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## Glyphosate uses, adverse effects and alternatives: focus on the current scenario in Brazil

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1 **Glyphosate uses, adverse effects and alternatives: focus on the current scenario in Brazil**

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9

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15

16

17 **Glyphosate uses, adverse effects and alternatives: focus on the current scenario in Brazil**

18 Brazil, a world leader in the consumption and sale of pesticides, especially glyphosate, appears to be at  
19 odds with other countries that increasingly ban these products in their territories. This study gathers the  
20 values of Acceptable Daily Intake and Maximum Residue Limits (MRL) in the European Union for  
21 dozens of substances and compares them with those accepted in Brazil concerning the most frequent  
22 crops. Also, the degree of toxicity and the effects of glyphosate on human health by ingesting food  
23 containing its residues are identified. The study shows that over the last decade, the sale and consumption  
24 of glyphosate and other pesticides have grown significantly in Brazil; in 2019, unlike European countries,  
25 Brazil has not only approved the sale and use of 474 new pesticides but has also renewed the sale of  
26 glyphosate and reduced the classification of its toxicity. Finally, this review identifies controversies  
27 between studies, discusses the difficulties of substituting glyphosate, and presents some more  
28 environment-friendly alternatives that have been evaluated in the literature.

29 Keywords: herbicide; toxicity; acceptable daily intake; maximum residue limits

## 30 1. Introduction

31 Food supply, quality and reduced pesticide usage have become topics of foremost importance to  
32 the global population. Thus, limiting the use of pesticides and artificial fertilizers is a common goal in  
33 several countries. Conversely, in Brazil in 2019, this topic gained strength after the government approved  
34 the sale and use of 474 new pesticides, the highest number in 14 years (de O. Gomes et al. 2020). Amidst  
35 so much controversy, one specific product stands out: glyphosate. Glyphosate is a herbicide and desiccant  
36 used in agriculture to control more than 160 weed species worldwide (Agostini et al. 2020; Gillezeau et  
37 al. 2019; Kenko et al. 2022). This common pesticide can be used in aqueous and spray forms and can be  
38 applied pre-harvest, post-plant and pre-emergence (Tomlin 2009). As a plant growth regulator and  
39 desiccant, glyphosate is applied at low levels (FAO/WHO 2016; IARC 2015). According to Landrigan  
40 and Belpoggi (2018), the production of this pesticide has increased significantly over the past few  
41 decades, with projections of about one million tons per year produced in the global market (over 140  
42 countries).

43 Researchers have shown that the use of glyphosate as a desiccant contaminates plants, and  
44 consequently, meats, fruits, and vegetables can have varying levels of this substance (Agostini et al.  
45 2020). Xu et al. (2019) reported on contamination of cereals and foods from glyphosate use, concluding  
46 that there is a lack of evidence regarding the carcinogenicity of glyphosate exposure on humans. Bai &  
47 Ogbourne (2016) stated that glyphosate, by being present in plants, water and soil, affects the entire food  
48 chain of herbivores and omnivores, exposing animals and humans to contamination by the diet. Some  
49 tests confirm the presence of glyphosate in the gastrointestinal tract of humans and mammals through  
50 ingestion, inhalation and skin contact. The presence of this substance stunts growth, damages the kidneys,  
51 causes liver hypertrophy and inflammation, and gastric diseases (Agostini et al. 2020; Benachour et al.  
52 2007; Gasnier et al. 2010; Mesnage et al. 2013). Brazil is one of the four countries with the highest sales  
53 and consumption of pesticides in the world (Paumgarten 2020). The number of people exposed to this  
54 poison is large; therefore, acute intoxications are more frequent and severe there. Pesticides have been  
55 known to cause health problems, both acute and chronic, especially in the rural population and in  
56 developing countries (Recena et al. 2006). According to Recena et al. (2006), herbicides account for  
57 13.4% of poisoning cases, with 2,4-Dichlorophenoxyacetic acid (usually referred to by its ISO common  
58 name 2,4 D), glyphosate and 4-Amino-3,5,6-trichloropyridine-2-carboxylic acid (better known as

59 Picloram) being the most frequently involved. In the Brazilian state of Mato Grosso do Sul alone, 47  
60 poisonings were caused by exposure to glyphosate between 1991 and 2002 (Recena et al. 2006).

61 Studies suggest that food containing glyphosate residues consumed by humans, its by-product  
62 aminomethylphosphonic acid (AMPA), and the surfactant polyethoxylated tallow amine used in the  
63 formulations, are seriously hazardous when the maximum residue limit (MRL) is above acceptable levels  
64 of the Theoretical Maximum Daily Intake (TMDI) of  $23.8 \mu\text{g kg}^{-1} \text{ day}^{-1}$  for adults (Williams et al. 2000).  
65 On the other hand, the Joint Food and Agriculture Organization (FAO)/World Health Organization  
66 (WHO), at the "Meeting on Pesticides Residues" in 2004, concluded that there was no need to establish  
67 an Acute Reference Dose (ARfD). Indeed, the short-term ingestion of glyphosate residues does not  
68 represent a risk to consumers. Furthermore, in the long term, the expected international daily intakes  
69 (GEMS/Food), based on the average value from field studies (STMR), were in the range of 0–1% of the  
70 Acceptable Daily Intake (ADI) of  $1 \text{ mg kg}^{-1}$  of glyphosate and AMPA, which is also not relevant to  
71 public health (FAO/WHO 2005).

72 Conversely, in Brazil, the National Agency of Sanitary Surveillance (ANVISA) assures that  
73 glyphosate is undergoing toxicological re-evaluation, and has so far concluded that the product does not  
74 meet the law's criteria for restriction, as it has not been classified as "mutagenic, carcinogenic, toxic for  
75 reproduction and teratogenic (causes malformation in unborn children)" (ANVISA 2019a). However, the  
76 UN International Agency for Research on Cancer (IARC) classified glyphosate as possibly carcinogenic  
77 to humans in 2015. Although there is little evidence of its carcinogenicity in humans, there is sufficient  
78 information to indicate that it causes cancer in laboratory animals. That same year, although the European  
79 Food Safety Authority (EFSA) objected to the studies, IARC confirmed its overall conclusion in 2016,  
80 stating that there is strong evidence to confirm the genotoxicity of glyphosate and AMPA to humans and  
81 animals, as well as to cause oxidative stress (González-Valenzuela and Dussán 2018; IARC 2015).

82 Between the years 2014 and 2016, out of 22,704 water samples analyzed, only 0.03% of the  
83 cases had glyphosate levels above those allowed (ANVISA 2019a). Yet, while in the European Union  
84 (EU) the acceptable level is  $0.1 \mu\text{g L}^{-1}$ , in Brazil it is  $500 \mu\text{g L}^{-1}$ , thus 5,000 times higher (ANVISA  
85 2018). The Program of Agrotoxin Residue Analysis (PARA) was created by ANVISA in 2001, with the  
86 aim of evaluating agrotoxin levels in food, based on MRLs. The purpose of this initiative was to create a  
87 structure capable of assessing the quality of food and monitoring the amount of residues in it (ANVISA  
88 2011).

89           Due to the questions on the impacts of glyphosate on human health, this study aims to clarify  
90 whether food containing herbicide residues may be hazardous to humans and to identify whether  
91 glyphosate residues in consumed food may be hazardous to human health, by evaluating reports from  
92 Brazil and around the world. We also discuss the ADI values established for this herbicide in Brazil and  
93 other countries. To do so, it was necessary to: (i) provide a definition of agrottoxins; (ii) present a brief  
94 history of glyphosate as a herbicide and its importance for agriculture; (iii) evaluate and compare ADI  
95 and MRL values of glyphosate residues in food; (iv) identify the degree of toxicity and what are the  
96 impacts on food consumed with glyphosate residues; (v) examine what the alternatives to glyphosate  
97 might be. This study on the impacts of food with glyphosate residues is important because it is the most  
98 widely used agrottoxin in the world, especially in Brazil. Thus, this research provides insights into the  
99 potential dangers of consuming food produced using glyphosate as an herbicide.

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## 102   **2.       Basic concepts**

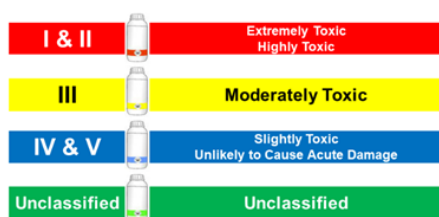
### 103   ***2.1 What is an agrottoxin?***

104   According to the Brazilian Law number 7.802/89 (Brazilian Federal Law number 7.802, 1989),  
105 agrottoxins can be defined as chemical or biological products that can be used in several environments,  
106 such as native or planted forest, other ecosystems, in industrial, urban and aquatic environments, and,  
107 mainly and most often, in agriculture and pastures. It is also possible that agrottoxins are used in urban  
108 health campaigns to modify the composition of fauna or flora, with the sole aim of inhibiting the harmful  
109 action of living pests. They can also be classified as pesticides, larvicides, insecticides, acaricides,  
110 nematocides, molluscicides, rodenticides, fungicides, and herbicides (Ahmed et al. 2021), which include  
111 defoliant, anti-sprouting agents, desiccants, and wood preservatives (Gupta and Crissman 2013). The  
112 correct classification of these products has very different connotations depending on the group concerned,  
113 being also called agricultural defenses (Neethirajan et al. 2018), agrochemicals (Nicolopoulou-Stamati et  
114 al. 2016), pesticides (Lemma et al. 2019) or simply poisons.

