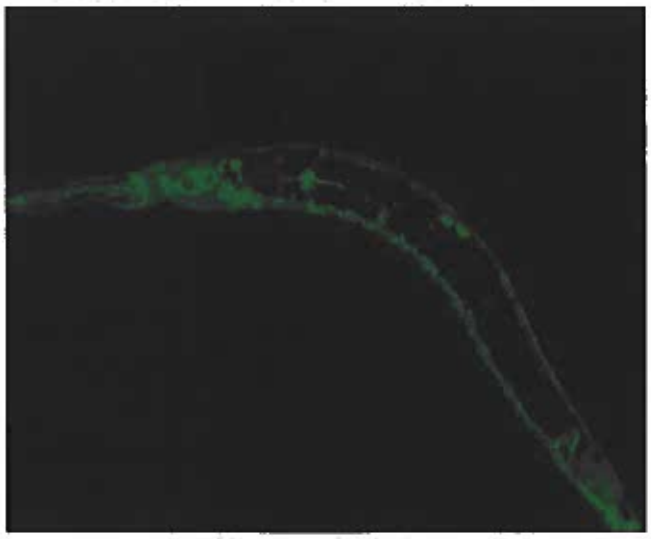
For instance, with the industrial compound bisphenol A (BPA), Kurrasch's main research focus, "we can look at the molecule and see that it binds to estrogen receptors, and can understand that the mechanism affects estrogen signaling," Kurrasch explains. But "I don't think that's well understood for glyphosate, because it's not clear what exactly it's binding to."

Some evidence suggests that it has an effect on mitochondrial function. In an experiment a few years ago, Kurrasch and her colleagues exposed zebrafish embryos to relatively low concentrations of glyphosate during specific windows of development. This appeared to alter mitochondrial function and cause a related decrease in basal respiration, which in turn impaired the locomotion of larvae.

Some other studies also suggest that glyphosate can reduce mitochondrial function as well as sperm motility in zebrafish at high concentrations, and can alter neurotransmitter activity in the brains of rats. However, it's early days for this field of research, Kurrasch notes. "The PR that it's safe is very strong, and I just don't think there's that much known in model systems, even."

Other researchers stress that the immediate toxicity of glyphosate is likely very low at most environmental concentrations, in contrast to the whole pesticide formulation it is usually used in.

The difference between glyphosate and Roundup



The nervous system of *Caenorhabditis elegans* labeled with a green fluorescent protein
MATTHEW A. SMITH

Glyphosate is rarely used on its own in the field. Herbicide formulations as a whole include a variety of other chemicals, such as surfactants to help glyphosate enter plant cells, and other additives that extend the product's shelf life. This spurred Kurrasch to compare the effects of glyphosate alone to the effects of Roundup (containing the same glyphosate concentration) in zebrafish. Remarkably, she found Roundup had the opposite effect as glyphosate by itself: The fish moved more, and basal respiration was higher. They also had different gene-expression profiles of mitochondria-linked genes in their brains. "It suggests that they have different mechanisms of action," Kurrasch says, "that glyphosate is doing something and these adjuvants are doing something else."

A problem for scientists investigating the physiological activities of pesticides is that herbicide-producing giants including Monsanto, Roundup's developer, or Syngenta, which produces the glyphosate-containing herbicide Touchdown, aren't required to make their full ingredients lists public.

In the U.S. and E.U., they are required to print on the packaging how much of the active ingredient the product contains. This typically isn't the case for other ingredients, which are considered "inert" because they don't contribute to the herbicidal activity of the formulation. "So that makes it very difficult for a toxicologist to test the different ingredients to figure out what's the most toxic, or what's contributing to it," says Vanessa Fitsanakis, a neurotoxicologist at Northeast Ohio Medical University. "From a research perspective, I can't tell which component might need to be changed [to reduce possible toxicity] in those formulations because I don't know what some of those components are."

