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GLYPHOSATE RESIDUES IN DRINKING WATERS AND ADVERSE HEALTH EFFECTS

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ABSTRACT

Introduction
Control of pesticide residues in waters, foods and environmental samples is a growing source of concern for the general population. Glyphosate is the most widely applied herbicide active ingredient and its residues can be found in drinking waters. Therefore monitoring studies of glyphosate residues in water samples has a great of importance.

Aim of the study. (1) To present the levels of glyphosate in various kinds of water samples, (2) to compare the levels of glyphosate residues with WHO and the international standards, and (3) to evaluate possible health effects related to glyphosate residue concentrations in the water samples.

Results. Glyphosate residues have been detected in all kinds of waters all over the world. It was reported that the most drinking water samples contained higher levels of glyphosate residues than its Maximum Contaminant Level. The levels of glyphosate residues may lead to health problems depending on the levels in waters. Various concentrations of the residues were found in ground and surface waters. The highest concentrations were found in regions with intensive agriculture. The findings indicated that the areas where located around the agricultural regions have glyphosate contamination risks in their water supplies.

Conclusion. Glyphosate authoritatively classified as a probable human carcinogen. Survey studies have been indicated that the residues of glyphosate can be frequently found in drinking water samples. In order to prevent the health effects sourced from the glyphosate, the residues should be monitored in ground, surface and drinking water samples.

Key words: Drinking waters, glyphosate, residue

INTRODUCTION

Nowadays, pesticides are crucial in modern agricultural applications but, due to their potential risk to the consumer, the control of pesticide residues in waters, foods and environmental samples is a growing source of concern for the general population. The worldwide consumption of pesticide, 47.5% is the share of herbicides, 29.5 % is the share of insecticides, 17.5 % is that of fungicides, and others account for 5.5 % only (1).

According to the Eurostat statistics, approximately 395.768 tons of active ingredients of pesticides are used in 2014 in European Union countries. Figure 1 shows the use of total pesticide amounts in European Union countries for several years. The consumption of pesticides, which declined at a certain rate from 2011 until 2013, has indicated an increase with great acceleration in 2014. It is thought that this increase will continue in the following years, especially when the course of consumption trend in the world is observed (Figure 2).

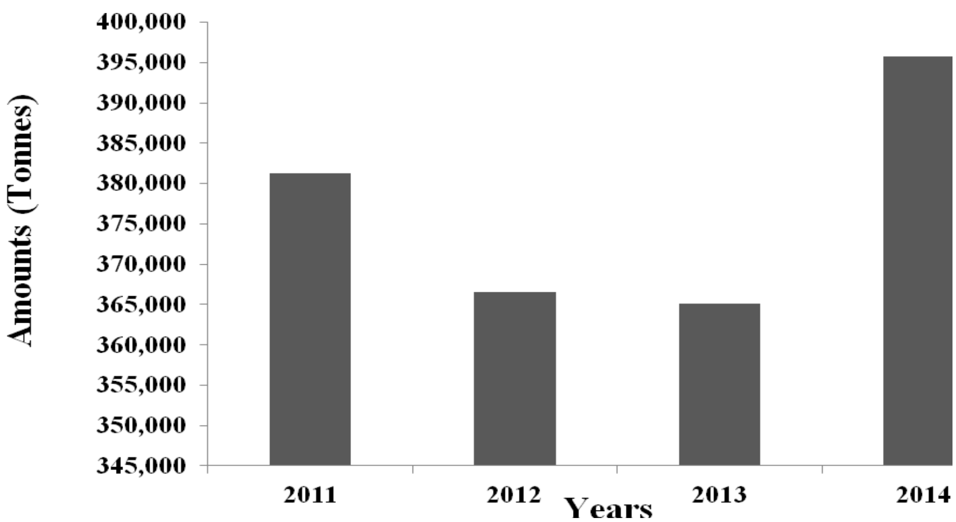

Figure 1. The consumption of pesticides in European Union countries for several years (tons) (2)

Consumption amounts of total pesticides in Turkey presented by the years in Figure 2. Obtained data from Turkish Statistical Institute showed that approximately 40.000 tons of pesticides are applied in 2013. Up to 8.000 tons of them were herbicides. The consumption rates proceed steadily compared to European countries.