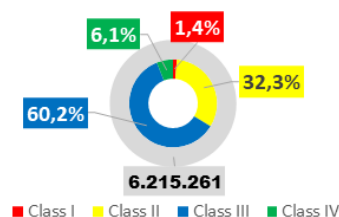
## 115 2.2 Agrottoxins in Brazil

116 The registration of agrottoxins is carried out by MAPA after a toxicological evaluation by ANVISA and  
 117 the Brazilian Institute for the Environment and Renewable Natural Resources IBAMA (BRASIL 2016).  
 118 The toxicological classification is based on the results of toxicological studies that are identified and  
 119 categorized into five “Classes” and one “Unclassified” (see Figure 1. a) Toxicological types and their  
 120 respective colors. Adapted from (ANVISA 2019c)a, according to the agreement established in RDC  
 121 Resolution n° 296, July 19, 2019 (ANVISA 2019b).

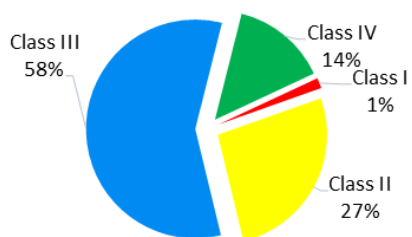
a) TOXICOLOGICAL AGROTOXIN TYPES



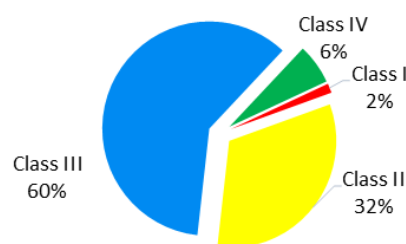
b) AGROTOXINS SALES (2009-2021)



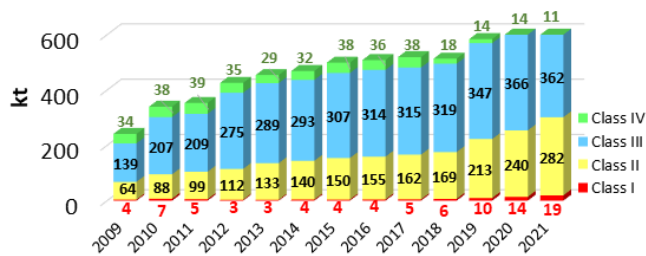
c) SALES OF AGROTOXINS IN 2009



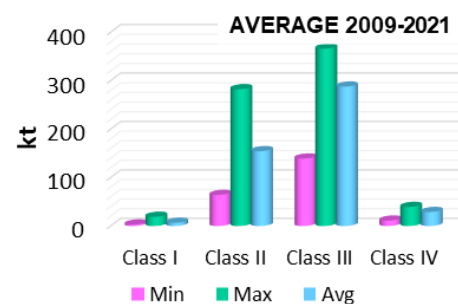
d) SALES OF AGROTOXINS IN 2021



e) PRODUCTION OF ACTIVE INGREDIENTS



f)



122

123 Figure 1. a) Toxicological types and their respective colors. Adapted from (ANVISA 2019c); b)  
 124 Percentages corresponding to the total tons sold per class in Brazil from 2009–2021; and comparison of  
 125 sales of agrottoxins in c) 2009 and d) 2021; e) Amount of agrottoxin sold per environmental risk class in  
 126 tons of active ingredient in Brazil (2009–2021) (IBAMA, 2022); f) Minimum, maximum, and average  
 127 tons of active ingredient separated per class sold in Brazil between 2009 and 2021 (IBAMA, 2022).

128

129 The color of the label is based on the "Pantone Matching System" (PMS) and is used to classify  
 the degree of toxicity of the product, as shown in Fig. 1a (ANVISA 2019c). From 2009 to 2021,

130 6,215,261 tons of active ingredients were sold. In this amount, the percentage of Class I was 1.4%, Class  
131 II was 32.3%, Class III was 60.2% and Class IV was 6.1%. Classes II and III accounted for 92.5% of total  
132 sales, according to Figure 1. a) Toxicological types and their respective colors. Adapted from (ANVISA  
133 2019c)b. Agrotoxin sales during this period were found to be higher in Class II and lower in Class IV,  
134 indicating that even with the changes in glyphosate regulation, as discussed later, a higher percentage of  
135 hazardous agrotoxins is observed (Fig. 1c, 1d).

136 In absolute values, it can be seen that the sale of Class II and III products increased more than  
137 Class I and IV between 2009 and 2021, in terms of distribution by environmental risk class and agrotoxin  
138 sales (Fig. 1e). Conversely, it should be noted that the percentage of Class I has more than tripled in 12  
139 years, with an increase in active ingredients from 4 to 19 thousand tons. Fig. 1f shows the minimum,  
140 maximum, and the arithmetic average of sales of agrotoxins from 2009 to 2021. Class I varied by more  
141 than 4 times, Class II by more than 3 times, Class III by more than 2 times, and Class IV by about 3  
142 times.

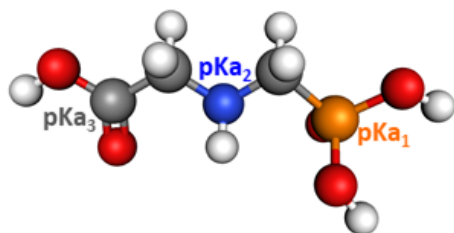
### 143 **2.3 What is glyphosate?**

144 Glyphosate was discovered in the Monsanto Company by a group of scientists led by Dr. Franz in 1970.  
145 It was commercialized as a water-soluble salt in 1971 and introduced to the European market as a  
146 herbicide in 1974 (Gasnier et al. 2010; Gillezeau et al. 2019; Pereira et al. 2020). Today, it is the best-  
147 selling herbicide in the world, and is now present in over 130 countries. The first and largest producer of  
148 glyphosate is Bayer-Monsanto, formerly Monsanto Corporation. However, other companies producing  
149 and selling the product include Syngenta, Cheminova, Agripec, Helm, Atanor, Nortox, Sinon and  
150 Milenia. The pioneering brand in the synthesis of glyphosate is RoundUp®, sold by Monsanto (Dorta et  
151 al. 2018). The chemical name of glyphosate is N-(phosphonomethyl) glycine, and it is an herbicide with  
152 the natural formula  $C_3H_8NO_5P$  (Fig. 2), with a substituted glycine chemical group, a molecular weight of  
153  $169.1 \text{ g mol}^{-1}$ , a Class IV toxicological classification.

154



## A) GLYPHOSATE FORMULA



## B) SUMMARY OF GLYPHOSATE PROPERTIES

Property	Data/Value
IUPAC Name	2-(phosphonomethylamino) acetic acid
Molecular Formula	C <sub>3</sub> H <sub>8</sub> NO <sub>3</sub> P
Structure	zwitterion (pure)
Chemical class	Pesticides → Herbicides, Other
Odor/Color/Form	odorless white powder
Decomposition	488.15 K (darkens)
Melting point	503.15 K
pH (1 wt. % solution in water)	2.5
Solubility in water (298.15 K)	1.2 g L <sup>-1</sup>
Volatility (298.15 K)	negligible
Density	1.74 g cm <sup>-3</sup>
Vapor pressure	1.94 × 10 <sup>-7</sup> mm Hg at 318.15 K
Dissociation constants (see a)	pKa <sub>1</sub> = 2.34 (293.15 K); pKa <sub>2</sub> = 5.73 (293.15 K); pKa <sub>3</sub> = 10.2 (298.15 K)

155

156 Figure 2. a) Structural formula of glyphosate (ANVISA 2020); b) Overview of physical properties of  
 157 glyphosate.

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### 3 Glyphosate uses: consumption of agrotoxins and glyphosate in Brazil

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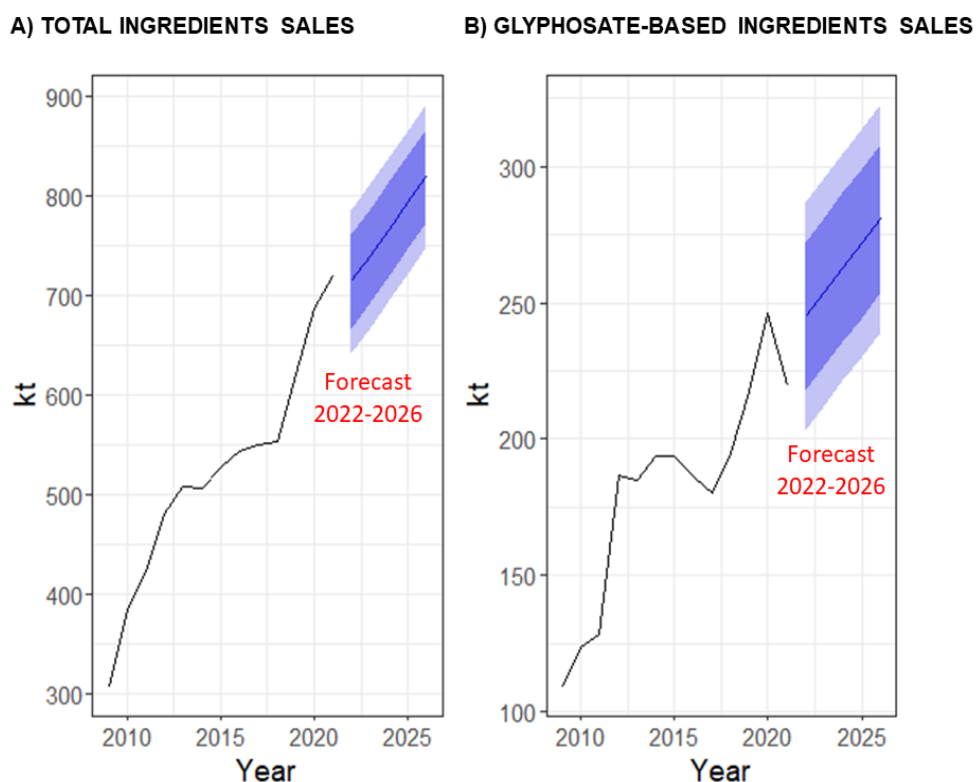
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Fig. 3a shows a dramatic increase in the consumption of agrotoxins from 2006, reaching the mark of 719 thousand tons of active ingredients in 2021. Between the years 2002 and 2021, the consumption has been multiplied by about 4, from 145 thousand tons to 719 thousand tons of active ingredients. This figure also shows the forecast of agrotoxin consumption in Brazil for the years 2022 and 2026, considering the period 2009-2021. For the forecast of this time series, the Holt's two-parameter model, also known as linear exponential smoothing, was used as these data show a temporal trend but no seasonal pattern (See Table S1 for the model parameters). Forecasting was done using the R language in open source software RStudio, where the "holt" function from the "forecast" package was employed (Hyndman et al. 2022).

