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Effects of Glyphosate on the Environment and Human Health

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ABSTRACT

Glyphosate is a herbicide of a wide spectrum that alters the production of amino acids in plants, leading to their death. Due to its properties, it is used to eliminate weeds that interfere with human activity. The intensive use of this herbicide in the past decades has led to its frequent encounter in the environment as it has been detected in water, animals, and food destined for human consumption. Its impact on human health and the rest of living organisms has not been fully explored, given that many authors enter into contradictions with one another, specifically surrounding the role of surfactants in the commercial presentation of herbicides. The use of pesticides can have significant impacts on ecosystems, threatening bio-cultural diversity due to genetic contamination from transgenic crops. The effectiveness of Glyphosate-based herbicides in weed control is diminishing due to weed tolerance. However, the use of herbicides remains prevalent in large-scale crops due to the challenges of organic food production. In addition, the probable conflict of interest by the agrochemical industry does not bring a full picture with respect to the actions that world governments should take. Banning GLP-based herbicides may lead to the use of other pesticides, in which the long-term impacts will require further studies. The motivation for this research is the review of the latest advances of glyphosate in the world, considering the use and prohibitions of this herbicide, its interaction with water and soil, as well as the effects on both the environment and health. The search for information for this paper was carried out in the Mendeley, Elsevier, and Springer databases by filtering by the suitable keywords.

INTRODUCTION

Glyphosate (GLP) is currently the most used herbicide worldwide (Singh et al. 2020, Martins-Gomes et al. 2022). It was patented in 1970 by the Monsanto company, and since 1974, it has started to be commercialized as an active ingredient of the product Roundup®. This formula has been tested in more than 100 crops and more than 130 countries (Cruz 2013). It is a non-selective herbicide of a wide range (which means that it can be used in any crop that can tolerate it) and is post-emergent, of which its chemical formula is $C_3H_8NO_5P$, it is a weak organic acid, consisting of a glycine molecule and a phosphonomethyl molecule (MamaCoca 2000). The yearly sales of GLP represent 11% of the total agrochemical products worldwide. It is found in 750 commercial presentations, and its use has increased since the introduction of GMOs and the patent release in 2000 (CIBIOGEM 2019).

PATHWAYS OF TRANSFORMATION, LOCATION, AND EXPOSURE

Transgenic Crops and Their Role in the Use of Glyphosate-Based Herbicides

The herbicidal activity of GLP is based on its capacity to block the pathway of the enzyme Shikimato (a common route to biosynthesize aromatic compounds primarily in bacteria and plants) by inhibiting the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS). Due to the inexistence of these amino acids, the synthesis of proteins in vegetable cells stops, ceasing its growth, which leads to its death (CIBIOGEM 2019).

Transgenic crops are defined by the transfer of foreign genes of animal, vegetable, microbial, or viral origin to cultivated plant species (Chaparro 2011). The bacteria

Agrobacterium tumefaciens has been used to confer the gene that gives the crop tolerance to GLP, codifying an enzyme (EPSPS) that is not affected by the herbicide (Villalba 2009). The use of GMOs is widely spreading around the world, and their use puts their wild predecessors at risk of "transgenic contamination" through the spread of genetic material via pollination (Ribeiro 2020). For example, in Argentina, practically 100% of soy, 100% of cotton, and up to 98% of corn that gets cultivated on a yearly basis is a product of transgenic crops (ArgenBio 2021). Mexico imports more than one-third of its national corn consumption, and this comes primarily from the United States, a country in which more than 40% of the crops coming from this grain are of transgenic origin (Ribeiro 2020). In Uruguay, almost 100% of soy crops make use of RR (Roundup Ready) soy seeds, those of which contain a gene of the *Agrobacterium* sp. A bacteria that brings forth GLP resistance. In the United States, at least 50% of corn and cotton seeds and approximately 80% of canola seeds contain transgenic RNA (Ribeiro 2020).

The sum of these two factors, together with the demand of the population and industry, as well as the unrelenting interest of medium and large companies to increase production in order to supply the necessary crops on a global scale, has encouraged the excessive use of herbicides as a common practice in the development and production of large-scale agriculture. This is without considering the potential for long-term environmental and health damage.

Glyphosate Transport and Interaction in Soil

GLP shows a high potential for soil adsorption, therefore restricting its transport in the soil (Gandhi et al. 2021). Recent studies state that the sorption capacity of GLP is quite higher than that of other pesticides, reducing the risk of leaching (Hagner et al. 2015). Consequently, significant amounts of GLP residues have been found in soil samples, as indicated by (Aparicio et al. 2013, Gunarathna et al. 2018).

A global analysis using a large dataset from different countries shows that residues of GLP and its degradation product aminomethylphosphonic acid (AMPA) have been found on the soil surface (30 cm) and in the root zone (30-100 cm). The observed GLP residues' concentration can be correlated with the annual doses of application. (Maggi et al. 2020).

Despite the information previously stated, (Kremer & Means 2009) does not discard the possibility of GLP lixiviation; this is due to the fact that the herbicide is applied with a mix of fertilizers that may contain phosphorus, which may compete with GLP molecules during the adsorption in soils leaving GLP available for lixiviation.

In addition, (Hernández 2019) indicates that an increase in pH leads to an increase of the negative charges present in both the soil and GLP molecule, which encourages electrostatic repulsion, making the molecule prone to lixiviation.

For this reason, it is important to understand the processes involved in the potential pathways of dispersion of this contaminant where it causes adverse effects on any natural system. Studies of GLP leaching and impact are being developed in Mexico and other countries to propose control and management solutions.

Glyphosate Transport and Interaction in Water

In general, the surface water in agricultural areas is more susceptible to agrochemical contamination through surface run-off, direct overspray, and spray drift (Lutri et al. 2020, Cruz 2013). Groundwater pollution with herbicides is generally lower in groundwater reservoirs than in surface water reservoirs due to degradation in the unsaturated zone (Mueller & Senseman 2015). Nevertheless, several studies have demonstrated the potential for leaching and vertical transport to groundwater (Lupi et al. 2015, Okada et al. 2016).

