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Glifosato y cáncer: cuando la ciencia, la políticay la industria converge

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RESUMEN

El glifosato es un herbicida de amplio espectro no selectivo y sistémico, cualquier planta puede absorberlo a través de sus tejidos. Su función consiste en destruir las plantas consideradas “malas yerbas” por los agricultores, es decir aquellas que “roban” espacio, luz, agua y nutrientes a la siembra. Otro de los usos del glifosato ha sido la aspersión aérea del químico para combatir cultivos de coca, amapola y marihuana, en países como Colombia, lo cual ha terminado por afectar la biodiversidad de áreas selváticas, al impactar más allá de las especies y los cultivos que son objetivo En el año 2015, la International Agency for Research on Cancer, concluyó que el glifosato es una sustancia probablemente cancerígena, a pesar de que algunas agencias, como la Autoridad Europea de Seguridad Alimentaria (EFSA), han dicho que no implica un riesgo y otras han minimizado los peligros, siempre y cuando se use “apropiadamente”, como la Agencia de Protección Ambiental de Estados Unidos (US EPA). En el presente artículo se revisan estas posturas a la luz de estudios científicos que han evaluado el impacto del uso del glifosato sobre la salud humana, especialmente como agente potencialmente cancerígeno.

Palabras clave: *glifosato; cancer; investigación; evidencia*.

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Glyphosate and cancer: when science, policy and industry converge

ABSTRACT

Glyphosate is a non-selective and systemic broad-spectrum herbicide; any plant can absorb it through its tissues. Its function is to destroy the plants considered "weeds" by farmers, that is, those that "steal" space, light, water, and nutrients from crops. Another of the uses of glyphosate has been the aerial spraying of the chemical to combat coca, poppy and marijuana crops, in countries like Colombia, which has ended up affecting the biodiversity of jungle areas, by impacting beyond species and crops that are objective In 2015, the International Agency for Research on Cancer concluded that glyphosate is a probably carcinogenic substance, despite the fact that some agencies, such as the European Food Safety Authority (EFSA), have said that it does not imply a risk and others have minimized the hazards, as long as it is used "properly", such as the United States Environmental Protection Agency (US EPA). This article reviews these positions considering scientific studies that have evaluated the impact of the use of glyphosate on human health, especially as a potentially carcinogenic agent.

Key words: *glyphosate; cancer; research; evidence*.

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INTRODUCTION

Glyphosate: N-phosphonomethylglycine (C3H8NO5P), is a weak organic acid consisting of a glycine and a phosphonomethyl particle. It is a systemic and non-selective broad-spectrum herbicide, used in agricultural and forestry crops for elimination of deep-rooted perennial plant species and against grasses and Sedge (Cyperus rotundus) (WHO, 1994).

It was created in 1950 by the Swiss chemist Henry Martin, working for the pharmaceutical company Cilag, which was later acquired by Johnson & Johnson (Dill, Sammons, Feng, et al., 2010). Its action mechanism is the inhibition of the enzyme 5-enolpyruvylshikimate-3-phosphate synthase interfering with the synthesis of phenylalanine, tyrosine and tryptophan (Ostera, Malanga & Puntarulo, 2016). It is mainly absorbed by leaves, which is why it is applied to this part of the plant, although it can also be injected into trunks and stems (Smedbol, Lucotte, Maccario, et al., 2019). Most glyphosate presentations contain glyphosate isopropylamine salt (Cox, 1998). Its physical form is a white, odorless, crystalline powder, soluble in water and insoluble in organic solvents.

It has low solubility in organic solvents and high solubility in water (Lane, Lorenz, Saxena, et al., 2012). Degradation in soils occurs mainly by action of microorganisms and can take between 2 to 142 days. In water it is absorbed by suspended particles and degradation is slower than in soils, reaching an average life of 7 to 10 weeks in natural waters (Varona, Henao, Díaz, et al., 2009; Nguyen, Rose, Rose, et al., 2016; Annett R, Habibi H, Hontela, 2014) although according to Borggaard & Gimsing (2008), and Vereecken (2005), the average life in In water it can be from a few days to around three months, and according to Székács & Darvas (2012), its average life in water and soil can be several months, or even a year, depending of the soil composition.

