Glyphosate and the microbiome

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Pesticides are substances that are used in agriculture and public health to control pests. The word “pesticide” comes from the English *pest* meaning “harmful insect or plant, parasite”, and “-cide”, from the Latin *caedere*, “to strike, to shoot, to kill”. Pesticide use has been recorded as far back as 4500 years ago in ancient Mesopotamia, where Sumerians used elemental sulphur compounds to control insects and mites. About 3200 years ago the Chinese were using mercury and arsenic for body lice [1]. In fact, until the middle of the 20th century various nature-derived compounds and toxic plants were used for pest control [2]. The Second World War marked the beginning of the synthetic pesticide era with the discovery of the insecticidal effects of Dichlorodiphenyltrichloro-ethane (DDT) by Paul Muller, which earned him the Nobel Prize in Medicine. Now, eighty years later, the use of DDT is banned in many places because of its incredibly harmful effects [3].

Today, synthetic pesticides continue to be used extensively in agriculture. Approximately 2 million tons of pesticides are utilized annually worldwide, with China being the major user, followed by the USA, Argentina, Thailand, Brazil, Italy, France, Canada, Japan and India. The most common pesticides are herbicides, making up 47.5% of all global pesticide use [4].

Glyphosate was first synthesized in 1950 by the Swiss chemist Henry Martin and twenty years later by the Monsanto chemist John E. Franz. It has become one of the most widely used herbicides by volume [5] and is marketed by Monsanto under the brand name Roundup. Glyphosate is a broad-spectrum systemic herbicide and crop desiccant. Systemic herbicides act to kill the entire plant by spreading through its vascular system after being absorbed by the leaves or roots. Due to its broad spectrum action, meaning that it can target a wide range of organisms, glyphosate was quickly adopted by farmers for weed control after Monsanto introduced genetically engineered glyphosate-resistant soybean, maize, cotton, canola, alfalfa and sugar beet varieties. These “Roundup Ready crops” allowed farmers to kill the weeds without killing the crops. Their popularity is reflected in the total volume of glyphosate applied by farmers, which rose from 51 million kg in 1995 to 747 million kg in 2014 [5].

According to James, 85–95 % of genetically modified (GMO) crops worldwide are specifically engineered to be grown using glyphosate-based herbicides [6]. According to the ISAAA (International Service for the Acquisition of Agri-biotech Applications) [7], by 2019 the global surface area under GMO cultivation was 190 million hectares, which was about 10% of the total cultivated area. Benbrook et al. 2023 [8] found that glyphosate and one of its decomposition substances (AMPA, Aminomethylphosphonic acid), were present in relatively high and rising levels (over 1 ppm) in soybeans grown in the U.S., Canada, Brazil, Argentina and Paraguay, amounting to 86.6 % of the soybeans produced globally in 2014. The main GMO crop in the European Union is the MON810 maize (engineered by Monsanto) and, according to the ISAAA, 70% of all animal feed imported into the European Union in 2019 came from genetically modified plants. Since trace amounts of pesticides, or pesticide chemical residues, can remain in or on crops after they are harvested, dietary exposure to glyphosate is now ubiquitous and for the most part, unavoidable [8]. Indeed, a study was conducted in 2011 on an urban population in Berlin who had no direct contact with glyphosate or with agricultural activity: all participants had glyphosate residues in their urine [9].

Although glyphosate was considered to have low toxicity for human beings, evidence to the contrary has begun to surface. Despite justifications given by regulators and glyphosate-based herbicide (GBH) registrants over the last 40 years, more than 80 positive glyphosate genotoxicity assays published since 2016 show clear and compelling evidence that both glyphosate and formulated GBHs are genotoxic, i.e. they harm an organism by damaging its genetic material (DNA). For example, in a study of 76 farmers working with glyphosate-based herbicides all the farmers showed statistically significant increases in the frequency of signs of DNA damage compared to unexposed controls [10]. The data suggests that the DNA damage is caused by oxidative stress, a destructive imbalance in the body associated with a long list of diseases. In addition, doses of glyphosate and Roundup that regulators have claimed to be safe have also been shown to cause liver lesions (fatty liver changes, necrosis) [11]. Benbrook et al. 2023, found multiple studies that highlight the impact of exposure to GBH on human reproduction and the incidence of certain cancers, especially non-Hodgkin lymphoma [8].