Several recent reports suggest that water supplies in areas having intensive agricultural activities might be at high risk of contamination by GLP (Cengiz et al. 2017). In agricultural areas and groundwater of Mexico, GLP concentrations have been detected and associated with sampling sites in proximity to GLP-resistant soybean fields (Rendon-von Osten & Dzul-Caamal 2017).

In Sanchís et al. (2012), the authors analyzed GLP in Spain's groundwater, confirming that, despite the low mobility of this compound, the herbicide is capable of migrating towards the unconfined aquifer.

GLP residues have also been detected in groundwater samples from Argentina (Okada et al. 2018, Alonso et al. 2018), Ireland (McManus et al. 2017), Canada (Van Stempvoort et al. 2016), Australia (Davis et al. 2013), China (Geng et al. 2021). All studies show that the presence of GLP in groundwater depends fundamentally on the characteristics of the soil and the form of application of the herbicide. It has been established that GLP is accumulated for periods longer than 4 years when leached into groundwater (Okada et al. 2019).

Flows of surface water, such as run-off and stream discharge, are dispersal media for GLP and AMPA residues, leading to potential long-range ecosystem contamination within watersheds and along rivers (Maggi et al. 2020). Some recent studies have detected the presence of GLP in surface water (Gunarathna et al. 2018, Mac Loughlin et al.

2020, Mörtl et al. 2013) and even in marine environments (Mercurio et al. 2014, Skeff et al. 2015).

Government agencies should have programs for the control and monitoring of contaminants, as they play a crucial role in the proper management of risk in both agricultural and urban areas potentially contaminated by agrochemicals. Similarly, research into the interaction of GLP with water should continue, taking into account the hydrogeochemistry of any area of interest.

Glyphosate Persistence

GLP has a half-life in aquatic mediums of 2 to 91 days (Singh et al. 2020b). This information coincides with that of Duarte et al. (2003), for they mention that in a study conducted in Canada, the persistence of GLP was 12-60 days in pond water. In soils, (Singh et al. 2020b) report that the half-life of the herbicide is 2 to 251 days. The persistence of GLP in pond sediments is evidenced by a study conducted in Missouri in which bottom sediments were studied, resulting in an average life of the herbicide of 120 days. However, more than one year of half-life was attributed to sediments of Oregon and Michigan (Duarte et al. 2003).

Mercurio et al. (2014) conducted studies with coastal seawaters sampled from the Great Barrier Reef containing native bacteria from this ecosystem (taking into consideration that these intervene in the degradation of the herbicide). These results indicate that the half-life of GLP at 25°C in low light conditions is 47 days, increasing to 267 days in darkness at 25°C and 315 in darkness at a temperature of 31°C. According to these authors, the information previously stated suggests that the persistence of GLP in seawater is moderate when kept in low-light conditions but highly persistent in conditions of complete darkness.

Torrado (2018) referenced studies that speak of a large GLP persistence in soils, considering that the initial degradation is faster than the subsequent degradation. This author indicated that persistence of 249 days had been found in agricultural soils and from 259 to 296 days in eight forestal sites in Finland, while 335 days in Canada and from 1 to 3 years in 11 forestal sites in Sweden. The same author mentions that the half-life of GLP might be between 3 to 22.8 years.

The persistence of LPG in both water and soil indicates the possible existence of bioaccumulation processes in natural systems, creating a pathway of exposure that is not only immediate but may persist even when the agrochemical is no longer used in a given area.

Mechanisms for the Degradation of Glyphosate and Its Metabolites

GLP transforms into AMPA as soon as it comes into contact with water while maintaining the toxic aspects of its precursor (Poiger et al. 2017) and lengthening its half-life (Gandhi et al. 2021). Microbial pathways primarily achieve the degradation of GLPand. It is the population of *Pseudomonas* spp. that influences the most in this process, which results in the main metabolite of GLP ($C_3H_8NO_5P$) known as AMPA (CH_6NO_3P), which's chemical structure is depicted in Fig. 1 (Martínez et al. 2012).

The microbial biodegradation of GLP can be performed in water, solids, and aquatic sediments through the rupture of the C-N bond, which produces AMPA. In the same way, the AMPA is biologically degraded, releasing carbon dioxide. This reaction thrives under aerobic conditions (WHO 2005). Schuette (1998) revised the degradation pathways of GLP, focusing on conditions of forest environments; in Fig. 2, the proposed pathway is presented by the author.

Besides AMPA, have been identified the presence of metabolites like N-methylamino-methylphosphonic acid, glycine, N,N-dimethylaminomethylphosphonic acid,

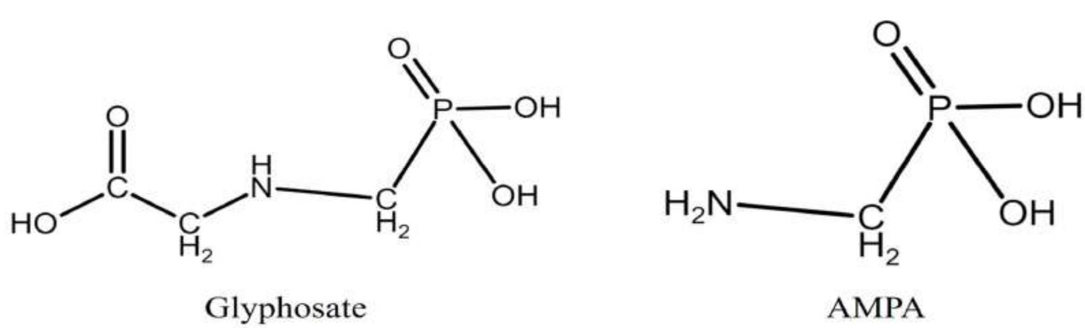

Fig. 1: Molecules of GLP and its metabolite AMPA, adapted from (You et al. 2013).