There are several routes for glyphosate contamination in surface waters, mainly through drift during application or as surface runoff after application, but it does not necessarily contaminate groundwater, as it can be absorbed and degraded in deeper layers of the soil ground before reaching them (Annett, Habibi & Hontela, 2014; la Cecilia & Maggi, 2008).

Studies carried out to evaluate the toxicity of glyphosate and its metabolite: AMPA (Aminomethylphosphonic Acid) in aquatic organisms (Gomes, Smedbol, Chalifour, et al., 2014; Henao, Montes & Bernal, 2015; Van Bruggen, He, Shin, et al., 2018), have shown that glyphosate can cause oxidative stress in fish and consequently cellular damage.

On the other hand, some studies consider glyphosate to be of low risk to animal health, since its mechanism of action affects a specific physiological process of plants, different from that of animals (Berry, 2020).

It has also been reported that concentration levels of Glyphosate used in aerial spraying campaigns are so low that they do not represent a significant risk to human health (Solomon, Anadon, Carrasquilla, et al., 2007). According to Cerdeira and Duke (2010), high levels of residues of glyphosate and AMPA have not been detected in surface waters or on surfaces in areas where they are widely used, and these substances are less harmful than most of the herbicides replaced by glyphosate. Likewise, a panel of experts concluded that glyphosate, glyphosate formulations and AMPA do not represent a genotoxic risk since the evidence related to a mechanism of carcinogenicity due to oxidative stress is not conclusive and the data profiles are not consistent with findings of genotoxic carcinogens (Brusick, Aardema, Kier, et al., 2016).

Evaluation of glyphosate effects on health and environment is essentially based on observational studies in which there could be confounding factors due to occupational exposure (Camacho & Mejía, 2017), such as Varona´s study (2009), in which high urinary concentrations were found in rural population living near areas sprayed for coca eradication, with levels of 7.6 μg/L, higher than those found in Europe: 0.02 μg/L (23).

METHODOLOGY

The research is qualitative, and the documentary review technique was used, carrying out an analysis and theoretical reflection through different sources about the study.

Reliable, duly documented scientific publications obtained from bibliographic databases (Scopus and Web of Science) were reviewed and the search, evaluation, analysis, and synthesis of information was carried out in a structured and sequential manner.

RESULTS AND DISCUSSION

Epidemiological studies

Research in humans (De Roos, Zahm, Cantor, et al., 2003; Paganelli, Gnazzo, Acosta, et al., 2010) and domestic animals (Shehata, Schrodl, Aldin, et al., 2013) suggest associations between glyphosate exposure and adverse health outcomes. Congenital malformations have been reported in young pigs fed soybeans contaminated with glyphosate residues (Kruger, Schrodl, Pedersen, et al., 2013), so this could be a contributing factor to similar birth defects seen in humans living in and near exposed agricultural regions (IARC, 2015).

Regarding carcinogenicity, in the Agricultural Health Study (Andreotti, Koutros, Hofmann, et al., 2017), no association was observed between its use and any solid tumors or lymphoid neoplasms in general (including non-Hodgkin lymphoma). However, some evidence was found (RR: 2.04, 95% CI: 1.05-3.97) of an increased risk of acute myeloid leukemia among workers with 20 years of exposure.

In contrast, Myers et al., (Myers, Antoniou, Blumberg, et al., 2016) indicated that there may be a causal link between exposure to Glyphosate and Non-Hodgkin Lymphoma. A systematic review carried out by Schinasi and Leon (2014)) found an association between use of glyphosate and appearance of B-cell lymphomas (RR: 1.8; 95% CI: 1.2-2.8).

Other study (systematic review and meta-analysis) published in 2015 by Chang and Delzell (2016), about relationship between exposure to glyphosate and risk of different types of cancer, found a positive association for non-Hodgkin lymphoma (RR: 1.3; CI 95 %: 1.0-1.6) and multiple myeloma (RR: 1.4; 95% CI: 1.0-1.9), and no association with Hodgkin lymphoma, leukemia and some subtypes of non-Hodgkin lymphoma, although the authors acknowledged that there were a limited number of studies included, some of which were weak.

