

# ROUNDUP

## What is a Pesticide?

The term *pesticide* does not refer solely to a substance that kills bugs. It refers to a broader class of chemicals that destroy animals or plants that are detrimental to humans, crops, livestock or forestry. Subcategories include insecticides, herbicides, fungicides, and rodenticides, among others. Thus, the medical literature on the herbicide in *Roundup* and its ingredients often appear under the general heading of "pesticide research".

## What is a Surfactant?

A surfactant (a surface acting agent) generally refers to a large class of compounds that are able to reduce the *surface tension* in a liquid. For example, surface tension in water - *the slight attraction that exists between the water molecules at the surface* - essentially creates an elastic membrane that can resist a small amount of force. Surface tension also causes water placed on an object to bead up.



Surfactant molecules are able to collect at the surface, separate the water molecules and thus weaken the surface tension membrane. They may also act as a *wetting agent* because by reducing surface tension, they can cause water to spread evenly over a surface.

Surfactants are used in countless products as an additive to enhance the product's effectiveness (e.g., they allow dyes to penetrate fabric evenly). In medicine, for example, some chemotherapy agents cannot penetrate cancer cells until a surfactant is added.

## Monsanto's Roundup

In 1974, Monsanto introduced a product it called "*Roundup*" that was capable of killing weeds, grasses and other leafy plants. There were several formulations of *Roundup*, but the principal ingredients were **glyphosate** - a molecule patented by Monsanto in 1974 as a *post-emergence* herbicide (effective *after* the weed starts to grow), and a surfactant known as **POEA** (polyethoxylated tallow amine). [Note for Product ID purposes: Monsanto also used the word "*Roundup*" in the 1960s for a *pre-emergence* weed killer it marketed with presumably different ingredients. It also used different tradenames for consumer/retail, agricultural and commercial variations of the product (e.g. *Roundup Pro*, *Ranger Pro*, *Accord XL*, etc.)]

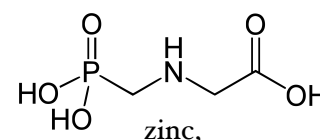


Because *Roundup* would indiscriminately kill weeds and the desirable crops that were being invaded, Monsanto gradually introduced a number of genetically-modified crops that were immune to *Roundup*. Starting in the mid-1990s, Monsanto began selling "*Roundup Ready*" soy beans, and then corn, cotton, alfalfa, canola, and sugar beets. (Not surprisingly, these products have since cross-bred with the weeds to produce glyphosate-resistant weeds.)

*Roundup* is also utilized to reduce moisture in grain and other crops before harvesting. This explains why *Roundup* residue has been detected in cereals. In 1999, a year before its main U.S. Patent expired, Monsanto reported worldwide glyphosate-related product sales of \$2.48 billion. In 2018, Bayer A.G. (Germany) acquired Monsanto.

## Glyphosate

The ingredient **glyphosate** (pronounced glyph·o·sate | \ 'glī-fə-, sāt, or alternatively gly·pho·sate | \ 'glī-fə-, sāt) can be traced to a patent issued to a Swiss company in the 1950s. It was then patented by Stauffer Chemical in 1964 as a *chelating agent* - a compound that readily binds to and removes calcium, manganese, cobalt, and other metals. It was primarily intended to clear the mineral buildup in pipes and boilers. (US Patent 3,160,632). In 1974, a patent was issued to Monsanto for glyphosate as an herbicide (US Patent 3,799,758).



## Non-Hodgkin's Lymphoma

Non-Hodgkin's Lymphoma (NHL) refers to a group of cancers of the lymphatic system. The cancers are classified according to the type of lymphocyte involved: B-cell lymphomas (85% of cases) and T-cell lymphomas (15%). There are a dozen or more different lymphomas within each of these categories. The subtypes are also grouped by how fast they grow and spread: an *aggressive* form of NHL known as diffuse large B-cell lymphoma (DLBCL) and an *indolent* form known as follicular lymphoma, are the most common.

Per the National Cancer Institute, about 75,000 new cases are diagnosed every year in the U.S, resulting in 20,000 annual deaths, making NHL the 7th most common cancer. In 2000, the International Classification of Diseases (ICD) definition of NHL was expanded to include multiple myeloma (MM) and chronic lymphocytic leukemia (CLL).

## Agricultural Health Study

The Agricultural Health Study (AHS) is a government-funded *prospective* health cohort study begun in 1993, with three follow up interviews or questionnaires, the last being in 2014. The most recent "study update" was issued in November 2017. The cohort includes 4,916 commercial pesticide applicators from Iowa and 52,395 private applicators, mostly farmers, from Iowa and North Carolina, who were applying for renewal of their pesticide applicator's license. They were initially questioned about their pesticide use before any had developed cancer. Over the years, as some participants developed cancers, they were grouped according to those who self-reported using a particular



In 1983, Monsanto was issued an additional patent (US Patent 4,405,531) for glyphosate salt, effectively extending the *Roundup* herbicide patent to the year 2000.