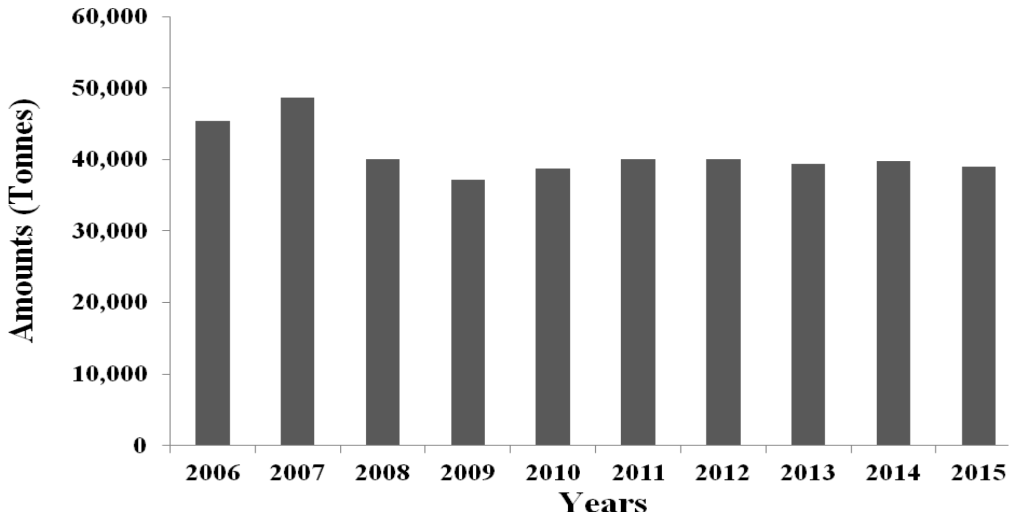

Figure 2. The consumption of pesticides in Turkey from 2006 to 2015 (tons) (3)

Glyphosate is the most widely applied herbicide active ingredient used for agricultural and non-agricultural purposes. It is a non-selective contact herbicide that kills plants by inhibiting the synthesis of aromatic amino acids required for protein formation (4). More than 750 different commercial formulas contain glyphosate as an active ingredient (5).

Glyphosate is used extensively with genetically modified herbicide-tolerant crops. Agricultural sites with the largest glyphosate use include soybeans, field corn, cotton, pasture and hay. In non-agricultural areas, glyphosate is widely applied in forestry, industrial weed control, lawn, garden and aquatic environments (6).

Worldwide consumption rates of glyphosate between 1975 and 2014 years indicate that there is ongoing increase in the trend. Especially with the emergence and distribution of genetically modified plants since 1996 (7) total consumption increase for glyphosate reached 393% between the years 1995-2004 (Table 1).

Table 1. Increase rates of glyphosate consumption globally (8)

Periods	Total consumption (million kg)	Increase (%)
1975-1984	130.5	-
1985-1994	387.3	197
1995-2004	1909.0	393
2005-2014	6133.0	221

From 1994 to 2014, globally over 7.5 billion kilograms of glyphosate active ingredient have been applied. Details from a survey of glyphosate usage in the world are given in Figure 3 (8). The table shows that glyphosate has increased dramatically in the total amount of applied. Correspondingly to the increase in glyphosate consumption, pollution of surface and ground waters by glyphosate has also increased (9-12).