Another meta-analysis carried out by Zhang et al., (2019), concluded that human exposure to glyphosate is associated with the risk of non-Hodgkin lymphoma (RR: 1.41; 95% CI: 1.13–1.75) and that there is a greater risk of Non-Hodgkin Lymphoma in groups that have greater exposure to the herbicide (RR: 1.45; 95% CI: 1.11-1.91), although the same authors indicate that due to the heterogeneity of the studies included, the numerical estimates must be interpreted with caution. In addition, this meta-analysis was based on risk estimates from the included studies at the highest reported exposure level obtained from analyzes with the longest latency period.

Kabat, Price & Tarone (2021) reviewed the work of Zhang et al., (2019) performing a sensitivity analysis to determine how the definition of exposure and the choice of latency period affect the summary estimate discussed previously, so in their own meta-analysis they included the more up-to-date results from case-control studies, noting that at higher exposure levels there is evidence of an association between glyphosate and non-Hodgkin lymphoma and this association was stronger when estimates from one study analysis were included cohort with a latency of 20 years (RR: 1.41; 95%CI: 1.13-1.76) and a latency of 15 years (RR: 1.25; 95%CI: 1.01-1.25); however, considering constant exposure without a latency period, the summary RR with updated estimates was 1.05 (95%CI: 0.87-1.28).

Donato, Pira & Ciocan (2020) published in 2020 a systematic review/meta-analysis in which, in addition to studying relationship between glyphosate and non-Hodgkin lymphoma, they included Multiple Myeloma. The RR for Non-Hodgkin Lymphoma was 1.03 (95%CI: 0.86-1.21), for higher exposure categories the RR was 1.49 (95%CI: 0.37-2.61); Multiple Myeloma: 1.04 (95% CI: 0.67-1.41); diffuse large B-cell lymphoma: 1.31 (95%CI: 0.93-1.75); follicular lymphoma: 0.82 (95%CI: 0.93-1.70) and chronic lymphocytic leukemia: 0.85 (95%CI: 0.20-1.49). Despite, authors reported limitations, mainly due to underlying studies, as the majority were case-control, with potential bias as result of comparability lack, as well as possible residual confounding that would result in direction unknown bias, and the fact that meta-analysis for non-Hodgkin lymphoma included unadjusted results and higher summary risk estimates.

Although epidemiological data provide evidence an increased cancer risk in human populations (Kruger, Schrodl, Pedersen, et al., 2014), further in vivo studies at environmentally relevant doses are needed to distinguish the combination of factors that can lead to morbidity and mortality.

IARC, EPA and EFSA position

The International Agency for Research on Cancer (IARC) in 2015 classified glyphosate as "probably carcinogenic to humans" (Group 2A). Although IARC characterized the evidence for carcinogenicity in humans as "limited" based on data available for Non-Hodgkin Lymphoma, it considered the evidence for carcinogenicity in experimental animals as "sufficient" based on the occurrence of kidney tubule carcinoma, hemangiosarcoma and pancreatic islet cell adenoma in rodents. This Agency consult 17 experts from 11 countries, whose evaluations of more than 100 investigations were published as volume 112 of the IARC Monographs. These pointed to an increased risk of non-Hodgkin lymphoma in farmworkers, which was confirmed in animals and in experimental studies. The category of "probable carcinogen" is used when there is evidence that does not allow ruling out a risk but is not conclusive either.

The U.S. Environmental Protection Agency (US EPA) considers that glyphosate "is not potentially carcinogenic to humans" (EPA, 2016). Both entities used different methodologies and the US EPA reviewed toxicological profile proposing new reference values and carried out a risk assessment for some representative uses (Tarazona, Tiramani, Reich, et al., 2017). It should be noted that US EPA cited 43 regulatory trials, in addition to 65 trials published in peer-reviewed journals. Of these, none of the regulatory trials and 75% of published reported evidence of a genotoxic response after glyphosate exposure. In the other hand, IARC considered a total of 118 genotoxicity trials for glyphosate and AMPA. The EPA analysis covered 43% of these trials. In addition, IARC reviewed another 81 trials that explored other potential genotoxic mechanisms, primarily related to sex hormones and oxidative stress, of which 77% reported positive results. According to Benbrook (2019), IARC placed considerable weight on three positive studies in exposed human populations, while US EPA placed little or no weight on them.