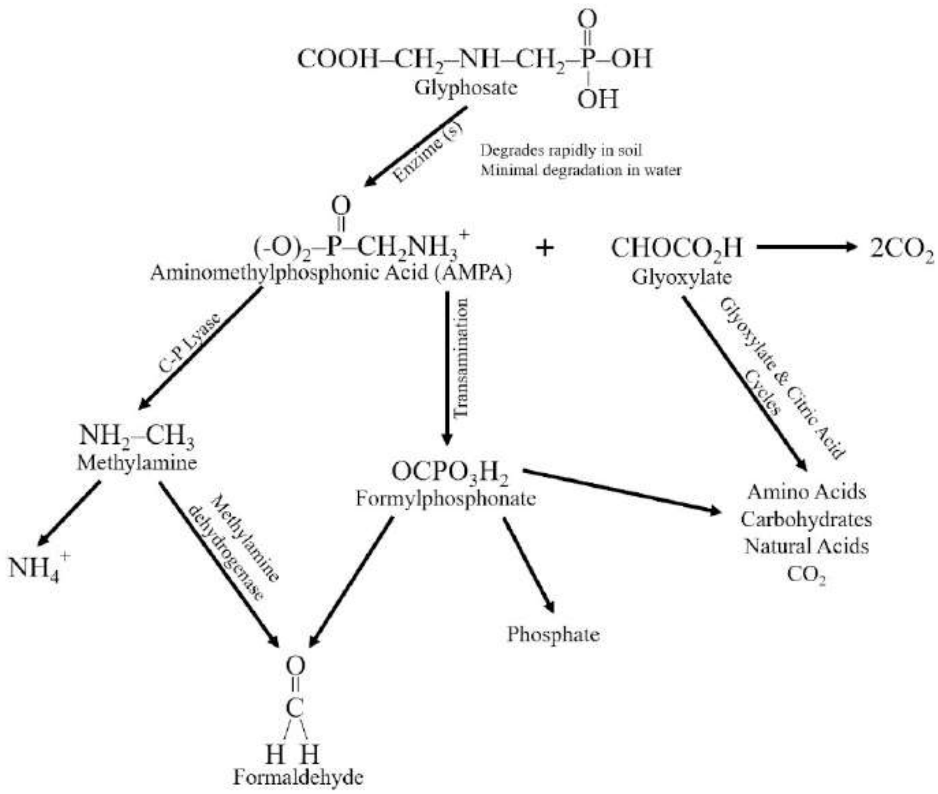

Fig. 2: GLP degradation pathways, Adapted from (Schuette 1998).

hydroxymethylphosphonic acid, and two other unknowns that all together do not exceed 1% of initial reactive (MamaCoca 2000).

EFFECTS ON THE ENVIRONMENT AND HEALTH

Effects of Glyphosate on Vegetation

Several studies indicate that pesticides and fertilizers are major factors that can affect the flora of natural and semi-natural habitats adjacent to agricultural fields; these studies have unanimously documented that sub-lethal herbicide doses reduce and delay plant flowering of non-target vegetation, resulting in overall declines of plant species richness within agricultural areas (Strandberg et al. 2021). Recent research even studies the long-term GLP persistence in perennial forest plants beyond one year after treatment (Botten et al. 2021).

The effects of low doses of GLP and sowing seasons on the macronutrient and micronutrient contents in the leaves and grains of common beans have specifically been studied (Pacheco de Almeida Prado Bortolheiro & de Almeida Silva 2021). Other studies have observed concentrations of GLP in legumes (Jarrell et al. 2020) or cereals (Cruz & Murray 2021, Xu et al. 2019).

Therefore, the constant use of GLP has been associated with an increase in herbicidal resistance by weeds associated with soy, corn, and cotton crops. At least 69 countries have informed their corresponding environmental authorities about the presence of some pesticide-resistant weeds (Bonny 2020).

Effects on Soil Microbial Activity

It has been detected that GLP that is applied on soil can interfere with the synthesis of some compounds related to microbial growth, therefore affecting the communities present in this medium, even though the prolonged exposure to the herbicide has led to certain bacteria taking advantage of GLP molecules and the intermediates in the degradation process, to obtain C, N, P, and energy for its growth (Boccolini 2019, Hernández 2019, Johnsen et al. 2001).

De María (2004) expressed that in fungi, bacteria, and plants, the pathway of the Shikimico acid is present, which means that bacteria are also susceptible to GLP effects. This fact may impact the soil biodiversity, like in the particular case of *Bradyrhizobium* sp. (genus of bacteria, many of which are nitrogen-fixing bacteria), given that the presence of GLP inhibits their growth, affecting the symbiotic nitrogen fixation as well.

In addition to what was previously stated, pesticides have the potential to encourage the development of certain microbial communities in soil. It is known that GLP can promote the growth of fungal pathogens like *Fusarium* sp., which can harm other life forms. The fungi are capable of causing harm to the crops, poisoning the soils, and causing congenital disabilities in humans (Duarte et al. 2003).

Hussain et al. (2009) warned that pesticides that are applied to soils can influence chemical reactions such as the mineralization of organic material, nitrification and denitrification, ammonification, redox reactions, methanogenesis, and a decrease in soil enzymatic activity, which may serve as key indicators of soil health.

It is therefore important to propose solutions aimed at the use of other methods of crop care and conservation, the formulation of new agrochemicals, and the appropriate treatment of water and soil in areas without agricultural production that have been affected by LPG.

Remediation Techniques

Degradation of GLP can be achieved using abiotic and biotic means, like absorption, photolysis, thermolysis, and biodegradation with catabolic enzymes (Singh et al. 2020b). GLP degradation is accomplished mainly by various soil microorganisms (Sun et al. 2019).

The site exposure history and nutrient amendment would substantially alter the biodegradation of GLP and AMPA, showing that ammonium and phosphate, which are key ingredients in fertilizers, can enhance GLP biodegradation (Maggi et al. 2020). A complicating factor here is that phosphate can decrease GLP adsorption to the soil, thus increasing the risk of transport by run-off to rivers, aquifers, and ecosystems that have less GLP pre-exposure (Bento et al. 2018).

