Glyphosate: Miracle or Mayhem

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Abstract

After forty years of using glyphosate (phosphonomethyl glycine) in agriculture, the popular chemical faces an uncertain future. This broad spectrum systemic herbicide, commonly known as *Roundup,* has been used to manage weeds in many agricultural practices including a large volume of transgenic crops. Left uncontrolled, some of these weeds can reduce crop yields drastically. An herbicide that controls weeds only and does not affect the crop seems a perfect farming innovation, but the extensive use of glyphosate is causing reason for concern. Once considered a modern miracle and one of the most important advancements in weed control of the twentieth century, glyphosate has been increasingly marginalized as unsafe to human health. The historical success of Roundup may be unraveling as the consequences of overuse have left herbicide residues in multiple environments. Increasingly, there is credible evidence that glyphosate and its metabolites could adversely affect healthy cell development in humans, promoting the need for more study. This report highlights the important historical development of Roundup and *Glyphosate Resistant* (GR) crops, its unique mechanism of action, and accelerating evidentiary support of toxicity in human and ecological regimes.

Glyphosate: Miracle or Mayhem?

In the synthetic era of weed management, no herbicide has dominated the industry and been more successful than glyphosate. This broad spectrum chemical, commonly known as *Roundup*, has routinely been called a once-in-a-century marvel and the most perfect herbicide on the market (Duke and Powles, 2008). Glyphosate is utilized to kill unwanted plant material in both cropland and noncropland worldwide, but with the advent of glyphosate resistant (GR) crops in the mid-nineties, the herbicide's popularity soared. If GR crops could be planted and weeds controlled without substantive damage, glyphosate application seemed to be a miraculous innovation. Not only could a farmer increase yields, but also reduce tillage, compaction, and loss of topsoil, since superior weed management was achieved. Because of glyphosate's mechanism of action, rapid translocation, and inability of plants to detoxify the herbicide, it is highly effective and the first choice of many agricultural producers (Shaner, 2006). In fact, glyphosate is the only herbicide that deregulates the shikimate pathway, effectively inhibiting a plant's biosynthesis of aromatic acids (Reddy, Rimando and Duke, 2004). In addition to its prowess as an effective farming tool, glyphosate has long been considered the safest herbicide on the market as well. For many years Roundup was considered to be minimally toxic to humans, because there had been little consistent evidence of genotoxicity or carcinogenicity in mammals (DeRoos et al., 2005). Increasingly, credible evidence reveals glyphosate mixtures may indeed be affecting the long-term health of populations, stimulating the need for more studies (Benachour and Seralini, 2009). It is important for agricultural professionals to recognize the potential hazard of glyphosate, understand the relevance of public concern, and thoughtfully balance that concern against agricultural gains. Questions may be asked of glyphosate as the herbicide's effects

continue to be studied and evaluated. Consequently, a review of Roundup's history, its mechanism of action, and the accelerated controversy must be studied.

The historical impact of glyphosate and subsequent transgenic or genetically modified (GM) crops has dramatically changed the landscape of modern farming (Duke and Powles, 2009). The glyphosate molecule was first synthesized by Henri Martin of *Cilag*, a small Swiss pharmaceutical company, but he did not recognize its herbicidal potential. In 1970, John E. Franz of Monsanto Co. was the first to test glyphosate as an herbicide; soon after it was patented for use (Duke and Powles, 2008). In 1974, glyphosate was first introduced on the market in the form of isopropylamine salt, a post-emergence and non-selective herbicide. It became evident that the herbicide was highly effective as a non-selective control practice and plant geneticists began to develop glyphosate tolerant crops in order to control weeds with minor damage. In 1996, the first GR transgenic crop, soybeans, was released. As more and more genetically modified crops were introduced, glyphosate rapidly became the largest selling herbicide in the world (Cerdeira and Duke, 2006). In fact, rapid adoption was such that by 2009, 90% of soybeans, 70% of cotton, maize, and canola, and 95% of sugar beets planted in the United States were GR varieties (Duke and Powles, 2009). These "roundup-ready" crop lines contain a gene derived from *Agrobacterium* sp. strain CP4, which encodes a glyphosate tolerant enzyme called CP4 5-polpyruvyshikimate-3-phosphate (EPSP) synthase. The enzyme expression within crops allows post-emergent control of weeds with the application of glyphosate (Funke et al., 2006). Glyphosate currently dominates the world's market in herbicide usage because of the extent of acreage planted in GR crops. Shaner (2006) wrote "Since 1996 and the introduction of glyphosate resistant crops, the amount of herbicide used on soybeans, corn and canola has increased by more than ten times."