178



179

180 Figure 3. Forecast of the production of agrototoxin sales in Brazil from 2022 to 2026: (a) total ingredients  
 181 sales; (b) sales of glyphosate active ingredients only (data from IBAMA 2022).

182

183

184 Fig 3b shows the sale of glyphosate in Brazil from 2009 to 2021. It can be seen that in 2012,  
 185 almost 187 thousand tons of glyphosate active ingredient were sold, 46% more than the 128 thousand  
 186 tons sold in 2011. From 2009 to 2021, the sales of the product in Brazil have been multiplied by about 2.  
 187 In 2009, there were 109 thousand tons and in 2021, 219 thousand tons. Glyphosate-based products were  
 188 by far the most sold active ingredients in Brazil in the latest 2022 report, followed by 2,4-D with 62  
 189 thousand tons, which highlights the importance of glyphosate in Brazil (IBAMA 2022). Fig. 3b also  
 190 shows the forecast of the consumption of glyphosate-based ingredients in Brazil from 2021 to 2026,  
 191 considering the period 2009-2020. The Holt's two-parameter model was applied for the same reasons and  
 using the procedures detailed above.

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The increase in the sale of glyphosate is primarily due to the growth of transgenic products -  
 soybeans, corn and cotton. Over the past 20 years, transgenic plants have been genetically modified to  
 obtain two characteristics. The first is the biosynthesis of insecticidal toxins found in plants called  
*Bacillus thuringiensis* (Bt). When a caterpillar or larva feeds on soybeans, cotton or corn roots (mainly Bt  
 corn), it ingests these toxins and dies. The second characteristic is the modification of the plants'

197 metabolic pathways: called herbicide-tolerant (HT) plants, these plants are highly resistant to glyphosate  
198 application (Benbrook 2018). Due to genetic deliberate modification, their seeds have become more  
199 resistant to glyphosate, and in order to improve productivity and increase farm profit, producers have  
200 considered glyphosate as one of the best solutions to achieve their goals. Currently, almost 92% of the  
201 soybeans produced in Brazil are transgenic and cover an area of 57.2 million hectares (Medina 2022), i.e.,  
202 more than countries such as France, Spain or Germany. With such a large area, total control of the crop is  
203 particularly difficult and may result in an earlier harvest. Some concerns are related to: (i) the need to dry  
204 some crops for harvest (e.g. beans, wheat and oats); (ii) the unpredictable nature of the weather; and (iii)  
205 the control of late-season weeds that escape further control steps (Benbrook 2016, 2018). When faced  
206 with an unexpected event, glyphosate is used as a desiccant to standardize the operation and harvest.  
207 Another reason that stimulated the sale of glyphosate was the expiration of Monsanto's patent in 2000,  
208 offering other companies the possibility to produce agrottoxins with glyphosate, which led to a more  
209 competitive market. These factors stimulated the consumption of glyphosate in Brazil, without revealing  
210 its impacts on human health (ABRASCO 2019).

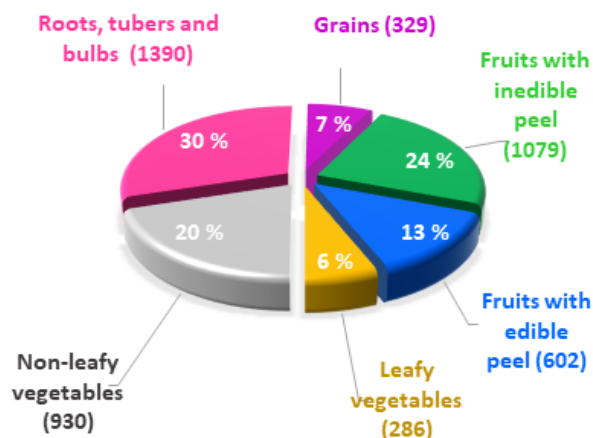
### 211 *3.1 Contamination of food by agrottoxins*

212 Accidents involving agrottoxins occur worldwide, such as those related to the ingestion of contaminated  
213 food. Contamination through ingestion can occur due to the excessive use of agrottoxins in agriculture and  
214 the failure to respect the degradation time of the product (ANVISA 2020), as well as the accumulation of  
215 agrottoxins in the food chain, such as organochlorines (Jayaraj et al. 2016). In Brazil, however, a new  
216 study coordinated by ANVISA has shown that contaminated vegetable food is safe for human  
217 consumption. Between 2017 and 2018, PARA analyzed more than 4,616 samples from 14 different foods  
218 that represent 30.86% of the food on consumers' tables (Table S2) (ANVISA 2019d).

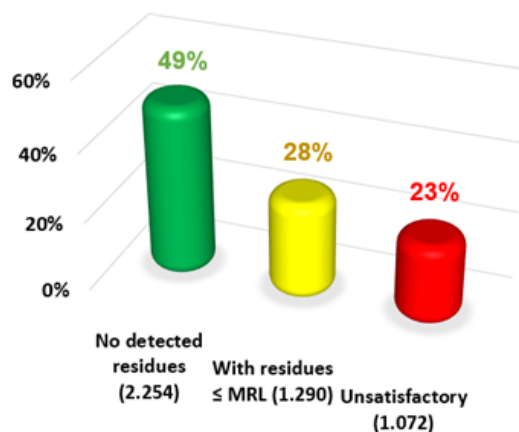
219 Of a total of 4616 samples, 7% were cereals, 24% were fruits with inedible skins, 13% were  
220 fruits with edible skins, 6% were leafy vegetables, 20% were non-leafy vegetables, and 30% were roots,  
221 tubers and bulbs (**Erreur ! Source du renvoi introuvable.**). In 49% of these samples, there were no  
222 residues, 28% presented acceptable MRL concentrations, and 23% were considered unsatisfactory. This  
223 means that 77% of the samples were satisfactory (**Erreur ! Source du renvoi introuvable.**).

224

## A) FOOD TYPES

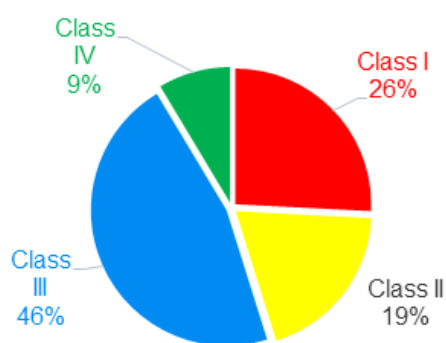


## B) SAMPLES DISTRIBUTION

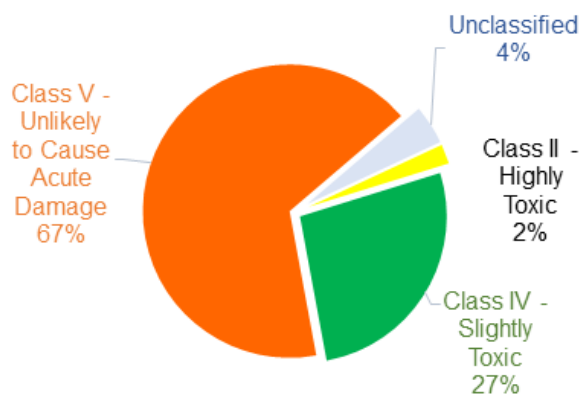


## C) TOXICOLOGICAL CLASSIFICATION

### BEFORE 2019



### AFTER 2019



225  
 226 Figure 4. a) Distribution of samples per food type: figures in parentheses are the numbers of samples per  
 227 food type; b) Distribution of results obtained from 4,616 samples monitored during the 2017/2018 cycle  
 228 of the 2017-2020 Multi-Year Plan. Report of the analyzed samples of 2017-2018 (ANVISA 2019d); c)  
 229 Toxicological classification of glyphosate-based herbicides (DIÁRIO OFICIAL DA UNIÃO 2019).  
 230 Classes I and III are not shown in GLYPHOSATE AFTER 2019 because no glyphosate-based ingredient  
 231 is classified in these categories.  
 232