What concerns Fitsanakis, whose work is funded by the National Institutes of Health, are the findings of previous studies that the commercially available product is much more toxic to cells and animals in the lab than glyphosate alone. "The data are overwhelmingly in agreement that glyphosate by itself is relatively nontoxic," she says.

Instead of trying to tease out which of the chemicals in the mixture are doing what, Fitsanakis has decided to look at the effects of glyphosate-based herbicides in the formulations farmers use. Her experiments involve soaking nematode worms, *C. elegans*, in Touchdown—in concentrations used by pesticide applicators—as a model to understand what effect the product could have on the nervous system of animals.

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glyphosate-containing herbicides can have this effect on cells, Fitsanakis wanted to see if the two are linked, and whether pesticide exposure can increase the risk for developing such diseases.

In a study published this January, she found that in *C. elegans* worms, exposure to Touchdown could increase the activity of specific reactive oxygen species—which cause oxidative stress—and also mitochondrial inhibition. The worms also showed neurodegeneration in both dopaminergic and GABAergic neurons. This was at concentrations at which occupational agricultural and pesticide workers would routinely be exposed to, Fitsanakis says.

This doesn't mean that exposure to glyphosate-based compounds will cause neurodegenerative disease, she cautions. They may be one of many risk factors that predispose people to developing sporadic forms of Parkinson's disease in later life.

"And when that person with [a] genetic risk factor encounters something in the environment, like a pesticide that inhibits mitochondria, then those things together [can start] a neurodegenerative process."

Glyphosate in the real world

William Reeves, Chemistry Safety and Outreach Lead at Monsanto, is not surprised about the results of such studies. The surfactants used in Roundup are similar to those used in regular household products, he explains, which cause membrane degradation and subsequent mitochondrial breakdown in high doses. "You would see the same thing with dish detergent, you would see it with hand soap," he tells *The Scientist*.

He says that concentrations of glyphosate and Roundup generally applied in previous studies greatly exceeded those that would be normally found in real-world environments. In particular, studies where whole animals or cells are submerged in herbicide solutions aren't reflective of real-world situations, he notes, as the herbicide is not being used according to instructions. For instance, the label directs pesticide applicators to use chemical-resistant gloves and protective eyewear when applying Roundup, and to not apply the formulation directly to water.

"It's the same thing as the Tide Pod challenge," where a chemical formulation is not being used according to its label, he says. "You get the membrane solubilized, [organs] stop functioning, and that's really what ends up causing the damage."

Researchers are not only concerned about the immediate consequences of improper use of the chemicals by applicators, but also about potential effects caused by chronic

The effects are going to be subtle and

exposure to applicators or animals—via the skin or through inhalation, for instance—as well as what happens when they accumulate in the environment.

"[Glyphosate] doesn't create a completely poor functioning brain, or have major effects on brain development," says Kurrasch. "The effects are going to be subtle and accumulative over years of exposure. And it's going to be tricky to convince regulatory bodies that there's a problem, if that's the case," she says.

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—Deborah Kurrasch, University of Calgary

Fitsanakis says that while presenting her work publicly, scientists from Monsanto or Syngenta will occasionally show up and politely challenge her research. "The scientists that I have spoken to from Monsanto and Syngenta are very convinced that the glyphosate by itself is nontoxic. I agree with them on that. Where I disagree . . . is that you can have an active ingredient that is nontoxic, but that does not mean that the commercial formulation is also nontoxic."

A moving target

To makes matters more complicated, there are many different commercial formulations, which can differ by company, country of purchase, agricultural use or home use, or even by the batch.

Herbicide makers also seem to change their formulations, according to Peter Roslev, an environmental toxicologist from Denmark's Aarborg University. In his recent studies on the effects of glyphosate on aquatic environments, funded by the university, "we did not see the same difference between the commercial product and the pure chemical, compared to older studies," he says.

Daphnia magna, showing fluorescently labelled food it has consumed
PETER ROSLEV

What concerns Roslev about glyphosate is its effect on a small yet important organism,

the water flea *Daphnia magna*.