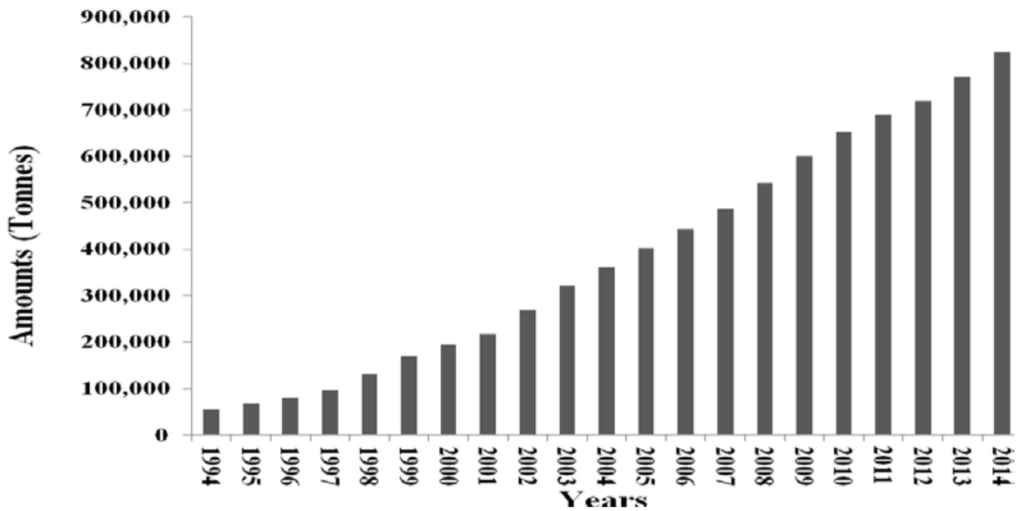

Figure 3. Total glyphosate use in the world (kg) (8)

According to the data obtained from U.S. Environmental Protection Agency (EPA), in terms of glyphosate consumption amounts in USA, in 1993 glyphosate ranked in 11th place among other pesticides. In 1995, 1997 and 1999, it has risen to the 7th, 5th and 2nd places, respectively. From 2001, glyphosate took the first place as most commonly used conventional pesticide active ingredient in the agricultural sector of USA (13). The Ministry of Food, Agriculture and Livestock in Turkey was reported the glyphosate usage was 305 tons in 2001, and consumption of glyphosate was reached to 4.500 tons in 2013.

Glyphosate was first discovered by a Swiss chemist Dr. Henri Martin in 1950 (14). On the other hand the herbicidal activity of glyphosate was identified in 1970 and introduced by Monsanto (a US chemical company) as an end-use formulation in 1974 (15). Glyphosate is a broad-spectrum systemic total herbicide and plant desiccant. Chemical structure of glyphosate is presented in Figure 4 and the chemical properties are presented in Table 2.

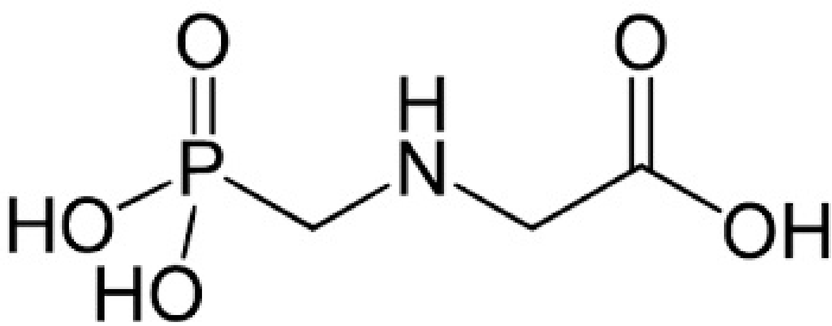

Figure 4. Glyphosate chemical structure

Table 2. Physical and chemical specifications of glyphosate (16)

IUPAC name	*N*-(phosphonomethyl)glycine
Other names	2-[(phosphonomethyl)amino]acetic acid
Chemical formula	$C_3H_8NO_5P$
Molar mass	169.07 g·mol^{-1}
Appearance	white crystalline powder
Density	1.704 (20 °C)
Melting point	184.5 °C (364.1 °F; 457.6 °K)
Boiling point	Decomposes at 187 °C (369 °F, 460 °K)
Solubility in water	1.01 g/100 mL (20 °C)