Glyphosate's target site and mode of translocation in plants is unique in the herbicide field. Roundup inhibits EPSP synthase (EPSPS), the enzyme catalyzing the second to the last step of the shikimate pathway occurring in the plant cell chloroplasts (Funke et al., 2006). The shikimate pathway, or the shikimic acid pathway, is responsible for producing aromatic amino acids: tyrosine, phenylalanine, and tryptophan. Over 30% of carbon fixed by green plants is routed through the shikimate pathway (Shaner, 2006). These amino acids are involved in many vital systems of plant physiology, including: signal transduction processes, reduction of oxidized chlorophyll (radical species), flavonoid biosynthesis, and lignin production. The last product of the pathway, chorisimate, is a precursor for many secondary plant metabolites containing the aromatic groups: phenylpropanoids, alkaloids, indoleacetic acid, and quinones (Shaner, 2006). These aromatic plant metabolites account for a significant portion of a plant's dry weight and are necessary for continuous growth.

Glyphosate is such a potent herbicide because of its ability to diffuse into leaf, stem, and root tissue and translocate in the plant to apical meristems, root meristems, and underground reproductive tissues (Shaner, 2009). Further, glyphosate has not only been successful because of its ability to translocate within plants, but also because plants are unable to rapidly detoxify the herbicide. The acid form of glyphosate is not easily absorbed; however salt formations solve this problem and are more readily taken in by leaves. Because of this, the formulation of glyphosate is critical. The herbicide needs to transverse several membranes: the plasma membrane of cells, chloroplast in shoots, and plastid membrane of roots (Shaner, 2006).

Genes for EPSPS are highly expressed in meristems, blooms, stems, and mature leaves of cotyledons (Weaver and Hermann, 1997). Consequently, it has been determined that the same tissues in which genes for EPSPS are highly expressed are also the most sensitive to glyphosate

(Feng et al., 2003). EPSPS, although encoded in the nucleus, translocates into the chloroplast, where aromatic amino acids are synthesized (Hermann, 1995). The inhibition of EPSPS by glyphosate results in an accumulation of shikimate-3-phosphate and shikimate in plant tissue (Amrhein et al., 1980; Hermann, 1995). Shikimate-3-phosphate and phosphoenolpyruvate (PEP) form a tetrahedral intermediate prior to forming the product EPSP. The glyphosate molecule binds with shikimate-3-phosphate and forms a resembling tetrahedral which causes an inhibition in EPSPS activity. This inhibition results in reduced feedback of the pathway, leading to massive carbon flow of shikimate-3-phosphate, which is then converted to high levels of shikimate (Duke and Powles, 2008). Because of the lack of enzyme potential in normal pathway reactions, "free shikimate" builds up in the chloroplast. In tomato plants, the buildup of shikimate has been known to burst chloroplasts when treated with glyphosate (Shaner, 2006). With these factors working against the plant, it becomes incapable of building the materials or signaling processes necessary to conduct many systems of physiology.

Non-resistant plants exposed to glyphosate quickly show signs of serious life cycle effects such as stunted growth, loss of green color in their leaves, wrinkling, malnutrition, and complete death of tissue cells. "The first phytotoxic effects of glyphosate inside the leaves of *Amaranthus retroflexus* are degradation of chloroplasts in parenchyma cells, indicated by the change of a dark green color into yellowish green within hours after application (Fuchs et al., 2002)." This indicates rapid diffusion of herbicide into leaf cells and that glyphosate has great movement potential and can be considered "phloem-mobile." The herbicide moves with photosynthates from absorptive foliar sites to "sink tissue," which can be described as the areas of translocation that are not the source of sugars, but where they are absorbed and used. Glyphosate does not appear to be readily metabolized in plants, or at least a mechanism of

tolerance has not been found (Shaner, 2009). Death of the plant could take four or up to twenty days after exposure to herbicide.