Despite the natural biodegradation of GLP, large volumes of wastewater with high concentrations of complex organics such as formaldehyde, GLP, and GLP from GLP manufacturing are difficult to degrade before reaching treatment plants; a novel technique being studied to remove GLP from wastewater is Supercritical water oxidation (SCWO) (Li et al. 2021).

Another recent remediation technique is a blend of photocatalysts with UV light that has come into the limelight for their ability to treat pollutants like pesticides. The photocatalytic degradation can break GLP down into non-toxic compounds like CO_2, water, and inorganic ions (Singh et al. 2020a). This mechanism depends on the photocatalytic oxidation reaction triggered by highly reactive oxidation and hydroxyl radicals (Xu et al. 2011). The benefits of photocatalysis comprise cost-effectiveness, stability, and non-toxicity, whereas its manipulation in situ is a critical disadvantage, this degradation method proved to be optimal for removing GLP in sewage treatment (Wang et al. 2016).

Many of these treatments require large investments, both financial and infrastructure. Thus, there is a growing interest in low-cost alternative techniques, and the use of polymeric membranes is a potentially attractive option because they are cheap, easy to produce, and have good adsorption characteristics (Carneiro et al. 2015).

An eco-friendly strategy like bioremediation would be another promising alternative to overcome the environmental and health risks derived from GLP use and its residues. Therefore, it has become essential to study GLP biodegradation driven by microbial degraders; numerous studies have revealed microbial capacity as a robust and useful tool in bioremediation (Singh et al. 2020b).

In this research, some investigations study wild plants tolerant to GLP and identify those microorganisms associated with the rhizosphere that could have the capacity to degrade GLP (López-Chávez et al. 2021).

The ideal plant for phytoremediation can adapt to the contaminated site, grow fast, produce a large amount of biomass, and develop a deep and extensive root system. Furthermore, it produces high levels of xenobiotic-degrading enzymes. It should be competitive with other plants, accumulate large amounts of pollutants, and be efficient in transferring them from the roots to the aerial parts of the plant (Del Buono et al. 2020).

The extension of this field of knowledge can be directed towards the study of real cases to assess environmental toxicity, as well as the comparison of different treatment alternatives, without neglecting the current need for environmental policy and regulation of herbicides.

Glyphosate's Toxicity on Animal Species

GLP's toxicity has been evidenced in several animal species with contradictory results (Salazar-López & Aldana Madrid 2011), Indicates that the presence of GLP in an aquatic medium leads to a delay in fish and algae growth, prevents sea urchin hatchings, and induces histopathological changes in tilapia gills. Mann & Bidwell (1999) affirm that GLP Isopropylamine in water is practically non-toxic, as it did not present mortality among four Australian frog species.

With contradictory results to those previously presented, Relyea (2012) conducted a study with wood frogs (*Rana sylvatica* or *Lithobates sylvaticus*), leopard frogs (*R. pipiens* o *L. pipiens*), and American toads (*Bufo americanus* o *Anaxyrus americanus*) exposing them to different concentration levels of the commercial product formulation Roundup Original Max®. This author concluded that GLP-based herbicides could cause high mortality rates in the three different tadpoles of the amphibian species, decreasing the growth of wood and leopard frogs. In addition, the researcher identified morphological changes in these two species at this stage of their metamorphic process.

Relyea (2005) researched the impact of pesticides and herbicides on the biodiversity of an aquatic community that consisted of algae and 25 animal species. The Roundup product decreased species richness by 22% and eliminated two tadpole species.

Krüger et al. (2014), found GLP in the lungs, liver, kidney, brain and intestinal wall of danes piglets. The pigs presented atrophy in ears and legs, cranial and spinal deformities, and one even showed a hole in its skull, and another one showed one huge eye and another that hadn't developed. The authors indicated that a higher number of studies were required to prove or exclude the role of the herbicide in the previously stated deformities.

In a study using zebrafish (*Danio rerio*), Roy et al. (2016) exposed this species' embryos to GLP, and the results indicated that the herbicide is toxic to the fish's heart development.

Although GLP is considered to be a pesticide that shows low toxicity to animals (Duke & Powles 2008), an increasing number of studies have shown that GLP has various sublethal effects on the honeybee gut microbiota, foraging behavior, developmental processes, and antioxidant pathways (Magal et al. 2019, Tan et al. 2022, Motta et al. 2018, Rossi et al. 2020).

Aparecida et al. (2013) refer to estuary contamination by sediments with herbicide residues (mostly diuron, atrazine, hexazinone, and ametrine) dragged by rivers. A fact that makes them partially responsible for the "regressive death" of mangroves. In addition to what has been previously stated, the authors indicate that herbicide contamination in seawater could influence the health of the Great Barrier Reef.

The effects of GLP on little animals have been studied recently. These studies analyze the effects of GLP on plankton (Sabio y García et al. 2020), fishes (Díaz-Martín et al. 2021, Bernardi et al. 2022), and mice (Thanomsit et al. 2022, Ait Bali et al. 2017). Larger mammals have also shown disorders associated with GLP, like cows (Wrobel 2018), piglets (Qiu et al. 2020), and hares (Martinez-Haro et al. 2022). Even large marine animals like manatees are exposed to GLP (De María et al. 2021).

It is also necessary to take into account the possible presence of this herbicide in livestock feed since it can affect both productivity and health (Sørensen et al. 2021). GLP residues have been found in soybeans and corn, which play an important role in animal nutrition (Pöppe et al. 2019). GLP exposure on an animal's per kg basis is 4 to 12 times higher than that of humans (Zhao et al. 2018).

It would be interesting to determine the relationship between the doses given in the various studies mentioned above and the concentrations reported in different environments and ecosystems in order to get a true picture of the current and future damage that could be caused throughout a food chain.

Acute Exposure of Animals to Glyphosate

GLP oral administration in bunnies, rats, and sheep indicated absorption of the minor gastrointestinal tract lower than 30%-36%. This chemical compound settled primarily in the bones; in rats, GLP did not go through any important biotransformation as it presented the AMPA as the only metabolite at a concentration between 0.2% and 0.3% of the initial applied dosage. (FAO/WHO 1994). A study conducted by the WHO (2005) indicated that rats absorb approximately 20% of the AMPA and that most of it is eliminated through urine.