Gut health and the gut microbiome, which are influenced by the diet, play an important role in the health and wellbeing of human beings due to bidirectional communication within multiple systems throughout the body. As previously mentioned, glyphosate's toxic effects are broad-spectrum: it kills many different pests and microorganisms. Glyphosate kills plants by inhibiting an important enzyme in a series of biochemical reactions called the "shikimate pathway" that produces essential proteins for growth in both plants and microorganisms [12]. Humans do not have the shikimate pathway in their cells, which originally led regulators and industry to argue that glyphosate is non-toxic to humans. But since the number of health-giving bacteria and microorganisms in the human body is close to the number of human cells, and the vast majority reside in the gastrointestinal (GI) tract [13], the impact of glyphosate on the gut microbiome becomes extremely relevant to human health. Moreover, according to Brewster et al. 1991 [14], glyphosate is primarily excreted in the feces, making the GI tract the biological component that is most exposed and vulnerable to the highest concentrations of this substance.

Barnett et al. 2022 [12] found that environmental exposure to glyphosate GBH has a negative impact on neurodevelopment and behavior across generations, through acting indirectly on the brain and nervous system via the gut-brain-microbiome axis. Additionally, Tsiaoussis et al. 2019 found strong evidence that exposure to pesticides, as well as to heavy metals, nanoparticles, polycyclic aromatic hydrocarbons, dioxins, furans, polychlorinated biphenyls and non-caloric artificial sweeteners affect the gut microbiome and have an impact on the development of metabolic, malignant, inflammatory or immune diseases [15]. In another recent study, glyphosate was shown to promote cancer by stimulating human breast cancer cell proliferation [16]. Different studies have also investigated the effects of glyphosate on the gut microbiome in rats, cows, pigs, honey bees and turtles. A recent study with rats by Mesnage et al. 2021 [17] shows that glyphosate and GBH can inhibit the shikimate pathway of bacterial population in the GI tract and cause alterations in the population of gut microbiota. The accumulation of shikimic acid in the rats' guts observed in the study can be linked to deleterious health effects. In addition, maternal transfer of the gut microbiome can affect the immune system and neurodevelopment across generations [12].

Of the population of gut microbiota that is affected by exposure to glyphosate, Barnett et al. 2022 list *Lactobacillus spp.* which plays a significant role in the gut-brain-microbiome axis and affecting mental health in particular, and the *Ruminococcaceae* family which produces a variety of metabolites that can alter mood and behavior [12]. Reductions in *Ruminococcaceae* populations within the gut microbiome have been shown to be associated with Parkinson's disease, Schizophrenia, depression and altered social behaviors. *Bacteroides spp*. and *Lactobacillus spp*. are both highly susceptible to glyphosate: exposure to glyphosate reduces the abundance of short-chain fatty acid (SCFA) producing bacteria, which include *Ruminococcaceae*, *Butyricoccus spp*., *Lactobacillus spp*., *Clostridium spp*., and *Bacteroides spp*. SCFAs play a fundamental role in maintaining gut homeostasis and barrier function, and in the gut-brain-microbiome communication axis. Decrease in SCFA populations is associated with numerous disease states, including autism spectrum disorders, mood disorders such as depression and anxiety, and Alzheimer's and Parkinson's disease.

These findings highlight the immense damage caused by glyphosate and its products to both the environment and human health. Its introduction into agriculture could mark a new disruption between the human being and nature, seen as we begin to discover the correlation between glyphosate and its products, and alterations to the gut microbiome and the development of neuropsychiatric and neuroinflammatory disease states. As one of the most frequently detected pesticide residues found in foodstuffs today [18], making it difficult if not impossible to avoid ingesting, glyphosate poses a real danger for humankind through disrupting the symbiotic relationship between the human host and their gut microbiome, and creating disorder in the gut-brain connection. Seen from an anthroposophical perspective, exposure to glyphosate through our food can sever the relationship between our will and our thoughts.

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