The enormous success of glyphosate control on GR crops has led to increased treatments and consequently, the rise of GR weeds as well. When subjected to consecutive treatments year after year in the same field, natural selection of genotypes in weeds, which are resistant to glyphosate, become more prevalent. The resistance has to do with gene amplification or "gene copies" of EPSP. In an elegant study (Gaines et al., 2010), genomes of resistant plants were found to contain five times to more than one hundred and sixty times the copies of EPSP genes than did genomes of susceptible plants. The more copies of EPSP a weed contains, glyphosate is unable to bind enough enzymes to effectively inhibit the pathway. Other than EPSP gene amplification, reduced glyphosate translocation has also been studied in *Conza canadensis* and *Lolium rigidum.* The translocation reduction tends to be more effective in these species, enabling a higher resistance than EPSP mutations in other weeds (Gaines et al., 2010). The recovery of plants by reduced translocation may involve impaired phloem transport and differences in the expression of target enzymes in select tissues and physical cell/tissue barriers (Lorentz et al., 2011). Overall, the most prevalent crop yield losses are due to glyphosate resistant *Amaranthus palmeri*, which also uses the mechanism of EPSP gene amplification for resistance. This aggressive weed has a particularly strong resistance to glyphosate and is becoming more problematic (Gaines et al., 2010). With escalating GR weeds, farmers should limit exclusive use of glyphosate and utilize other methods of herbicide practice and crop rotation by incorporating an integrated weed management program (Al-Khatib et al., 2013).

Only green plants, some fungi, and a limited number of microorganisms have the target site EPSPS of glyphosate (Henderson, 2010). Therefore, conventional wisdom dictates that the

herbicide will not affect humans and mammals and is of low risk to public health because of the lack of a certain shikimic pathway and necessary amino acids. A thorough review of safety and risk assessment factors of glyphosate, published in 1999, concluded glyphosate posed no substantive health risk after an extensive study of adult pesticide applicators and their children (Williams, Kroes and Munro, 1999). Even though glyphosate residues have been well known to exist in drinking water (Annett, Habibi and Hontela, 2014), the herbicide has historically been considered benign to the environment (Monsanto, 2005). In fact, the Environmental Protection Agency (EPA) in 1974 with the Safe Drinking Act, set limits of glyphosate residue in drinking water. Currently (2015), these limits are held at 0.7 mg/L or 700 ppb, based on the best available science to prevent unnecessary health risk to the public. It has always been reasonable to expect, with extensive use of glyphosate, that traces of the herbicide would be found in food products for consumption (Samsel and Seneff, 2013). Because of the acknowledgement of these residues, it was not surprising when glyphosate was detected in the urine of 118 children of farm and non-farm Iowa families as well. Studies concluded that children obtain the same amounts of chemical from food wherever recorded (Curwin et al., 2007). Whether these residues pose an imminent threat to public health is still being studied and debated today.

It has long been confirmed that glyphosate quickly metabolizes in soil (Rueppel, et al., 1977). Recent research, however, has shown that residues of the herbicide can remain much longer (Vereecken, 2005). For many years, glyphosate studies revealed a very short half-life in soil because of microbial degradation. The main breakdown product of glyphosate in the soil is called aminomethylphosphonic acid (AMPA), which is further broken down by soil microbes (Reddy, Rimando, and Duke, 2004). The half-lives of glyphosate in the soil range from just forty-eight hours to two hundred and forty days (Battaglin, W. et al., 2005), but glyphosate

residues can remain in the soil for up to three years (Vereecken, 2005). Consequently, humans have more opportunity to come in contact with glyphosate from dietary and occupational exposure as residues in water and soil persist for longer periods (Chaufan, Coalova and Molina, 2014).

Since we know there is glyphosate residue in food we eat, water we drink, and in soil we could be exposed to, could it pose a legitimate health risk to humans? The answer, interestingly, is probably not immediately. One interesting medical study compiled the records of patients who had consumed large portions of the active ingredient glyphosate in surfactant mixtures either accidently, or in suicide attempts (Seok et al., 2011). Surprisingly, immediate effects of extreme ingestion of glyphosate were rarely found to end in fatality. Out of fifty-nine patients who had ingested large volumes of Roundup, all were found to have immediate risk for hypotension, mental deterioration, respiratory failure, and arrhythmia, but only two patients actually died. These deaths were attributed to refractory shock, metabolic acidosis, and respiratory fever. The final clinical outcomes of the remaining fifty-seven patients were benign, concluding that cardiovascular, respiratory, kidney, and mental functions were completely restored to normal levels. The study also surmised that the volume of surfactant contained in ingested material had a direct impact on toxicity (Seok et al., 2011). Consequently, it is reasonable to believe that glyphosate is minimally toxic after ingestion of large amounts of herbicide and that the additives in Roundup mixtures may be more toxic than the active ingredient itself.