Monsanto claimed that glyphosate was completely safe for humans because it *only* inhibited an enzyme called EPSPS, which produces three specific amino acids via a process unique to plants (the *shikimate pathway*). Numerous studies have since demonstrated that glyphosate also has an adverse impact on animal life.

## POEA

In order for *glyphosate* to be effective, it must spread out over the surface of the leaf and penetrate the plant cells inside. Monsanto achieved this by including the surfactant POEA (polyethoxylated tallow amine) in its formulation of *Roundup*, at least until 2000. POEA is not a single identifiable compound. It refers to a range of non-ionic surfactants derived from animal fat that have complex and variable hydrocarbon chains. In 2016, POEA was reportedly the subject of an agreed ban by the EU because of its own potential toxicity.

POEA is referred to as a co-formulant or adjuvant to glyphosate in *Roundup* formulations. It may comprise as much as 15% of pre-2000 *Roundup* formulations. Monsanto also used POEA variants that it claims are proprietary. One criticism of Monsanto, and other researchers, was that they focused on the health effects of glyphosate in isolation, while ignoring the possible contribution of POEA to the overall health effects of *Roundup*. This is considered a significant omission since the primary exposure pathway for glyphosate is absorption through the skin, and surfactants like POEA are intended to greatly enhance absorption.

## Health Effects

Much of the medical literature that purports to study glyphosate or glyphosate-based herbicides (GBHs) or formulations (GBFs) has not reported an association between glyphosate and cancer. Most notably (according to Monsanto), the recently updated **Agricultural Health Study** failed to identify an association. *And yet...*

A relative risk of about 1.3 for Non-Hodgkin's Lymphoma has been reported in several peer-reviewed case-control studies, *Chang & Delzell* (2016). The relative risk has been reported to rise to 2.0 or slightly higher when the focus is upon subjects with more than 2 days of exposure per year, *McDuffie* (2001), or more than 10 days total exposure, or when diagnosis occurs more than 10 years after exposure, *Eriksson* (2008). **Most recently, a meta-analysis of prior studies reported that exposure to GBH increased the risk for NHL by 41%.**

pesticide and those who did not.

The AHS on glyphosate is subject to criticism because it uses “imputed” glyphosate exposure for the 37% of the cohort that did not respond to a follow up questionnaire administered 5 years after enrollment. “Historic” use was applied to guesstimate exposure of 37% of the cohort, without consideration of the enormous increase in GBH use following the start of the study. (GBH use in the U.S. reportedly went from 6-8 million pounds in 1987, to 180-185 million pounds in 2007, following the introduction of genetically-engineered, glyphosate-tolerant crops in the mid-1990s.)

As of 2005 (the study-imposed cancer cutoff date), there were 575 reported NHLs in the cohort. How many properly belong in the “unexposed” group? The study assumed that 135 of them had no exposure, and since the number of NHLs in the exposed group was proportionally lower, the incident rate ratio (RR) was below 1. However, if some of the assumedly unexposed had actually been exposed, the RR would have increased.

To the chagrin of Monsanto, the AHS update was the first to report a “possible” association with heavy glyphosate use and acute myeloid leukemia (AML).

## Any Federal Preemption?

Monsanto tries to make much of the fact that the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), 7 U.S.C. §136 et seq. (1996), requires that pesticides be registered before sale. Once registered, Monsanto contends that the label approved by the EPA is immune from criticism and cannot be unilaterally amended.

However, the act expressly states “In no event shall registration of an article be construed as a defense for the commission of any offense under this subchapter.” One such offense is “misbranding”, defined as using a label that lacks a warning or caution that is adequate to protect health and the environment. 7 U.S.C. §136(q)(1)(F), (G).

### Zhang (2019).

There are also some published animal studies and mechanistic studies that support the conclusion that *Roundup* can cause NHL. The 2017 IARC Monograph (Vol. 112) on glyphosate concluded that there was “strong evidence that glyphosate is genotoxic”, which together with the positive association reported in several case-control studies, led IARC to classify glyphosate as “probably carcinogenic to humans (Group 2A)”.

There are also some studies that show that exposure to certain pesticides (including GBHs) can cause a greater than 2.0 increase in the development of a chromosome translocation defect, t(14;18), which is consistent with the claim that glyphosate can cause double-strand DNA breaks. This particular mutation is often present in the most common NHL subtypes (follicular lymphoma and diffuse large B-cell lymphoma).