Pandey et al. (2019) exposed male adult rats to a dosage of the Roundup® product formulation ranging from 0 $mg.kg^{-1}$ to 250 $mg.kg^{-1}$ for 14 days; these results suggest that the herbicide that was administered via oral route propitiated hepatic inflammation and can lead to the development of fatty liver disease.

Dallegrave et al. (2003) conducted a study with pregnant rats in which a dosage of the herbicide Roundup®, commercially distributed in Brazil, was administered 500 $mg.kg^{-1}$, 750 $mg.kg^{-1}$, and 1000 $mg.kg^{-1}$ of weight from day 6 to 15 of the gestation period. The rats that were treated with 1000 $mg.kg^{-1}$ presented a 50% mortality. The researchers conducted a cesarean operation on the 21st day of pregnancy. They found bone alterations in 15.4%, 33.1%, and 57.3% of the treated fetus with 500 $mg.kg^{-1}$, 750 $mg.kg^{-1}$, and 1000 $mg.kg^{-1}$, respectively.

Chronic Exposure of Animals to Glyphosate

In rats, it has been shown that prolonged exposure (lasting 26 months) to GLP in a dosage of up to 32 $mg.kg^{-1}$ of weight significantly increases the presence of tumors in interstitial cells (in charge of testosterone production) (WHO 2005).

Mesnage et al. (2017), in a study that lasted 2 years in which rats were administered a dosage of GLP equivalent to 4 $ng.kg^{-1}$ of corporal weight per day, concluded that chronic exposure to the herbicide may result in renal and hepatic damage with possible health implications within animal and human populations.

A sub-chronic exposure in rats (12 months) to GLP-based herbicides from juvenile age until adult, with a dosage ranging from 250 $mg.kg^{-1}.day^{-1}$ to 500 $mg.kg.day^{-1}$, induced a decrease in corporal weight and locomotive activity in addition to an increase in anxiety levels and behavior that may be interpreted as depression which suggests that the chronic exposure of rats to these herbicides may cause neurobehavioral changes (Ait Bali et al. 2017).

Despite the previously stated information, Agostini et al. (2020) mentioned that the chronic effects of GLP remain practically unexplored, indicating that more studies are necessary to shed light on the subject.

Human Exposure Pathways to the Glyphosate

GLP use, according to the WHO (2005), represents diverse risks to human health. The first one of these risks comes from direct contact with the skin or through inhaling, even though these risks are directly related to the workers who apply the product and the populations surrounding the application area. It would be expected that the most significant risk would come from food destined for human consumption that is exposed either directly or indirectly to GLP, such as animals, cereals, and legumes.

Peillex & Pelletier (2020) mentioned that GLP and its metabolite AMPA have been detected in soil, water, plants, food, and animals in addition to human urine, blood, and breast milk. These authors indicate that the urine of workers exposed to GLP can expect concentration levels that range from 0.26 $\mu g.L^{-1}$ to 73.5 $\mu g.L^{-1}$ and 0.16 $\mu g.L^{-1}$ to 7.6 $\mu g.L^{-1}$ in the general population.

Therefore, it is necessary to carry out research aimed at monitoring the long-term effects on human health, the care and protection of workers directly exposed to LPG, and the development of public policies focused on monitoring and regulating safe food for the population.

Glyphosate and its Metabolites in Water and Food Destined for Human Consumption

The main source of chronic exposure to GLP is food. Residues of GLP have been found in crops, drinking water, and tissues of animals that are destined for human consumption (Gandhi et al. 2021, González Ortega & Hagman Aguilar 2018, Hernández 2019).

Toccalino et al. (2012) mentioned in a study focused on water wells used for public supply in the United States that herbicides were among the most common organic contaminants. In another study conducted in the agricultural zone of Hopelchen, Mexico, GLP was detected in 90% of underground water samples (with a concentration ranging from 1.41$\mu g.L^{-1}$ to 0.44 $\mu g.L^{-1}$); in the three studied communities, the herbicide was present in purified water (with a max concentration of 0.44 $\mu g.L^{-1}$) and in bottled water which was sold by industry in Merida (this last one presented lower levels of GLP, with a concentration of 0.35 $\mu g.L^{-1}$) (Rendon-von Osten & Dzul-Caamal 2017). In human urine, GLP was found at a max concentration of 0.47$\mu g.l^{-1}$ (WHO 2005).

In summation, the GLP concentrations concerning human consumption exceeded the limits of 0.1 $\mu g.L^{-1}$ established by the European Union (Mesnage et al. 2017) without exceeding those established by the Mexican Official Standard, NOM-201-SSA1-2015.

Effects on Human Health

GLP and AMPA, its main degradation metabolite, are known to persist in the environment and can be found in house dust (Curwin et al. 2005), soil, air, surface water, and groundwater (Bai & Ogbourne 2016, Cosemans et al. 2022). One of the main concerns in relation to GLP is the possible effects induced on human health; they are mainly indirectly exposed to GLP through contaminated food, posing a potential long-term threat to human health (Cosemans et al. 2022, Louie et al. 2021).

Concerning the deaths caused by pesticides, the International Organization of Consumers Union informed that every four hours, a worker in the agricultural sector dies due to acute intoxication. This is equivalent to 10,000 deaths per year and up to 375,000 intoxication cases in the same time period (Idrovo 2000). The WHO shows that nearly 1,000,000 intoxication cases due to pesticides arose in the eighties, and 70% of these cases happened in a work environment (Campuzano et al. 2017). Peillex & Pelletier (2020) indicated that dermal ingestion and inhalation are the main pathways by which GLP enters the human body.