Additionally, the European Food Safety Authority (EFSA) (2015), based on a technical evaluation by the German Federal Institute for Risk Assessment (BFR), indicated that it was "unlikely" that glyphosate was genotoxic or carcinogenic to humans and the World Health Organization (WHO) and the FAO (Food and Agriculture Organization of the United Nations) indicated that "glyphosate is unlikely to cause a carcinogenic risk to humans as a consequence of the dietary exposure", although they state that exposure up to 2000 mg/kg body weight has not been associated with some genotoxic effects in the majority of mammalian cases and therefore it is not necessary to establish a dose of glyphosate and its metabolites that can lead to disease (Food and Agriculture Organization of United Nations, 2016). This decision was supported by the European Chemicals Agency (ECHA) (2019).

Another actor in process is the AGG (Assessment Group on Glyphosate), a group formed in 2019 by France, Hungary, the Netherlands and Sweden. On June 15, 2021, this entity submitted the draft Renewal Assessment Report on glyphosate renewal to EFSA and suggested that glyphosate is not justified as carcinogenic; however, according to the AGG (2021), different working groups are waiting to discuss this position.

It should be noted that, unlike the US EPA, the EFSA concluded that there was no evidence of adverse effects on reproduction, but the hypothesis of glyphosate as a possible endocrine disruptor could not be ruled out due to the limited data on the subject (EFSA, 2015).

According to Benbrook, (2019) US EPA and IARC reached diametrically opposed conclusions about glyphosate genotoxicity because the US EPA relied primarily on registrant-commissioned, unpublished regulatory studies, 99% of which were negative, while that IARC relied primarily on peer-reviewed studies, of which 70% were positive, and EPA's assessment focused on typical dietary exposures of the general population, assuming legal uses on food crops, and did not take into account nor did it address generally higher occupational exposures and risks, whereas the IARC assessment encompassed data from typical dietary, occupational, and high-exposure scenarios.

Likewise, according to Torretta et al., (2018) some academics have demonstrated the direct participation of some pesticide-producing companies that, under the name of the Glyphosate task force, have carried out studies and defined their own conclusions and, according to these same authors, the WHO decision was questioned by Greenpeace, an organization that stated that the experts who dealt with the study only pronounced effects related to diet, such as taking glyphosate by ingestion, without making any reference to the combined effects of diet, exposure through the environment, pollution and the effect of the compound on fauna.

Situation in Colombia

Aerial spraying with glyphosate in Colombia was made official in 1992, through a public opinion statement issued by the Consejo Nacional de Estupefacientes (Varona, Henao, Díaz, et al., 2009), just over 10 years later, through Resolution 1065 of 2001, the Management Plan was established. Environment of the program to eradicate illicit crops with glyphosate. This standard was modified and complemented by Resolution 1054 of 2003, which describes the parameters for spraying operations and spraying nuclei were established in 8 departments (Ministerio de Medio Ambiente, 2001; Ministerio de Ambiente Vivienda y Desarrollo Territorial, 2003): Putumayo, Caquetá, Guaviare, Meta, Cauca, Nariño, Antioquia and Norte de Santander and were suspended by Consejo Nacional de Estupefacientes (2015) in Resolution number 0006.

Different scientific publications have been carried out around this topic in the country. Camacho and Mejía (2017) evaluated the effects of aerial fumigation with Glyphosate to reduce illicit crops on health outcomes in Colombia, finding that exposure to herbicides leads to an increase in dermatological and respiratory problems, and abortions. On the other hand, according to Mejía & Restrepo (2016), aerial fumigation campaigns are ineffective in reducing coca cultivation, since the most conservative estimates indicate that for each additional hectare sprayed with herbicides, coca cultivation is reduced by approximately 0.035 ha, which implies that, to reduce the amount of coca cultivation in one hectare, almost 30 ha would have to be fumigated and the average cost of eliminating 1 ha is approximately USD $74,000.

Varona et al., (2009), published a descriptive study on 112 individuals from the sprayed areas of Huila, Tolima, Putumayo, Guaviare, Santander, Antioquia, Magdalena and La Guajira. Half of participants stated the use of pesticides in their work, the average use time was 84.8 months with an intensity of 5.6 hours/day; Of the individuals who were quantified with glyphosate, 64.3% reported its use in agricultural activities. A statistically significant relationship was found between the use of terrestrial (manual) glyphosate and levels of this herbicide in urine (OR=2.54; 95%CI 1.08-6.08).