Increasingly, scientists agree that the most compelling and credible evidence of glyphosate risk to humans may be genetic (Prasad et al., 2008). When studying the potential risks of glyphosate, the most reliable genotoxicity assessment for human health factors is conducted in mammals by induction of chromosomal aberrations (CA) and micronuclei (MN). On this

premise, glyphosate was shown to indeed induce CA and MN in Swiss albino mice (Prasad et al., 2008). This is particularly important because of the genotoxicity capacity in mice liver and bone marrow cells and how these findings may affect human cells in the same manner. When human liver HepG2 cells were tested *in vivo*, glyphosate-based herbicides were shown to cause DNA damages and carcinogen, mutagen, and reprotoxin (CMR) effects (Gasner et al., 2009). Disruption of aromatase gene expression in human placental cells, studied *in vivo,* have also been affected by glyphosate and Roundup products, including a wide range of *adjuvants,* which are compounds added to herbicides to accentuate the active ingredient's effectiveness (Richard et al., 2005; Benachour and Seralini, 2009). Consequently, there has been a great deal of pressure for inert ingredients to be available for environmental monitoring. However, not much movement on reform of herbicide label contents has occurred which would enable better independent research and risk assessment studies. Manufacturers continually resist listing of such inert ingredients, citing protection under confidential business information, or "trade secrets" (Cox and Surgan, 2006). Given that many of these ingredients are not listed, debate ratchets upward over possible health effects of Roundup mixtures on agricultural workers exposed and adds more gravity to toxicological studies, which indicated that glyphosate residues in food, feed, or in the environment should be classified as CMRs (Cox and Surgan, 2006).

Just recently, in the annual conference of the World Health Organization in September 2015 at Geneva, Switzerland, it was determined that glyphosate was one of three herbicides which should be reevaluated as possible risks to public health (WHO, 2015). The subsequent interpretations of many recent studies shall have an important impact on the groups' outcome and recommendations going forward. The actions of WHO and other government agencies around the globe may be influenced by pressure exerted by those outside of agriculture, who

often deliver persuasive reports of glyphosate dangers along with negative views of other herbicides. One such group, *Friends of the Earth* in England compiled a thirty page critical review of glyphosate practices as persuasive literature to reduce its use. The authors suggested the apparent risks and benefits of glyphosate and glyphosate-tolerant crops could no longer be assessed in isolation, but must progress with other approaches of production which significantly limit Roundup practices (Buffin and Jewell, 2001). Another recent scathing review released by independent author, Rosemary Mason, contained fifty pages of well-sourced discussion entitled *Glyphosate: Destructor of Human Health and Biodiversity* (2013). Regardless of an agricultural professional's opinion after reading these reviews, it is evident that the compilation of material was impressive, extensive, and thought-provoking.

Glyphosate will most likely remain the subject of many scientific studies for the foreseeable future. It continues to be a fascinating molecule with unique properties and target site of inhibition. For the last forty years, Roundup has been used extensively around the globe to treat GR crops with enormous success. In retrospect, there appears to be moderate evidence of glyphosate health risk, comparative to the weight of its overall use. We would do well to remember, however, that public policy is many times shaped by the loudest voices and glyphosate is not immune to this phenomenon. The scientific community will assuredly debate glyphosate, its agronomical impact, and possible risks to human health, but whether there is enough evidence to limit use of Roundup remains unclear. Whether research will conclude a glyphosate alarm is warranted or not, it is important to base interpretation on proven studies rather than speculation or assumptions. As agriculture professionals study glyphosate, the extraordinary innovation of its development should be acknowledged, but careful consideration should be given to potential adverse effects and importance of further studies. There is a succinct

possibility glyphosate could be curtailed in agricultural practices, especially in the most concentrated areas of use today. If proven convincingly, will agricultural communities be able to accept the truth about the herbicide's long term health effects? As the possibilities of glyphosate are navigated, perhaps we should all be "roundup-ready" and duly prepared for an uncertain future.

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