Several studies reported associations between GLP exposure and different health disorders (Cosemans et al. 2022) including i) cancer (Franke et al. 2021, Leon et al. 2019), ii) decrease in gestation time (Lesseur et al. 2022), iii) effects on lactation (Ruiz et al. 2021), iv) respiratory diseases (Pandher et al. 2021, Hoppin et al. 2008), and v) neurological diseases (von Ehrenstein et al. 2019). Laboratory studies have demonstrated the absorption of GLP in the human gastrointestinal tract and absorption of GLP via dermal route, ingestion, and inhalation (Torretta et al. 2018). Recent studies show immune-endocrine alterations induced by GLP (Muñóz et al. 2021, Maddalon et al. 2021). Other researchers emphasize the importance of human biomonitoring studies as a measure of internal exposure (Connolly et al. 2020, Ferreira et al. 2021, Faniband et al. 2021).

Peillex & Pelletier (2020) mentioned a correlation between GLP-based herbicides and a major frequency of spontaneous abortions, premature labor, and diverse deformities like harelip and Down syndrome. In Colombia, Camacho & Mejía (2017) compared health records and aerial fumigation records of the GLP herbicide to tackle the illicit cocaine crop. The results indicated that exposure to these pesticides relates to the increase in the number of spontaneous abortions and medical consultations concerning dermatological and respiratory illnesses.

The use of transgenic seeds and the GLP herbicide could worsen the current situation concerning bacterial antibiotic resistance, a fact that represents one of the biggest threats to humanity in the future (OMS 2020). In a study, bacteria *Escherichia coli* and *Salmonella enterica* serovar Typhimurium were exposed to the Roundup formula, which found an increase in the bacteria's resistance to antibiotics like Kanamicina and Ciprofloxacina (Kurenbach et al. 2015).

In light of this information, there is an urgent need to promote a conscious collaboration between decision-makers in government, society, the health sector, and agribusiness to address the challenges posed by GLP contamination, always keeping public health at the forefront.

Effects on Human Cells

Agostini et al. (2020) mentioned the presence of multiple studies conducted in the last 40 years regarding healthy and tumoral cells, in which many alterations were found due to GLP exposure to formulations that contain it as an active ingredient with highly varied effects depending on the type of cell, the commercial formulation of GLP used, exposure time, dosage, and the applied methodology.

Ledoux et al. (2020) indicate that it has been shown that GLP causes damage to the DNA of human mammary epithelial cells placental and umbilical cord cells, and induces effects regarding the mortality of sperm.

Neurological and Neurobehavioral Alterations

Exposure to pesticides used in agriculture has been associated with the risk of developing Parkinson's (Gorell et al. 1998). Burchfield et al. (2019) reference multiple authors that relate the inhibition of mitochondria with Parkinson's disease. In addition, they indicate that the classic toxins used for the research regarding this disease exert their toxicity through similar mechanisms to those of the herbicide.

Burchfield et al. (2019) evaluated the toxicity of the Touchdown® herbicide, which contains GLP as an active ingredient. They made use of the nematode *Caenorhabditis elegans,* treating it with the agrochemical for 30 minutes. The obtained results from the oxygen consumption indicated mitochondrial inhibition, a decrease in ATP levels, and an increase in hydrogen peroxide levels in comparison to those of the control groups.

In addition, it has been reported that GLP, as well as its AMPA metabolite, decreases the activity of the acetylcholinesterase enzyme, which ends the neurotransmisor effect of the Acetylcholine. (Van Bruggen et al. 2018). The changes in the concentration levels of this enzyme or its properties relate to Alzheimer's, Parkinson's, and Miastenia gravis diseases. (Sánchez & Salceda 2008).

Possible Effects on Gut Flora

In animals, GLP can damage the microbial communities present in the intestine and can unleash a negative effect on the animal; an example of this is that of bacteria in charge of lactic acid production that can be generally affected by GLP present in foods and water. These produce antibiotics and are suppressors of the bacteria *Clostridium botulinum,* a pathogenic microorganism in animals. (Van Bruggen et al. 2018).

Rueda-Ruzafa et al. (2019) referenced the close relationship that exists between the digestive system and the central nervous system. In addition, they mention the effects of GLP on the human body concerning the intestinal dysbiosis induced by the herbicide. As an example of the relationship between the nervous and digestive systems, the authors indicate that the intestinal microbial density in autistic children is different from that of healthy children, given that those who have the disorder show a decrease in beneficial bacteria (*Bifidobacterium*). Despite what was previously stated, the authors concluded that more studies are necessary to clarify the role that GLP plays in the development of behavioral disorders.

Effects of Inert Compounds Included in Commercial Formulations on Human Health

With frequency, commercial herbicides that contain GLP as an active ingredient include surfactants, which are compounds that reduce the tension between two phases present in a molecule. These can increase the dermic absorption and the neurotoxic effects, genotoxins, and endocrines, in addition to decreasing mobility and increasing the environmental persistence of the herbicide (Cruz 2013). Some studies affirm that the surfactants that accompany the GLP (at least in the case of Roundup®) are the ones that show the major toxicological effects (Burger & Fernández 2004). The surfactant polyoxy-ethylene-amine (POEA), according to Brausch et al. (2007), is extremely toxic to aquatic organisms, capable of inhibiting the growth of the crustacean *Daphnia Magna* and causing similar effects on other organisms.

The surfactant POEA is derived from the grease of animal origin present in commercial formulations of herbicides like Roundup®. This herbicide is composed of 41.5% GLP and 16% POEA (Vargas 2018), even though the content of POEA may vary between 6% and 18%, according to its commercial presentation (Méndez 2015).

The POEA may contain as an impurity 1-4 dioxane, to which a carcinogenic capacity is attributed in animals, and kidney and liver damage in humans (Salazar López & Aldana Madrid 2011), according to the same authors, Folmar et al. (1979), used the herbicide Roundup® and technical grade GLP in fishes and aquatic invertebrates concluding that it is the surfactant of the commercial presentation (Roundup®), that plays the role of the primary toxic agent.

Martínez et al. (2007) showed in vitro studies with human mononuclear blood cells that the commercial presentation of the herbicide Roundup® has greater cytotoxicity (cellular toxicity) than the technical grade GLP, which suggests that the additives of the commercial formulations play an important role in the toxicity that is attributed to the herbicide.