### 233 3.2 Toxicological re-evaluation of glyphosate

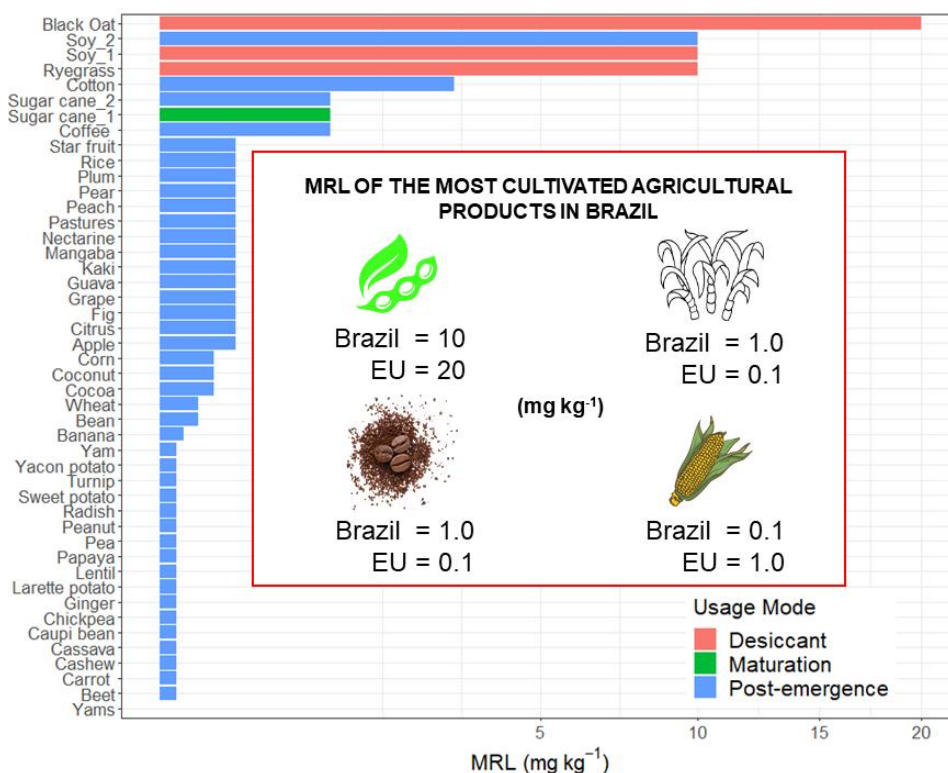
234 In several countries, especially those in the EU, the use of glyphosate is rejected by governments and  
 235 health organizations due to its link to diseases such as cancer. Unlike other countries, Brazil not only  
 236 renewed the sale of glyphosate but also reduced the toxicity classification in 2019. ANVISA reclassified  
 237 all 24 glyphosate-based products from Class I "Extremely Toxic" to Class V "Product Unlikely to Cause  
 238 Acute Damage" (Fig. 4c) (DIÁRIO OFICIAL DA UNIÃO 2019). Thus, no glyphosate product in Brazil  
 239 is now considered to have maximum toxicity.

240 The glyphosate packaging used to alert that the product may affect the cornea is now sold in the  
241 same way as a household product. Thus, only pesticides that cause death by ingestion or damage by  
242 contact with the skin and eyes now have a display corresponding to a maximum alert (de Ulysséa Leal  
243 and da Silva Lopes 2021). These measures will mainly affect the people handling the products, who  
244 usually see the degree of toxicity on the label. Initially, the label included a skull and crossbones symbol,  
245 but now it only includes a warning to be careful not to ingest or come in contact with the eyes or skin  
246 (Disner et al. 2021).

247 Politics directly affects regulatory agencies, which obviously also apply to the case of Brazil.  
248 Given that Brazil exports a plethora of commodities, and even though these agencies should be  
249 independent and in the public interest, organizations such as ANVISA are under constant pressure,  
250 especially from the regulated sector and the parliament (Nunes et al. 2021). Political interference also  
251 leads to the loss and extinction of councils such as the National Council of Nutrition and Food Safety  
252 (CONSEA) (Castro 2019). This change in toxicological classification can have an immediate impact on  
253 increasing the risk to workers' health.

### 254 *3.3 Maximum residues limit for glyphosate*

255 MRL levels are contrasting around the world. This means that exported products exceeding MRLs may  
256 be acquired with insufficient sampling or even below regulatory values (Handford et al. 2012). Countries  
257 that do not have an implicit MRL can use the acceptable MRL for human consumption, established by the  
258 Codex Alimentarius Commission (CAC), a subsidiary group of the Food and Agriculture Organization  
259 (FAO), and the World Health Organization (WHO). In the Brazilian legislation, the MRL for glyphosate  
260 is established by ANVISA; its values and the security breaks are in Table S3 (ANVISA 2020). As can be  
261 seen in Fig. 5, there are significant differences between crops. Examples of contrasting data include  
262 peanut (MRL = 0.01 mg kg<sup>-1</sup>) and black oat (MRL = 20 mg kg<sup>-1</sup>). It should be noted that some crops  
263 could be easily grouped together due to their similar MRL values. Conversely, two groups clearly stand  
264 out. Soybean, ryegrass, and black oat crops received significantly higher MRL values compared to most  
265 crops. Fig. 5 highlights that, compared to the MRL established by the EU, the Brazilian regulations are  
266 more stringent for soybean and corn, but less for sugarcane and coffee.



267

268 Figure 5. Maximum Residue Limits (MRL) in several crops. The different numbers given to soy and  
 269 sugar represent their application in different usage modes, shown as orange bars for desiccant, blue bars  
 270 for post-emergence, and green bar for maturation. EU stands for European Union, and the data were  
 271 obtained from the European Commission website (European Commission 2022). The insert gives the  
 272 MRLs in the EU and Brazil for the four most cultivated agricultural products in Brazil.

273

274

In 2015 and based on studies, IARC classified glyphosate as “Probably carcinogenic to  
 275 humans”, which places it in Group 2A. The other classification groups defined by IARC are Group 1  
 276 (“Carcinogenic to humans”), Group 2B (“Possibly carcinogenic to humans”) and Group 3 (“Not  
 277 classifiable as to its carcinogenicity to humans”) (International Agency for Research on Cancer 2013,  
 278 2021). However, neither the studies conducted by the EU nor the assessment made by the joint  
 279 WHO/FAO validated the IARC classification (Tarazona et al. 2017). Although glyphosate was not the  
 280 first matter of debate between IARC and the agencies, a great deal of attention has been paid to this topic.  
 281 In February 2019 and after 11 years of study, ANVISA concluded that glyphosate "does not fall within  
 282 the prohibitive criteria of Brazilian law". Thus, the product is not classified as carcinogenic, mutagenic,  
 283 toxic to reproduction or teratogenic, i.e., causing fetal malformation. It should be noted that the MRLs for  
 284 glyphosate allowed in clean water vary considerably by country or region. For example, in the EU they  
 285 are 0.1  $\mu\text{g L}^{-1}$ , in Brazil 65  $\mu\text{g L}^{-1}$ , and in the United States 700  $\mu\text{g L}^{-1}$  (Tiago et al. 2020).

286

287

From a chronic perspective, glyphosate was not considered a carcinogen until the IARC results  
 were published in 2015 (IHU 2019). This finding caused controversy and discussion, as regulatory

288 agencies took a stand against the IARC results, stating that they did not see this carcinogenicity attributed  
289 to glyphosate. It should be mentioned that IARC is an agency that studies and evaluates cancer issues and  
290 is not a regulatory agency, as is ANVISA in Brazil. Even with the opposing position of the regulatory  
291 agencies, IARC has taken into account its own studies about the chronic effects of glyphosate. IARC is  
292 not alone in this position, and studies have found a link between glyphosate exposure and non-Hodgkin's  
293 lymphoma (Leon et al. 2019; Myers et al. 2016; Zhang et al. 2019), in addition to acute myeloid leukemia  
294 (Cavalier et al. 2023).

295         Although some regulatory agencies claim that glyphosate is safe, some European countries have  
296 already banned or reduced the use of glyphosate, such as Italy, Spain, the Netherlands and Portugal, and  
297 others are in the process of withdrawing it from trade, such as France and Germany (Brovini et al. 2021).  
298 In the case of the European Union, glyphosate is currently allowed in agricultural activities until  
299 December 15, 2022 (European Food State Authority 2022). After this deadline, it will be necessary to  
300 obtain authorization from national authorities after a safety assessment has been carried out. The late ban  
301 on glyphosate may be due to the lack of other effective alternatives, particularly in no-till/conservation  
302 agriculture, which will face tough challenges in controlling weeds and abandoning cover crops (Kudsk  
303 and Mathiassen 2020). Moreover, the reduced availability of glyphosate will require more difficult and  
304 costly weed managements, in addition to incorporating multiple weed control techniques (Fogliatto et al.  
305 2020).

### 306 *3.4 Acceptable Daily Intake of glyphosate*

307 According to RDC number 10/2018, the ADI for glyphosate is 0.042 mg per kg of body weight (b.w.)  
308 day<sup>-1</sup> (ANVISA 2019e). However, this value is not consistent with those defined internationally, and  
309 there are no reference studies supporting the determined value. Hence, to define an ADI value, ANVISA  
310 considered international studies and discussions on the topic. The calculation of the new ADI for  
311 glyphosate was based on the "No Observed Adverse Effect Level" (NOAEL) of 50 mg kg b.w.<sup>-1</sup> day<sup>-1</sup>. In  
312 this way, respecting the security factor of 100, the new ADI is 0.5 mg kg b.w.<sup>-1</sup> day for glyphosate  
313 (ANVISA 2019e). ANVISA determined, after evaluating the studies of international regulatory agencies,  
314 the reference parameters for assessing the risk from glyphosate (DIÁRIO OFICIAL DA UNIÃO 2020):

- 315         • ADI of 0.5 mg kg b.w.<sup>-1</sup> day<sup>-1</sup>;
- 316         • ARfD of 0.5 mg kg b.w.<sup>-1</sup> day<sup>-1</sup> and

317       • Acceptable Operator Exposure Level (AOEL) of  $0.1 \text{ mg kg b.w.}^{-1} \text{ day}^{-1}$

318               With these values, the acute and chronic dietary risk assessment for glyphosate shows a safe  
319 level of exposure, without exceeding the acute and chronic reference doses, also encompassing residues  
320 in food and water (ANVISA 2019f).