Researchers from the Universidad de Los Andes (Monroy, Cortés, Sicard, et al., 2005), found that glyphosate, in high concentrations, has the potential to alter DNA structure in different types of human cells in in vitro cultures, as indicated in 2007 by Paz and Miño et al., (2007) in Ecuador.

Bolognesi et al., (2009) carried out a study developed in five regions, comparing two that did not have glyphosate spraying: Boyacá and Sierra Nevada de Santa Marta; two with glyphosate spraying by the PECIG program (Program for the Eradication of Illicit Crops by aerial spraying with the herbicide Glyphosate): Putumayo and Nariño and one with spraying for sugarcane ripening in Valle del Cauca. 137 women from 15 to 49 years old and their husbands were evaluated, blood samples were taken before the spraying, five days, and 4 months after there were evidence of chromosomal damage (micronucleus formation test) in the control of 5 days, in residents of Valle del Cauca, Nariño and Putumayo; at four the mean decreased significantly in Nariño, but not in Putumayo and Valle del Cauca. Therefore, the authors concluded that, in general, there is little genotoxic damage associated with glyphosate spraying for the control of illicit crops, which appears to be transitory.

A report from the Instituto Nacional de Cancerología (2019) compared incidence of non-Hodgkin lymphoma in three five-year periods: 1995 to 1999, 2002 to 2006, and 2007 to 2011, in two departments with no history of glyphosate spraying (Boyacá and Cundinamarca) with the departments of Antioquia, Caquetá, Cauca, Nariño and Putumayo that were the object of the PECIG. It was found that in observed periods Antioquia had the highest incidence rate for this lymphoma in men and women, except for the last five years in women, where Cauca and Cundinamarca had higher rates. By age, the age group over 65 ranks first in men and women, in all departments. In men, from 2007 to 2011, the highest rate in the 65-year-old group and over was in Antioquia, in the 55-64 age group in Putumayo, in the 45-54 age group in Antioquia, and in those from 15 to 44 and 0 to 14 in Putumayo, all these departments included in the PECIG. In women, the behavior was relatively similar, although the incidence rate in the 45-54 age group was higher in Boyacá (not PECIG). Regarding mortality from non-Hodgkin lymphoma in the period 2007 to 2013, the age-adjusted rate (x 100,000) for the country was 2.6 in men and only 2 departments included in the PECIG had equal or higher values: Antioquia (2.6) and Target (3.0); in women, the adjusted rate for the country was 1.8 and Cauca (1.9) and Antioquia (1.8) had equal or higher values.

Finally, in a pronouncement of the SAO Node in April 2021 (2021), its members indicate that IARC classification of glyphosate has not changed, so it should continue to be considered carcinogenic; however, it is mentioned that on March 26 they were summoned to the event: Socialization with experts on health risk management strategies, associated with the exposure of pesticides in Colombia, whose analysis seems to favor the use of glyphosate, for which they request government an in-depth analysis of the real meaning and scope of this study and indicate that they carried out clear and forceful comments on possible methodological problems in various aspects of the study such as the low participation of the affected communities and the lack of explicit exposure of the limitations of the study. methodological approach used.

CONCLUSIONS

Based on the elements of existing literature, it can be inferred that the position of the IARC (2015) which reflects the position of the World Health Organization, is still valid and is supported by systematic reviews and meta-analyses of the past five years. Although there are diseases that are caused by the risk of exposure to glyphosate, not all studies find strong associations with cancer.

In the country, more research must be carried out to determine an association between exposure to glyphosate and cancer, considering that the scientific evidence obtained favors the making of health decisions.

An evaluation of exposure to this agent is required, whose urinary levels would provide more accurate and quantitatively detailed information on the received biological dose, but they must be measured over time to reflect long-term exposure, since for the analysis of causality in cancer, the induction period (time between exposure and development of the disease is estimated at 10 years) (Rothman & Greenland, 2005; Mattiuzzi & Lippi, 2019).

It must be clearly considered and with a methodologically sound line based on the review of the literature and the opinion of experts on the topic of occupational exposure; for example, it is not known if farmers use the product properly and this can be determined through research and in the future implement an occupational surveillance system with the agricultural sector.

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