Kaczewer (2002) exposed the participation of polyacrylamide, included in commercial presentations such as Roundup (an additive that reduces the derivatization of GLP to AMPA during its sprinkling and acts as a surfactant). This additive, in addition to GLP in adequate conditions of light and temperature, contributes to the release of acrylamide. This last compound is a potent neurotoxin that affects the male reproductive function and causes congenital deformities and animal cancer.

Out of the GLP biotransformation, the metabolite glioxilite surges; in rats, Ford et al. (2017) showed that this compound could inhibit enzymes in charge of oxidizing fatty acids in the liver; in addition, treating the rats with GLP increases the levels of triglycerides and cholesteryl esters. In the same way, Duarte et al. (2003) mentioned that in the formulation of Roundup®, the surfactant present is between 20 to 70 times more toxic to fish than the technical grade GLP. Torrado (2018) cites a study in which the Rodeo® formulation, which has GLP as an active ingredient in addition to surfactants AL77 and Optima, was compared with Roundup® in cocaine crops and resulted in being four times more toxic.

Aparecida et al. (2013) stated in a study conducted with commercial formulations of GLP and their effects on the proliferation, survival, and differentiation of one mammal cellular line (fibroblastos 3T3-L1), concluding that the herbicide inhibits cellular proliferation and induces the apoptosis (death or destruction of the cell aiming to control its growth or development). Despite what was previously stated, Agostini et al. (2020) indicated that in blood cells, it has been found that the formulation Roundup® is weakly mutagenic.

In view of the above, the regulation of LPG and herbicides should be updated and, if necessary, tightened, taking into account the different products and combinations of this compound with different additives in order to make them safer for health. For this to be possible, research into the adverse effects of these agrochemicals must continue.

CASE STUDY: GLYPHOSATE PROHIBITION

Position of International Agencies

In 1985, the Environmental Protection Agency of the United States (USEPA) classified GLP as a possible class C carcinogen (there is evidence suggesting its potential carcinogenic effect) due to the presence of renal tumors in rats. Subsequently, in 1986, the same agency requested from a scientific panel an evaluation regarding the toxicity of GLP. This latter one concluded that the renal tumors in rats previously mentioned are, in reality, an increase in the adenomas (benign tumors). In 1991, in light of a new review, the USEPA changed the rank from class C to E, "Evidence of non-carcinogenicity for humans." A similar conclusion was reached by the same agency in 2015, given that, after their third review, the agency concluded that GLP "is not likely to be carcinogenic for humans." (Pedemonte 2017, EPA 2016).

In 2020, the USEPA declared that GLP does not represent a risk to humans as long as it is used in accordance with the instructions provided (WSDA 2020, Mayer 2021).

In 2015, the International Agency for Research on Cancer (IARC) classified GLP in the 2A group as a "probable carcinogen" due to the idea that the GLP-based formulations are probably carcinogenic to humans, primarily for linfoma no Hodgkin (type of cancer that forms in the lymphatic system) (Weisenburger 2021).

The European Food Safety Authority (EFSA) mentioned in 2015 that it was unlikely that GLP represented a carcinogenic danger to humans. The Food and Agriculture Organization of the United Nations (FAO) concluded in 2016 that it is unlikely that GLP represents a carcinogenic risk in humans through dietary exposure (EPA 2016).

Glyphosate Prohibition

In Colombia, through the 1214 resolution established in 2015, the sprinkling of GLP was suspended, making it one of the first countries in Latin America to take into account the negative effects of GLP as advertised by the WHO (Campuzano et al. 2017). Vietnam banned the registry, import, and use of products containing GLP in 2021. Meanwhile, the European Union, in 2017, renewed its GLP license for 5 more years, even though some countries that form part of it opposed the renewal. France announced its prohibition on all of its uses, including agricultural uses, by 2022, and Germany has plans to ban it by the end of 2023 (Ramírez 2021).

In Mexico, a decree was presented on December 31, 2020, at the Diario Oficial de la Federación, which states in its first article the gradual substitution of the use, acquisition, distribution, promotion, and importation of GLP and agrochemical products that contain it as an active ingredient for sustainable alternatives and culturally adequate that have the capacity to maintain production and that are safe for the environment and human beings, contributing to the biocultural diversity. This decree contemplates a period for the fulfillment of the previously stated objectives, starting at the decree's publication up until January 31, 2024. Despite what has been previously stated, in Mexico, there are authorized pesticides whose active ingredients (specifically 140 pesticides) are banned or not authorized by other countries, of which 65 are extremely dangerous according to the criteria established by the FAO and the WHO (Bejarano 2017).

Many authors dispute the decree released by the Mexican Government. (Alcántara-de la Cruz et al. 2021), Established a skeptical position regarding the Mexican government has decreed about application of technology and alternative methods focused on weed control since they established that successful cases have been conducted internationally in an almost exclusive manner and that their regional reach is limited. Also, the authors indicate that the prohibition of GLP may promote the use of other herbicides with similar or greater negative environmental impacts. Adding on to what has been previously stated, Bejarano (2017) mentioned that agricultural activity highly depends on pesticide use and that even with their use, the country is still unable to achieve auto-sufficient corn production, as one-third of the total national demand is imported. A crop that is basic in the Mexican diet.

According to Meftaul et al. (2021), GLP presents low toxicity compared with other herbicides, even though they do not dismiss its possible impact on human health and the fact that some microorganisms develop a resistance to it while others (beneficial aquatic and ground microorganisms) suffer prejudgemental effects. In addition, the weed's herbicide resistance and the probable negative impact on aquatic and land organism communities of great ecological importance make this a controversial subject.

Possible Conflict of Interest by the Agrochemical Industry

In 2015, the Monsanto Company obtained nearly 4,760 million dollars and 1,900 million in gross profits because of herbicide sales. These benefits are mainly due to their Roundup® formulation (Chatsko 2016).