## 321        4    **Adverse effects: possible risks of glyphosate to human health**

### 322    *4.1 Handling of glyphosate in agriculture*

323    The relationship between glyphosate used in agriculture and human health impacts has been a topic of  
324    study worldwide. Although there is still much to study, investigations show that accidents and deaths  
325    caused by agrottoxins are more common among rural workers and other professionals who handle the  
326    substance (Buckley et al. 2021; Gunnell et al. 2017; Hendges et al. 2019; Nankongnab et al. 2020).  
327    Londres pointed out that not only these groups endure the risks associated with this activity, but also their  
328    families. The author emphasized that contact with the pesticide during the washing of clothes used in  
329    such activities, for which no care is normally taken, is particularly critical (Londres 2011).

330            Curwin et al., (2005) investigated agricultural pesticide contamination in 50 households in Iowa,  
331    USA. The authors found the presence of 1,300 ng g<sup>-1</sup> of glyphosate in dust samples collected in farm  
332    houses that sprayed glyphosate within 7 days. In case of farm houses with no spray use in this period and  
333    nonfarm, the values were 1,000 ng g<sup>-1</sup> and 110 ng g<sup>-1</sup>, respectively. On the other hand, Curwin et al.,  
334    (2007) studied pesticide dose estimated for children in the same state. According to these authors, the  
335    highest estimated dose for glyphosate was 0.34 µg kg<sup>-1</sup> per day, not exceeding any of the United States  
336    Environmental Protection Agency (EPA) reference values for this pesticide.

337            Pesticide poisoning is responsible for more than 150,000 deaths per year worldwide, the  
338    majority of which are considered self-poisoning by ingestion and fewer cases related to topical or  
339    inhalation exposures when linked to occupational and accidental events (Eddleston 2020). In the case of  
340    Brazil, this number was around 4,000 Nascimento et al., (2020) showed that there has been a significant  
341    increase in agricultural poisonings in Brazil between 2007 and 2017, particularly in the South and  
342    Southeast regions. There was a considerable increase in the year 2013 and a decrease in the years 2014 to  
343    2016. However, the number of poisonings increased again in 2017, reaching the highest rate of  
344    poisonings in history, with more than 5,000 cases in Brazil, the South region having the highest growth  
345    that year compared to the others. The increase in agricultural poisoning cases can be associated with the  
346    dramatic growth in planted and cultivated area in Brazil between 2007 and 2017. This shows that there is  
347    a correlation between productivity, pesticide use and poisonings. However, the average poisoning was  
348    higher than the average planted and cultivated area, suggesting that other factors may have influenced the  
349    increase in poisonings in the country (Nascimento et al. 2020). Studies from the National System of

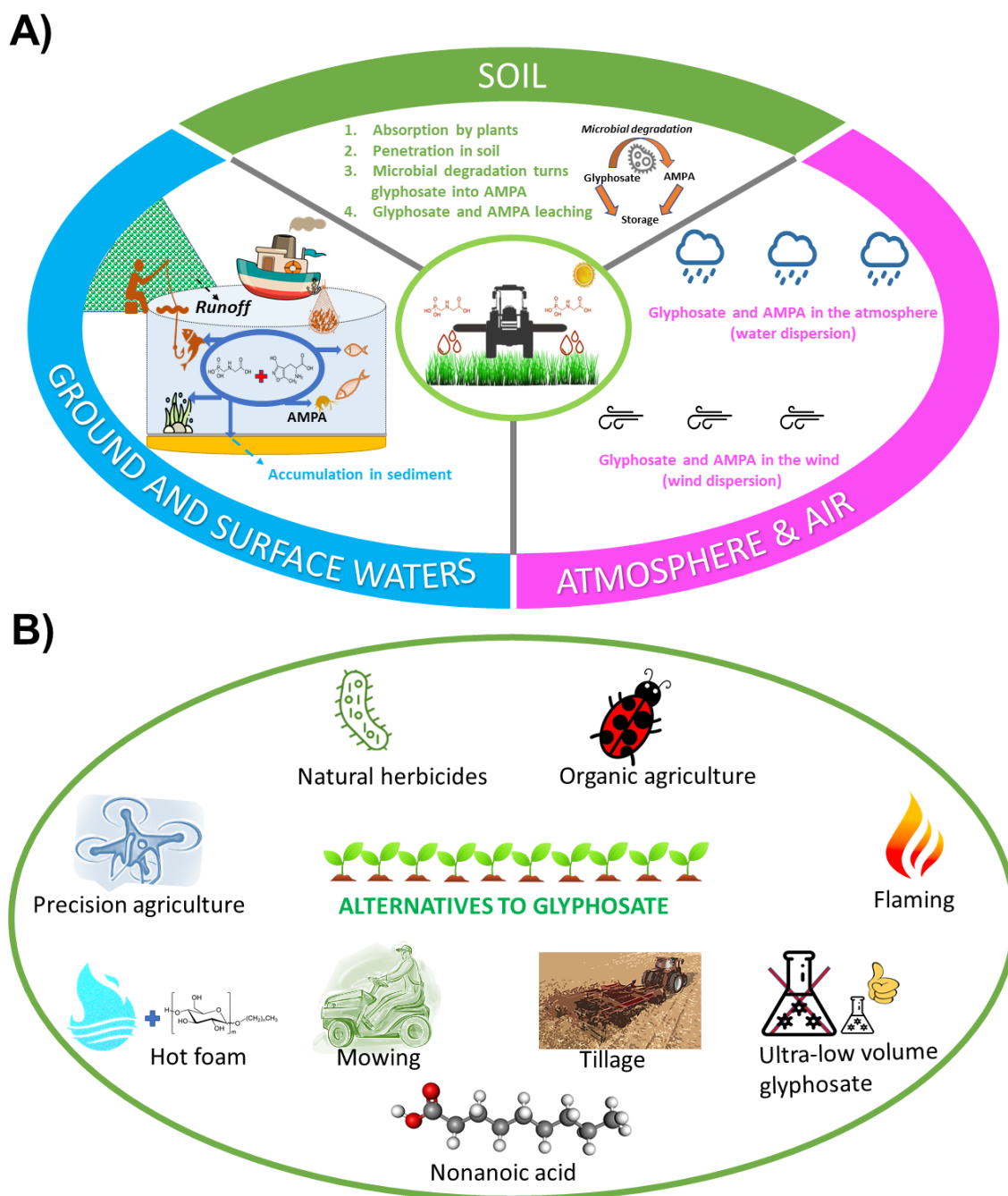
350 Toxicopharmacological Information (SINITOX) highlight that 61 workers died from agrottoxins  
351 (SINITOX 2017a) in Brazil in 2017. The use of agrottoxins is increasing in Brazil (see again Figure 3) and  
352 tends to continue to grow due to the agricultural model adopted in the country, through mechanization,  
353 fertilizers, and agrottoxins (SINITOX 2017b).

#### 354 **4.2 From soil to water contamination**

355 One of the most undesirable environmental impacts is the contamination of underground and surface  
356 water by agrottoxins. Avoiding contamination is extremely important for human health. If a water source  
357 responsible for supplying a city is close to an agricultural area that uses agrottoxins and does not follow  
358 the recommendations made to growers, or uses more than the permitted amount and does not properly  
359 dispose of the packaging, it can harm water quality, affecting millions of people, wildlife and domestic  
360 animals. Despite this concern, there is a lack of official monitoring of pesticide cocktails in the  
361 environment, in addition to limited research on this topic (PESTICIDE ACTION NETWORK UK 2019).

362 The stability of glyphosate in soil is given by the wide range of its soil sorption coefficient ( $K_{oc} =$   
363  $9\text{--}60,000 \text{ L kg}^{-1}$ ), where  $K_{oc}$  stands for the normalized partition coefficient between organic carbon and  
364 water (Giesy et al. 2000; Mackay et al. 2006; Pandey and Roy 2021). In other words,  $K_{oc}$  is defined by the  
365 propensity of a chemical to attach to soils, and also takes into account the correction for organic carbon  
366 content. pH plays an important role such that the sorption coefficient varies with soil pH, which is in the  
367 range 3.5–7.5 (Mackay et al. 2006). Villamar-Ayala et al. (2019) highlighted that the concentration of tri-  
368 and divalent cations, such as  $\text{Cu}^{2+}$ ,  $\text{Al}^{3+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Fe}^{3+}$ ,  $\text{Mn}^{2+}$ ,  $\text{Ni}^{2+}$  is also important, but no difference was  
369 observed between different soil types and organic matter contents. These authors also mentioned that clay  
370 minerals are responsible for the sorption of glyphosate in soil, which is enhanced at low pH and low  
371 organic matter content. Therefore, the amount of glyphosate adsorbed by the soil may vary significantly.  
372 According to De Amarante Junior et al., (2002), the degradation of glyphosate in soil can follow two  
373 routes: (i) the alteration of glyphosate to sarcosine resulting from bacteria (*Agrobacterium radiobacter* or  
374 *Enterobacter aerogenes*; enzyme C-P lyase) that enter the metabolism of microorganisms; and (ii) the  
375 transformation of glyphosate to AMPA. These mechanisms are presented in Fig. S1. One of the issues of  
376 the presence of pesticides in soil was assessed by Kenko et al., (2023), who demonstrated that glyphosate  
377 is among the high-risk pesticides for earthworms, resulting in significant risk to the terrestrial biota.