## Status of Roundup Litigation

For those who enjoy federal court, or cannot identify a diversity-destroying defendant, there is an MDL for *Roundup* (**MDL No. 2741**). The good news for plaintiffs is that it is based in San Francisco and, as test cases inch towards trial, the cases have survived a FRCP Rule 56 summary judgment challenge based on *general causation*. In a 68-page, comprehensive order **denying** Monsanto’s motion, Judge Chhabria gratuitously called the question a “close one” and described the plaintiffs’ *general causation* case as “shaky”, but he did outline the merits of plaintiffs’ case and endorsed the methodology of most of the plaintiffs’ experts (i.e., use of the Bradford Hill criteria). In January 2019, Judge Chhabria **granted** Monsanto’s request to bifurcate causation in the upcoming bellwether trials. **On March 19, 2019, the jury found in favor of the Plaintiff in “Phase 1” of the first bellwether trial (Hardeman vs Monsanto) - namely that his NHL was caused by exposure to Roundup. A week later, the same jury awarded \$5 million in compensatory and \$75 million in punitive damages to the Plaintiff.**

In California, a judicial coordination petition was granted in November 2017, based in Alameda County Superior Court (Oakland). See, **JCCP 4953**. In San Francisco, a school district groundskeeper who developed a rare subtype of NHL (mycosis fungoides), defeated a summary judgment motion by Monsanto (SFSC Case No. CGC-16-550128). The 47-page order by Judge Karnow, **denying** the MSJ, discusses the available science in great detail. The case proceeded to trial in July 2018, and the jury awarded \$39 million in compensatory damages and \$200 million in punitive damages. The trial judge upheld the compensatory award, and reduced the punitive award to \$39 million. An appeal and

The judge in the *Johnson* case ruled that since California tort law parallels the federal statute, and imposes no greater duty, there is no preemption. The judge, citing *Bates v. Dow Agrosiences, LLC* (2005) 544 U.S. 431, 434-435, 448, 451-453, also rejected Monsanto's argument that approval of the product by the EPA provided a basis for preemption. [The MDL judge is likely to rule on the issue in February 2019.]

## Strongest Cases

**Latency** is usually defined as the time from first exposure to cancer diagnosis. For NHL, glyphosate-induced latency (or latency from any cause) is not known with any precision. It appears that it should be more than 5 years, and the most compelling cases have a latency of more than 10 years, and perhaps as much as 20 years.

**Exposure** should be more than 2 days a year, greater than 10 days total, and involve significant contact with the skin, either through mixing, application, or spills.

**Disease** should refer to Non-Hodgkin's Lymphoma, and preferably one that includes a confirmed t(14;18) chromosome translocation, e.g. follicular lymphoma or diffuse large B-cell lymphoma.

**Risk Factors** should exclude radiation therapy, HIV, immunosuppressive therapy, and - depending on the NHL subtype - certain infections.



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cross-appeal were filed in December 2018. [Note: The *Johnson* case was exempt from the JCCP coordination because of Mr. Johnson's poor health.]

The vulnerability of the California verdict (and others) may lie in the fact that many of the studies treat NHL as a single disease, and do not focus on specific subtypes, especially the rare ones. Plaintiffs may be able to deal with this by arguing that glyphosate exposure causes B-cell or T-cell damage, which in turn manifests itself in many different lymphomas. An appellate court might reject the shared etiology argument and rule that sufficient evidence of general causation for Plaintiff's subtype of NHL is required.

In both the MDL and the *Johnson* case, the judges considered the most recent report of the Agricultural Health Study, but they did not agree with Monsanto that it should be dispositive of the general causation question. (These rulings are consistent with IARC's stated position).

## Punitive Damages Evidence

The order by Judge Karnow in San Francisco Superior Court also denied Monsanto's motion for summary adjudication on the issue of punitive damages:

"The internal correspondence noted by Johnson could support a jury finding that Monsanto has long been aware of the risk that its glyphosate-based herbicides are carcinogenic, and more dangerous than glyphosate in isolation, but has continuously sought to influence the scientific literature to prevent its internal concerns from reaching the public sphere and to bolster its defenses in products liability actions. [...] Ex. 14 (introduced to show Monsanto's internal belief that glyphosate may be dangerous in combination with surfactants as of 2002), Ex. 19 (introduced to show the Monsanto's employee believed it was inappropriate to say that Roundup does not cause cancer because Monsanto had not done carcinogenicity studies with Roundup as of 2009), Ex. 21 (introduced evidence that Monsanto had a practice of ghostwriting scientific literature about glyphosate in and around 2015), Ex. 22 (introduced as evidence that Monsanto ghost wrote scientific literature about glyphosate as far back as 1999), Ex. 24 (introduced as evidence of Monsanto's sponsorship of literature for the purpose of defending products liability claims regarding glyphosate in 2012), Ex. 25 (introduced to show that Monsanto calculated the benefits of securing certain experts to lend credibility to their sponsored studies in 2012). Thus, there are triable issues of material fact and I must deny the motion."

Plaintiff's Opposition to the MSJ in the *Johnson* case was placed under seal, but many of the punitive damages documents were released by the judge in the MDL case and are available on the internet.