Glyphosate binds tightly to the soil particles, reaching a persistence of up to 170 days and an usual half life of 45 to 60 days (10,17), but also the chemical is water soluble (18). Glyphosate has high water solubility (11,600 ppm at 25 °C) with an octanol-water coefficient (logKow) of -3.3. Glyphosate itself is an acidic compund, but it is commonly used in salt form, most commonly the isopropylamine salt (10). Experiments conducted for US EPA's reregistration eligibility decision (RED) indicate that glyphosate is stable in water at pH 3, 5, 6, and 9 at 35 °C. It is also stable to photodegradation in pH 5, 7 and 9 buffered solutions under natural sunlight. Based on its chemical characteristic, glyphosate-based herbicides can often contaminate drinking water sources and can be harmful for the health. These adverse effects for the nature and health have been observed especially in agricultural regions worldwide. There are considerable number of studies are available in the literature about the concerns for health effects of glyphosate.

The main metabolite of glyphosate is aminomethylphosphonic acid (AMPA). Glyphosate and its metabolite AMPA are reportedly present in waters, soils, fruits, crops and even human serum (19).

Residues of glyphosate in drinking water are important due to its high solubility in water, high consumption rate of usage and possible health effects. Therefore it is necessary to monitor its residue levels in drinking waters by reliable methods. In the light of these information; the objectives of the current review study were as follows: (1) to present the levels of glyphosate in various kinds of water samples which were collected from different countries, (2) to compare the levels of glyphosate residues with WHO and the international standards, and (3) to evaluate possible health effects related to glyphosate concentrations which were reported in the water samples.

MATERIALS AND METHODS

This review was studied by Assoc. Prof. Dr. Mehmet Fatih Cengiz (Akdeniz University. Food and Agricultural Research Center), Onur Basançelebi (Akdeniz University, Faculty of Engineering, Department of Food Engineering) and Assist. Prof Dr. Yasin Emre Kitiş (Akdeniz University, Faculty of Agriculture, Department of Plant Protection).

RESULTS AND DISCUSSION

Glyphosate is the world's best-selling chemical herbicide. In addition water solubility and polarity of this pesticide has been reported to be very high. Glyphosate may enter the surface and ground water via runoff due to the overspray applications or spray drifts (20). Therefore, traces of the glyphosate herbicide can be found in significant percentage of water samples.

According to the US Geological Survey Agency (USGS), the detection frequencies of glyphosate and AMPA in various environmental samples between the years 2001 and 2010 are presented in Figure 5.