378           Although some consider glyphosate to be rapidly absorbed by soil, making it difficult to  
379 contaminate underground water, it can percolate through soil porosity (Laitinen et al. 2006) or can be  
380 moved to water due to runoff (Feng et al. 2020) (Fig. 6a). According to Tsui and Chu (2003), most  
381 glyphosate reaches surface water bodies, i.e., 52%. Recently, Geng et al. (2021) studied the presence of  
382 two herbicides: glyphosate and glufosinate ammonium, and the main metabolite of glyphosate,  
383 aminomethylphosphonic acid, in agricultural groundwater and surface water in China from 2017 to 2018.  
384 These authors noted that several of these contaminants have been detected worldwide, with glyphosate  
385 concentrations in groundwater ranging from 0.025 to 25  $\mu\text{g L}^{-1}$ .  
386



387

388 Figure 6. a) Environmental pollution by glyphosate; b) alternatives to glyphosate reported in the  
389 literature.

390

391

392 Glyphosate is soluble in water ( $10\text{-}15.7\text{ g L}^{-1}$  at  $25\text{ }^{\circ}\text{C}$ ) (Sylwestrzak et al. 2021) and its  
393 commercial formulation uses surfactants to further increase its solubility (Solomon and Thompson 2003;  
394 Tsui and Chu 2003). Its half-life in aqueous media is 63 to 70 days, depending on whether it is in shallow  
395 or pond water (Villamar-Ayala et al. 2019). Glyphosate is typically found at concentrations below  $2\text{ g mL}^{-1}$   
396 and at a neutral pH, about 7.2. Villamar-Ayala et al. (2019) pointed out that the presence of  
glyphosate depends on a multitude of conditions. For instance, when spraying in dry weather and

397 temperatures between 6 and 20 °C, glyphosate may not evaporate and remain suspended in dust particles  
398 for up to 3 days after application.

399 Another source of water contamination is related to industrial effluents, including those from  
400 glyphosate synthesis industries and textile activities (Feng et al. 2020). In the latter case, glyphosate is  
401 used as a raw material for textile additives. Feng et al., (2020) highlighted that glyphosate, although  
402 highly recovered by nanofiltration systems, is of concern due to the high concentrations found in  
403 nanofiltration permeate wastewater, up to 3000 mg L<sup>-1</sup>. Fernandes et al. (2019) and de Castro Lima et al.  
404 (2020) showed that so-called modern agriculture contaminates rivers with pesticides in southern Brazil,  
405 especially the Guaporé River and its tributaries, such as the Marau River. Samples collected from the  
406 epilithic biofilm of the Guaporé River basin showed a concentration of 10 to 305 µg kg<sup>-1</sup> of glyphosate  
407 and a concentration of 50 to 670 µg kg<sup>-1</sup> of AMPA. In general, herbicide use begins in June, with the  
408 preparation of areas for wheat sowing, and extends to January, with the end of the soybean and corn  
409 sowing period. The peak application period is between October and January. Due to the indiscriminate  
410 use of herbicides in the urban area, the most affected areas are those located in the Marau sub-basin. This  
411 indicates that there is an uncontrolled application of glyphosate in the city of Marau and poses a problem  
412 for human and animal health. This problem is due to the fact that the river water is the source of supply  
413 for this city and glyphosate is a product of health concern (de Castro Lima et al. 2020).

414

#### 415 *4.3 Intake of foods containing glyphosate residues*

416 An FAO study highlighted that food containing glyphosate and AMPA residues can be of concern and  
417 toxic if the ADI is above the permitted level (Bai and Ogbourne 2016; FAO/WHO 2005). However, the  
418 established acceptable levels of MRL and ADI are controversial, as there are discrepancies among  
419 researchers. On the one hand, theoretical risks suggest that current MRLs should be distrusted, as they  
420 may result in greater health risks than predicted by conservative methods (Guo and Li 2021). On the other  
421 hand, for others, glyphosate presence and exposure in food has been detected in samples meeting  
422 regulatory criteria, i.e., below the MRL (Bou-Mitri et al. 2022; Zoller et al. 2018). Mielech et al., (2021)  
423 studied the risk of contamination from ingested food for infants and young children. These authors  
424 highlighted that for these groups, it is important to reduce the negative effects of contaminants by  
425 avoiding potentially hazardous foods, modifying the diet, and choosing the most appropriate meal

426 preparation methods. This is because these groups have higher resting metabolic rates, which is  
427 considered potentially critical with respect to toxin susceptibility (Mielech et al. 2021).

428         On the one hand, for many experts, there is no safe contamination level. On the other hand, for  
429 others, it is crucial to set limits to minimize the risk of poisoning. Residue levels may exceed the  
430 allowable limit when the dosage for product application does not follow label recommendations and  
431 instructions (Londres 2011). Unfortunately, to intensify the effect of the product on pests, growers apply  
432 more than recommended, either by the amount per hectare or by the number of applications. According to  
433 Londres, (2011), these attitudes, as well as failure to observe the period after product application, result in  
434 higher than allowed levels in food. Gélinas et al., (2018) emphasized that using the manufacturer's  
435 recommended level does not guarantee that the MRL will be lower than the values set by regulation,  
436 pointing to a case study in which glyphosate residues in wheat were above the Canadian regulation. One  
437 possible reason for these undesirable outcomes is that there are few studies on the effect of processing on  
438 glyphosate residues in cereals (Xu et al. 2019). According to Xu et al., (2019), more research is needed to  
439 understand the health issues associated with glyphosate exposure and consumption. These authors also  
440 stressed the importance of having more information on glyphosate degradation during grain storage and  
441 long-term safety.

442         In contrast to the 2015 IARC study that indicated glyphosate is possibly carcinogenic to humans,  
443 classifying it as Group 2A, the European Food Safety Authority (EFSA) classified glyphosate as neither  
444 carcinogenic nor toxic in 2017, if levels are low (EFSA 2017; Tarazona et al. 2017). In February 2019,  
445 research revealed that glyphosate increases by 41% the chance that a person exposed to it will develop  
446 non-Hodgkin's lymphoma, a type of cancer (Zhang et al. 2019). On the other hand, EPA concluded that  
447 glyphosate is not carcinogenic to humans in April 2019 and, in a temporary decision in January 2020,  
448 reaffirmed that glyphosate is not carcinogenic and poses no risk to human health when used according to  
449 the recommendations described in the product labels and instructions (Environmental Protection Agency  
450 2020). Clinical symptoms of acute poisoning include nausea, vomiting, and abdominal pain (Eddleston  
451 2020). As chronic effects, the most important are carcinogenic, neurological, developmental,  
452 reproductive, immunological and cardiovascular effects (Anakwue 2019). Considerable literature has  
453 recently been published on the toxic effects of agROTOXIN use, such as acute (Chefirat et al. 2021; Sinha et  
454 al. 2021), and chronic (Mohamed et al. 2022; Sule et al. 2022).

455

## 456 5 Alternatives to glyphosate

457 It is not easy to replace an effective and inexpensive herbicide. Moreover, glyphosate is used worldwide  
458 in different crops, geographical, environmental and climatic zones. Its applicability changes from hot and  
459 tropical areas to the coldest and most icy areas, yet it is a low-cost and highly effective weed control  
460 product. According to Torretta et al., (2018), the best path forward is not to think about developing a less  
461 harmful synthetic chemical molecule to replace glyphosate, but to change the type of agriculture and  
462 develop new farming techniques to manage unwanted pests. Among the alternatives, a few methods stand  
463 out (Fig. 6b): precision agriculture (Caratelli et al. 2022), natural herbicides (Crmaric et al. 2018), organic  
464 agriculture (Żelazny and Licznar-Małańczuk 2018), ultra-low volume glyphosate (Craig et al. 2014),  
465 flaming (Pergher et al. 2019), hot foam using alkyl polyglucoside (Martelloni et al. 2019) and nonanoic  
466 acid (Webber et al. 2014).

467

### 468 *5.1 Precision agriculture*

469 Large companies with financial resources are investing in precision agriculture (PA), using modern  
470 machinery, sensors, maps, video cameras, geographic information systems, autopilots, variable-rate  
471 sowers, light bars, drones, satellite monitoring, GPS and other resources (R. Finger et al. 2019; Monteiro  
472 et al. 2021). After mapping an area, fertilizer, agrototoxin and irrigation can be dosed according to the need  
473 of each specific point in the field (R. Finger et al. 2019; Nawar et al. 2017).

474 PA improves productivity and reduces costs of feedstock, agrototoxins, labor, and crop waste,  
475 while helping the farmer make a better decision in the treated area and still contributing to environmental  
476 protection. Meanwhile, due to the lack of methodologies and sensors capable of identifying the  
477 application of agrototoxins in a practical, accurate and real-time manner, weed control is still done  
478 manually. Another problem is that the development and operation of PA techniques are complex and  
479 involve multiple steps, in addition to requiring improvements to achieve commercial development  
480 (Monteiro et al. 2021). Due to the production cost, PA would only be economically viable in special cases  
481 (Inamasu and Bernardi 2013).

482

### 483 *5.2 Natural herbicides*

484 In 2019, researchers discovered a natural alternative to glyphosate (Brilisauer et al. 2019). It is a sugar  
485 molecule with the scientific name: 7-deoxy-sedoheptulose (7dSh) synthesized from the cyanobacterium  
486 *Synechococcus elongatus*. This substance inhibits the growth of several microorganisms, fungi and plants,  
487 as well as bacteria and yeasts, but it is harmless to animals and humans.

488 In brief, the details of the experiment performed with *Arabidopsis thaliana* seedlings are as  
489 follows.

490 (1) Morphological appearance of the plant 7 days after germination: the seedlings were  
491 cultivated in agar plates, under constant light and without 7dSh or glyphosate. The agar plates  
492 were set up and illuminated from above. The root and apical meristem of the plant were  
493 investigated. The authors also compared the seedlings that received glyphosate and 7dSh. The  
494 latter was more effective than glyphosate in inhibiting plant growth.

495 (2) Measurements of the distance between the root and the apical meristem of the plant  
496 were also presented by the authors. There was a significant difference between the sizes of the  
497 seedlings analyzed.