Burtscher et al. (2017) mentioned the participation of the International Agency for Research on Cancer (IARC), which classified GLP in 2015 as a possible carcinogen, threatening many companies' great businesses dedicated to herbicide production like Monsanto. In 2012, the same authors indicated that the authorized use of GLP as an active ingredient was about to expire, for which the companies of the agrochemical industry (Monsanto being one of them) responded by creating the "Glyphosate Task Force" which was financed by the agrochemical industry in charge of GLP based herbicide production with the objective of supporting the substance's safety.

Williams et al. (2000) suggested in a study that Monsanto backed up that GLP is not a carcinogen and does not present any risks to human health. Williams et al. (2012) indicated in a Monsanto-sponsored review that GLP does not affect reproductive health (in humans and/or animals), establishing that the toxicity presented in the studies can be attributed to surfactants that are a part of commercial presentations. Kier & Kirkland (2013) (Monsanto ex-employee and company consultant, respectively) indicated that GLP and the commercial formulations that contain it as an active ingredient pose a genotoxic risk that is insignificant under normal human exposure conditions. All of what was previously stated was described in accordance with Burtscher et al. (2017).

Burtscher et al. (2017) indicated that the studies and reviews sponsored by the industry that defend GLP safety present manipulations including "apparently calculated omissions," "incorrect representation of facts," "irrelevant data to confuse and deny scientific evidence," "distort and/or hide inconvenient facts and manipulate evidence to support their own arguments."

Acquavella et al. (2016) and Williams et al. (2016a) arrived at the upcoming conclusion: "Our review did not find any support in the epidemiological literature that backs up a causation between GLP and linfoma no Hodgkin." Brusick et al. (2016) mentioned in a review that: "GLP, the commercial formulations, and AMPA do not represent a genotoxic risk, and the data does not support the monograph of the IARC's genotoxicity." Chang & Delzell (2016), based on a review, conclude that: "No cause relationship between GLP exposure and any type of linfoma no Hodgkin risk was established."

Solomon (2016) indicates in a review that: "the IARC's GLP classification as a possible human carcinogen was conducted without a detailed exposure evaluation." Williams et al. (2016a) exposed in a review that: "the data does not support the IARC's conclusion regarding the GLP as a probable human carcinogen." Williams et al. (2016b) concluded in a review that: "GLP is not a carcinogen in laboratory animals." According to Weisenburger (2021), every review that was previously mentioned emerges from the pesticide industry's sponsorship to oppose the evaluation of the IARC in 2015.

Despite what has been previously mentioned, Bayer (current property of the Monsanto company) reached a massive settlement/agreement in which 11 billion dollars will be paid in the U.S. to those who claim to suffer from cancer, especially linfoma no Hodgkin due to repeated herbicide exposures after tens of thousands of lawsuits were filed regarding cancer (Ramírez 2021, Forbes México 2018, Ximénez 2020)

CONCLUSIONS

The available literature of the past century displays contradictory stands regarding the role played by GLP-based herbicides on human and environmental health.

Diverse authors have identified the toxicological potential of the "inert compounds" present in commercial formulations, establishing that, in some cases, these are more harmful than GLP. The studies that use technical grade GLP (pure compound) conclude with the frequency that the herbicide does not represent any important risks; meanwhile, other studies that use commercial formulations that contain GLP as an active ingredient advise about the negative effects that these other substances may induce.

In many reviews, the presence of probable conflicts of interest has been evidenced due to the author's relationship with the GLP-based herbicide industry, many of which have supported the substance's safety based on its use. Because of what was previously stated, it is necessary to conduct studies that are not influenced by economic interests, especially coming from the agrochemical industry.

The continuous study and monitoring of environmental impacts due to GLP is relevant since the development of the flora and fauna adjacent to the areas where this herbicide is used may be negatively altered. In addition, due to the transport of contaminants, concentrations of GLP have been found in distant aquatic systems, which could establish an important impact on high-valued ecosystems. Related to the soil, the natural processes that take place can be altered, causing a decrease in bacterial growth or, on the contrary, promoting the development of certain pathogenic agents.

Due to the presence of GLP fixed in organs and bones of animals, there are several results on the effects on fauna, altering the development and diversity of species, causing changes in morphology, generating diseases, and even mortality in certain groups. It is recognized that further studies are needed to explore the effects of GLP in animals since their level of exposure is even higher than in humans.

GLP is one of the most common organic pollutants present in multiple resources used by humans, which makes it a threat to current and long-term health. The main route of human exposure is ingestion through food since there are records of GLP concentrations in foods such as crops, natural and purified water, as well, as animal tissue. Other routes of exposure are dermal contact and inhalation, which has led to the presence of this contaminant in blood, urine, and breast milk.

Exposure to GLP is associated with diseases in various stages of human development, as well as alterations to the neurological, immune, and endocrine systems. There is a relationship between the presence of GLP and problems in gestation and birth; additionally, the increase in antibiotic resistance of some bacteria due to the presence of GLP presents a new panorama of challenges for humanity. In addition, some authors mention the need to conduct studies in susceptible human populations, such as children or people with special genetic traits, and others that contemplate the mix of contaminants (including agrochemicals).

Regardless of the negative impacts that may come from the use of herbicides, it remains true that a big part of large-scale crops is favored by the use of these pesticides, which in some way has made us dependent on the use of these substances, given that production of organic foods comes with important difficulties and their large scale application tends to not be viable, even though the use of GLP based herbicides seems to be reaching an end in its use to control weeds given that many weed species have developed a tolerance to these types of herbicides.

The GLP-based herbicide ban may promote the use of other pesticides, with impacts that can only be determined with certainty by long-term studies. GLP, regardless of becoming the most widely used herbicide, has been used for almost 5 decades (since its first appearance in the Roundup® product in 1974) and has not yet reached a scientific consensus regarding its impact on the environment and human health.

Without a doubt, the subject of herbicides encompasses many diverse aspects of human life, from health, environment, economy, and culture, which means that the subject cannot be approached through a reductive analysis.

STATEMENTS AND DECLARATIONS

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