Glyphosate can bind to soil particles in the environment, which can get into the watershed during heavy rainfalls and reach the freshwater environments that *Daphnia* call home. "Many of the organisms like the *Daphnia*, they actually live off the small particles in the water," he says. "They are . . . filter feeders, so if they filter the water, they will maybe have a concentrated dinner of pesticides."

When exposed to glyphosate alone, the swimming behavior of *Daphnia* will change, becoming slower. The effect is subtle at low doses, but "at higher concentrations, they stop [swimming] in the water," says Roslev.

In a study in 2016, he showed that glyphosate can bind to toxic metals, resulting in a r combined compound that is transported more easily in the environment, he explains and is also more toxic than glyphosate itself. The behavioral effect of glyphosate was much more pronounced when it acted as this "new compound."

If altered behavior makes the animals more or less vulnerable to predation, the effect could cascade through the ecosystem as many other life forms live off *Daphnia*. "It wil affect the food chain that they are part of," he says, although he hasn't yet tested this i field experiments.

Glyphosate and humans

Epidemiological studies in humans do show some weak links between glyphosate exposure and subtypes of non-Hodgkin's lymphoma, which played a big role in the IARC's decision. But an analysis last year drawing on data from the Agricultural Health Study, which included some 90,000 farmworkers and their spouses in Iowa and North Carolina over nearly two decades, showed no significant association between glyphosate and non-Hodgkin's lymphoma, nor with overall cancer risk (although it did show a weak association with acute myeloid leukemia).

Nevertheless, there are concerns about how much glyphosate we might be eating. Some crops have been genetically modified to be tolerant to glyphosate and therefore are sprayed to eliminate weeds growing in their midst. "And because of that, these crops . . . accumulate glyphosate in very high concentrations inside the plants," Félix Carvalho, a toxicologist from Portugal's University of Porto and secretary general of the European toxicologist organization Eurotox, writes to *The Scientist* in an email. "There is evidence that we are being exposed to increasing doses of glyphosate and other compounds of the herbicide formulation over the years. Such exposure is potentially deleterious."

One of the reasons why glyphosate is thought to be safe for humans is that, as a molecule, it's not soluble in fat, "and thus will not accumulate in our bodies very easily," Kurrasch

adds in an email. A recent EPA assessment of human health risks determined that glyphosate does not bio-accumulate after oral exposure.

Fitsanakis adds that based on the data she has seen, "the amount that we could be ingesting with food is relatively small," especially considering that the majority of glyphosate is used on field crops that we don't eat directly, she explains. Farmworkers' occupational exposure to the pesticide, and the adjuvants it is used with, is what concerns her most.

You would see the same thing with dish detergent, you would see it with hand soap.

—William Reeves, Monsanto

Although companies aren't required to publicly disclose the full compositions of their pesticide formulations, they must submit toxicity studies on the whole formulation, as well as its entire composition, to national authorities in order to get a product approved for market. History shows that on occasion, some authorities have seen the need to re-evaluate certain additives. For instance, Germany's authorities found in 2015 that the surfactant polyethoxylated tallowamine (POE tallowamine) contributed a large amount of toxicity to the herbicides it was used in, such as Roundup. This led to an EU-wide reassessment by the EFSA, which concluded that "a likely explanation for the poisoning occurrences observed in humans is that it is mostly driven by the POE-tallowamine component of the formulation." The E.U. subsequently decided to ban the use of the co-formulant. Its use is allowed in the U.S.

"If there was a very obvious acute toxicity to . . . non-target organisms, one would think that that had been discovered by now," says Roslev. "But you can only detect the effects that you are looking for, and that seems to be the history with many of these chemicals. There's always an unexpected effect that nobody thought about, that this compound used for this purpose actually has this side effect," he adds.

"The truth is often not black and white," he concludes in an email. "We therefore have an obvious responsibility as scientists to continue to screen for any overlooked side effects, because these chemicals are sold and used in vast amounts."

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