498 (3) The effect of glyphosate and 7dSh (with 260  $\mu\text{m}$  per seeding) on plant growth in soil  
499 after 18 days in a day/night cycle was also of interest. In this case, the authors found that  
500 seedling weight was significantly reduced after 7dSh and glyphosate treatments compared to the  
501 control. Moreover, the inhibitory effect of 7dSh was found to be notably greater than that of  
502 glyphosate.

503 For more details on the antimetabolites of the cyanobacterium "7dSh" in inhibiting the growth of  
504 microorganisms, one can refer to Brilisauer et al., (2019).

505 Experiments revealed that 7dSh blocks an enzyme of the shikimate pathway,  
506 dehydroquinate synthase (DHQS). Until now, the best known inhibitor was glyphosate. Initial  
507 investigations have shown that 7dsh is harmless to humans and animals. In addition, to test the effect of  
508 7dSh on aquatic organisms, the researchers exposed zebrafish embryos to the substance, which again  
509 proved to be harmless. Another key point reported by the researchers is that cyanobacteria have been  
510 producing this substance for millions of years without affecting the environment. The researchers state  
511 that, although there are no large-scale experiments with animals and further investigation is still needed,



512 7dSh should be considered a promising discovery and opportunity as a natural herbicide (Bioeconomy  
513 BW 2019; Brilisauer et al. 2019).

514 Nevertheless, some drawbacks associated with the use of 7dSH have been observed, such as the  
515 accumulation of 3-deoxy-d-arabino-heptulosonate-7-phosphate (Dayan et al. 2015). This compound is the  
516 substrate for 3-dehydroquinate synthase. In the case of glyphosate, rapid accumulation of shikimate was  
517 observed, which is a well-known biomarker of 5-enolpyruvylshikimate 3-phosphate synthase inhibition  
518 (Dayan et al. 2015). As a result of the mechanisms involved on the application of 7dSh on plants, reduced  
519 levels of tyrosine, phenylalanine and tryptophan (free aromatic amino acids) were noticed. According to  
520 Dayan (2019), the lower levels of these compounds are credited with impeding the biosynthesis of  
521 additional amino acids. As a result, branched-chain amino acids, including valine, leucine and isoleucine  
522 are accumulated, in addition to arginine. According to these authors, although 7dSh has not pre-  
523 emergence activity, its mixture with an adjuvant was effective in controlling *Abutilon theophrasti* in a  
524 post-emergence scenario. The rate used was 2 kg ha<sup>-1</sup>. However, no activity on *Setaria viridis* was found,  
525 implying selectivity.

### 526 **5.3 Organic agriculture**

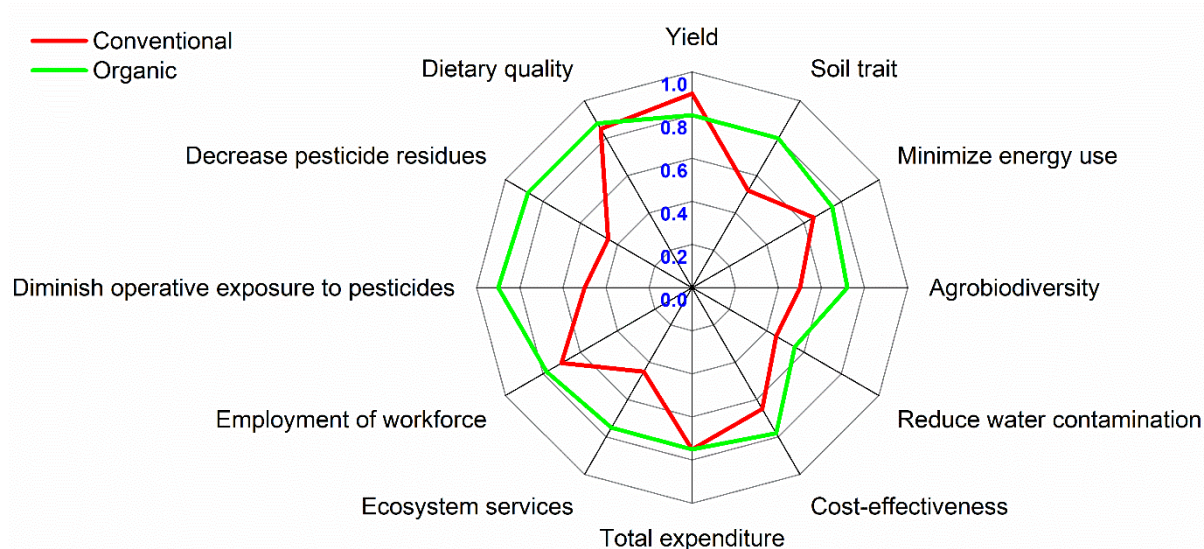
527 Organic agriculture (agricultura orgânica, in Brazil) is the most widely used term in Brazil. However,  
528 other terms are used to refer to products and methods of non-conventional agriculture, such as  
529 "alternative agriculture", "biological agriculture", "biodynamic agriculture", "organic-biological  
530 agriculture", "organic-regenerative agriculture", "natural agriculture", "ecologic agriculture", and others.  
531 All of these terminologies have similar purposes and techniques, which differ from current industrial  
532 chemical methods (Peixoto et al. 1995). Organic agriculture represents the ecological production  
533 management system in which biodiversity, biological cycles and soil productivity are stimulated. It is  
534 based on the reduction of synthetic materials, chemical feedstock, and especially agrottoxins. The main  
535 goal of organic agriculture is to preserve the well-being of ecosystems, humans and soils. While  
536 conventional agriculture uses synthetic pesticides and fertilizers, organic agriculture uses only natural  
537 products, such as pyrethrin, a pesticide found in the chrysanthemum flower, although its safety is still  
538 debated (Demeneix et al. 2020). Organic agriculture uses the natural environment to increase productivity  
539 by using some sustainable measures, such as: inserting natural insect predators (Headrick 2021), planting  
540 vegetables to add nitrogen to the soil (Martinez et al. 2021), crop rotation to confuse pests and renew the  
541 soil (Shah et al. 2021), organic and natural materials such as potassium bicarbonate (Sehsah et al. 2022;

542 Türkkan et al. 2018), and covers to control weeds and pests (Rowen et al. 2022). Organic agriculture does  
543 not use seed or animals that have been genetically modified (Naika et al. 2006).

544 In 1999, this agriculture occupied an area of 15 million of hectares in the world. In 2020, it was  
545 already 74.8 million hectares, i.e., a fivefold increase; half of this area is in Oceania, 23% in Europe,  
546 13.3% in Latin America, 8.2% in Asia, 5% in North America and 2.8% in Africa (FiBL 2022). Despite  
547 the spectacular growth of this area, it occupied only 1.6% of the world's agricultural surface in 2020.  
548 Brazil has 1.3 million hectares, making it one of the countries with the largest organic production areas  
549 (FiBL 2022). However, the share of organic production is only 0.6%, despite a growth of 92.0% in the  
550 last 10 years. According to the FiBL report, Brazil has the largest number of organic beehives, about  
551 630,000 (FiBL 2022). As of April 2022, according to MAPA's National Register of Organic Products,  
552 there are approximately 30,000 certified organic productions in Brazil (MAPA - Ministério da  
553 Agricultura 2022). However, this figure represents only certified producers and it is possible that this  
554 number is much higher when considering non-certified producers according to Vilpoux et al., (2021).  
555 This is possible given the difficulties producers face in certifying and renewing their organic products  
556 (Scalco et al. 2017).

557 Fig. 7 shows some of the differences observed in the comparison between conventional and  
558 organic agriculture. Organic agriculture has much better overall features compared to conventional  
559 agriculture for the selected benefits. While organic agriculture is more virtuous in terms of pesticide  
560 residues, worker exposure to pesticides, ecosystem services and soil traits, conventional agriculture has  
561 better yields, which is considered a crucial parameter for the producers. However, according to Reganold  
562 & Wachter (2016), the advantages of organic farming systems exceed the better yield achieved by  
563 conventional agriculture, providing a more profitable and environmentally sustainable scenario, better  
564 quality food and zero or lower concentration of pesticide residues. In addition, organic agriculture offers  
565 better delivery of ecosystem services and superior gains in social sustainability.

566



567

568 Figure 7. Conventional versus organic agriculture (data from Reganold and Wachter 2016).

569

570 According to Gomiero (2018), the main concerns with organic agriculture are related to its  
 571 ability to produce enough food, achieve affordability, and be able to provide food for the current and  
 572 future population. Another issue to consider is that organic agriculture cannot meet the food needs of the  
 573 global population due to its need for land expansion. A study from Washington State University,  
 574 published in February 2016 in the journal *Nature Plants* (Reganold and Wachter 2016), assures that  
 575 organic agriculture could be used to feed the entire world population. The same authors studied five  
 576 hundred possible scenarios to test whether organic production would be able to feed 9.6 billion people in  
 577 2050, without the need to expand the areas already used for agriculture. They concluded it would be  
 578 possible to produce food for everyone, provided we eat less meat and more plants. The reason for eating  
 579 less meat is that organic agriculture does not allow confinement of animals and does not aim to increase  
 580 animal protein productivity. Moreover, Soares et al. (2014) also mentioned other difficulties regarding  
 581 organic meat production mainly related to the production of fodder and grains, which are used as feed and  
 582 are crucial for animal health. Organic rations for feed supplementation are limited, especially in the dry  
 583 season, and pasture areas suffer from low fertility. In addition, as in conventional systems, unfavorable  
 584 climate at certain times of the year is a major limiting factor in the production of these feeds. The amount  
 585 of organic food would be sufficient to feed the global population in three scenarios: first, if 100% of the  
 586 people were vegan; second, if 94% of the people were vegetarian; and third if 39% were organic and 15%  
 587 had a Western-style meat diet. Therefore, it is not just a matter of producing enough, but transforming

588 agriculture into something more environmentally friendly to ensure a healthier, agrotxin-free diet for all  
589 (Reganold and Wachter 2016).

590 From an environmental perspective, several works have stressed that organic farming is usually  
591 favorable per unit area, but might be worse per unit product (Gomiero 2018; Mondelaers et al. 2009;  
592 Tuomisto et al. 2012). This is because nitrous oxide and ammonia emissions, in addition to nitrogen  
593 leaching, are lower per unit area but higher per unit product (Jouzi et al. 2017). An important advantage is  
594 the lower energy consumption, but disadvantages are the requirement of larger areas and higher  
595 eutrophication and acidification for each unit product (Tuomisto et al. 2012). There is a lack of  
596 information in the literature that could make the Brazilian population aware of organic food. Singh and  
597 Glińska-Neweś (2022) modeled the public's attitude towards organic food. The authors used big data, text  
598 mining and sentiment analysis with 43,724 Twitter posts without geographic restriction, but with only  
599 English-language tweets. Their sentiment analysis revealed two contrasting views of organic foods. For  
600 some, organic food is beneficial, while for others, there are doubts about whether this type of food is  
601 actually natural or even free of chemicals and pesticides. The authors did not find a relationship with  
602 price in their study. Nagaraj (2021) stated that most people are not interested in this topic or consider  
603 these products expensive. However, for those who are aware of its benefits, they tend to buy these  
604 products regardless of the price.

#### 605 *5.4 Hot foam*

606 In 1995, an easy and smart concept using hot air foam to kill both vegetation and pests was patented  
607 (Rajamannan 1995). This method, called hot foam, was considered an improvement over the hot water  
608 used for weed control. Hot foam uses not only hot water but also biodegradable foaming agents to  
609 produce a foam layer on the treated surface (Cederlund and Börjesson 2016; Martelloni et al. 2019).  
610 According to Martelloni et al., (2019b), this technique is attractive because it has a low level of risk to the  
611 human organism and also to the environment. Furthermore, it can be used to control various weed  
612 species. This is because the foam insulates the weeds from the adjacent air, improving energy transfer to  
613 the plant tissue, decreases energy use, and thus increases efficiency gains (Antonopoulos et al. 2023;  
614 Cederlund and Börjesson 2016). Compared to hot water alone, hot foam requires less water, is more  
615 resilient to climate change, is highly accurate and fast, in addition to offering longer heat transfer and  
616 reduced cost (Martelloni et al. 2019; Peerzada and Chauhan 2018).

617 Antonopoulos et al., (2023) recently published the hot foam method as an option for non-  
618 chemical weed control in perennial crops. The authors found that its performance is equivalent to that of  
619 glyphosate when applied to control weeds in olive groves, although some optimization of the use of hot  
620 foam is needed under other soil and weather conditions.

621

### 622 *5.5 Nonanoic acid*

623 Nonanoic acid, also known as pelargonic acid, is a C<sub>9</sub> straight-chain saturated fatty acid and exists in  
624 nature as esters of the pelargonium oil (National Library of Medicine 2022). In addition to its use as a  
625 herbicide, it is used in the formulation of lacquers and plasticizers, and has antifungal features. As a weed  
626 killer, nonanoic acid is used to control weed growth in enclosed and open areas (e.g. walkways,  
627 greenhouses and schools), as a chemical thinning practice on flowers (e.g. pear and apple trees), and as a  
628 sanitizer (Environmental Protection Agency 2000). The U.S. Food and Drug Administration (FDA) does  
629 not consider the application of this acid to be hazardous in terms of food contamination, but the label  
630 instructions must be strictly followed. In addition, the FDA approves its use as an ingredient in  
631 commercial products applied to peel fruits and vegetables (U.S. Department of Agriculture 2006; U.S.  
632 Food & Drug 2009). Nonanoic acid should be used up to 24 hours before harvest, when used in food  
633 crops, to ensure that a minimal residue remains on food (Environmental Protection Agency 2000).

634 Flower thinning is important because it facilitates fruit production every year, reducing  
635 uncertainty, and increasing fruit yield and quality. According to the EPA, there are five main reasons to  
636 consider nonanoic acid safe: (1) it is already present in food plants, so humans are routinely exposed to  
637 this compound; (2) its uses as a weed killer and blossom thinner are not predicted to be possible causes of  
638 increased risk, and small amounts of this compound are considered non-toxic; (3) the product label, if  
639 followed, provides information on the possible risks associated with the use of this acid, which are related  
640 to its skin and eye irritation characteristics; (4) toxicity tests on various organisms have shown negligible  
641 toxicity; and (5) nonanoic acid does not accumulate as it decomposes rapidly in any environment  
642 (Environmental Protection Agency 2000). Nonetheless, the EPA emphasizes that care should be taken to  
643 prevent drift outside of desired areas to avoid contact with non-target plants.

### 644 *5.6 Comparison of methods*

645 Antonopoulos et al., (2023) compared hot foam to other weed control options, such as mulching, mowing,  
646 and pelargonic acid. Biomass reduction was found to be 75-96% compared to the above options,  
647 depending on the type of biomass and the option evaluated. These results indicate that hot foam could be  
648 an attractive alternative, especially compared to glyphosate, as it is environmentally friendly.

649 Martelloni et al., (2020) also compared the efficacy of four weed control methods: glyphosate  
650 (ultra-low volume), flaming, hot foam and nonanoic acid. They found that weed control was only truly  
651 effective when flaming and hot foam were used, with values above 99% on weed control. Travlos et al.,  
652 (2020) studied pelargonic acid products and several essential oils as herbicides against several weed  
653 species. The authors found that the concentration of pelargonic acid can play the major role in weed  
654 control. The selection of natural products rich in these compounds is crucial. Nevertheless, in the case of  
655 broadleaf weeds, low concentrations of pelargonic acid were sufficient. Another interesting point is that  
656 lemongrass/citronella and pine oil behave as contact-burn herbicides, while manuka oil showed systemic  
657 activity. The use of a mixture of manuka oil and pelargonic acid completely eliminated cleaver plants,  
658 which demonstrated that manuka oil can increase the systemic activity of natural herbicides.

659 Mainardis et al., (2020) compared flaming, mowing and tillage weed in a vineyard. With regard  
660 to flaming, the authors assessed flame weeding powered by biomass. Their results indicate that flaming is  
661 comparable to tillage and is more efficient than mowing in controlling weeds. Flaming benefited small  
662 plants and managed weed excess, but also indicated a potential negative impact on species competition  
663 and persistence. Jacquet et al., (2021) demonstrated the microeconomic effects of a glyphosate ban. The  
664 authors also evaluated mechanical weed control as an alternative to chemical weed control with  
665 glyphosate in French vineyards. According to the authors, the use of alternatives to glyphosate in  
666 vineyards could hamper profits, which depend on the type of vineyard, labor, availability of equipment,  
667 and marketing. Kanatas et al., (2021) evaluated several alternatives for weed control in perennial crops.  
668 The alternatives were glyphosate, mowing, pelargonic acid (twice), and cover crop residues. As  
669 alternatives to glyphosate, pelargonic acid and mowing showed the best results for broadleaf weeds. In  
670 olive groves, flazasulfuron and penoxsulam+florasulam were most effective against hairy fleabane  
671 [*Conyza bonariensis* (L.) Cronquist]. Cover crop residues indicated suppression ability for citrus  
672 orchards. Sportelli et al., (2022) compared continuous mowing, flaming, and tillage in terms of yield. The  
673 living mulch system managed by an autonomous mower has been successful in the vegetable crops  
674 evaluated. It indeed promotes organic vegetable production and uses less energy than flaming and

675 conventional tilling. Furthermore, the autonomous mowers provided acceptable commercial yields of  
676 fresh vegetables and small dry weed biomass with minimal energy demand.

677

## 678 **6 Conclusion**

679 Driven by the increase in the production of transgenic foods - soybean, corn, cotton - glyphosate is the  
680 most sold and used herbicide in Brazil, and will tend to increase even more in the coming years. In  
681 contrast with new regulations from several European countries, Brazil renewed the sale and reduced its  
682 toxicological classification. The allow MRL of glyphosate allowed in clean water in Brazil is 5,000 times  
683 higher than in the EU, raising health concerns, such as non-Hodgkin's lymphoma.

684 Profit-driven interests may lead to attempts with the focus on discrediting opposing studies.  
685 Several eco-friendlier alternatives exist, but glyphosate products replacement remains challenging.

686 Remain vigilant about glyphosate's impact on health and the environment is pivotal.  
687 Policymakers should attentively assess evidence and rank human and environmental health over  
688 economical interests. In this scenario, research investment related to sustainable alternatives and  
689 promotion of eco-friendly practices on agricultural can pave the way for a safer and more  
690 environmentally friendly landscape.

691

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1178 Competing interests

1179 The authors declare that they have no competing interests.

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1181 Authors' contributions

1182 All authors contributed to the study conception and design. Data collection and analysis were performed  
1183 by Leandro Goulart de Araujo and Daniel Froes Zordan. The first draft of the manuscript was written by  
1184 Leandro Goulart de Araujo and Daniel Froes Zordan and all authors commented on previous versions of  
1185 the manuscript. Alain Celzard and Vanessa Fierro supervised all steps of this investigation. All authors  
1186 read and approved the final manuscript.

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1188 Ethics approval and consent to participate

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1197 Availability of data and materials

1198 The datasets used and/or analysed during the current study are available from the corresponding author on  
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