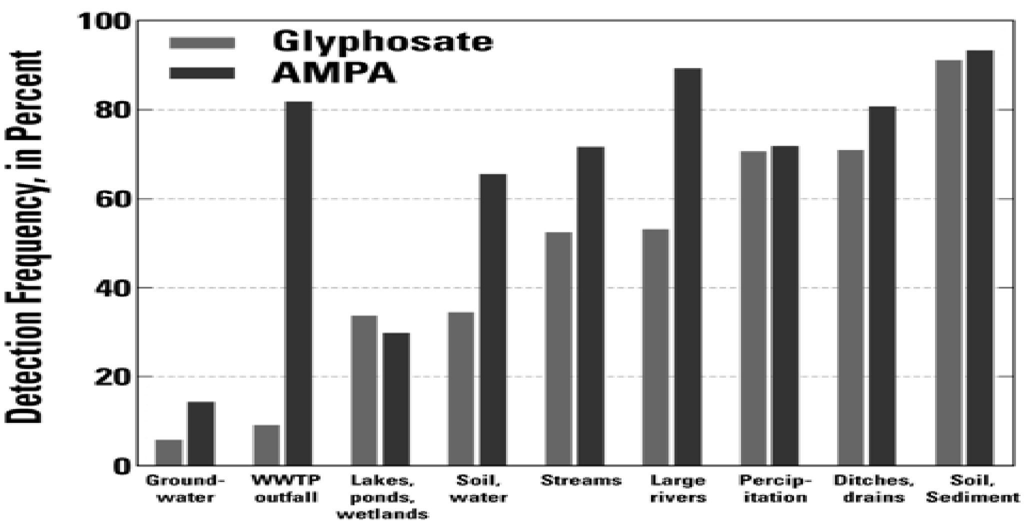

Figure 5. Detection frequencies of glyphosate and AMPA in various environmental samples (%) (18)

The urban use of glyphosate contributes to glyphosate and AMPA residues in streams in the United States. AMPA was detected much more frequently (67.5%) compared to glyphosate (17.5%) (21). Collected samples in water bodies from twenty-three locations, including natural protected areas and agricultural areas in southern Mexico indicated that glyphosate residues were present in all samples (20)

Aparicio et al. demonstrated that glyphosate and AMPA residues are present in soil and stream samples. Sixteen agricultural sites and forty-four streams of Argentina were sampled three times during 2012. In cultivated soils, glyphosate was detected in concentrations between 35 and 1502 μg kg^{-1}, while AMPA concentration ranged from 299 to 2256 μg kg^{-1}. In the surface water studied, the presence of glyphosate and AMPA was detected in about 15% and 12% of the samples analyzed, respectively. In streams sediment glyphosate and AMPA were also detected in 66% and 88.5% of the samples respectively (22).

In a geological survey of "United States Department of the Interior", 2135 ground- and surface-water samples, 14 rainfall samples, and 193 soil samples were investigated from 2001 through 2006. According to the results, glyphosate and AMPA were detected in surface water, in ground water and rainfall samples. The data indicated that trace levels of glyphosate and AMPA may persist in the soil from year to year (23).

There are inadequate data for the countries of Finland, Greece, Ireland, Italy, Portugal and Spain, to make evaluations. A number of reports on pesticides in surface water and groundwater by the French Environmental Agency (*Institut Français de l'Environnement*) for 2001 and 2002 indicated the presence of glyphosate in both surface water and groundwater, especially in surface water. In 2002, glyphosate was detected in about 37% of the surface water samples obtained from 862 monitoring sites (24, 25, 26)

Glyphosate may interact with water-soluble organic matter, clay particles and iron oxides which also belong to the colloidal fraction. Therefore, this interaction may lead to colloid-facilitated transport of glyphosate (17). Table 3 summarizes the residues of glyphosate in various type of water in some different countries.

Table 3. Examples of previous reports of glyphosate residues in water samples.

Country	Time period	Water type (number of samples)	Concentration range (µg/L)	Technique	Reference
Argentina	2011-2012	Streams (44)	<0.1–7.60	LC/MSMS	(22)
Brazil	2010-2011	Natural water	<309-1150	Uv-vis spec.	(27)
Brazil	2013-2014	Tap water	2.3-3.3	HPLC-PDA	**(28)**
Canada	2010-2013	Groundwater (345)	<0.010-0.663	IC/MSMS	(29)
Spain	2007-2010	Groundwater (129)	<0.009-0.939	LC/MSMS	(11)
Spain	2005-2006	Surface and ground water	<0.05-0.85	LC/MSMS	(30)
Germany	1994-1996	Surface water (735)	<0.05-0.590	HPLC-FLD	(31)
Hungary	2010-2011	Surface (42) and ground water (14)	<0.12 – 0.98	ELISA	(12)
Sweden	1998-1999	Groundwater	<0.05-0.93	GC/MS	(32)
USA	2001-2010	Groundwater (1171)	<0.02-2.03	LC/MSMS	(18)
USA	2001-2006	Surface and ground water (2135)	<0.10 – 99	LC/MSMS	(33)

Table 3 indicates that the glyphosate residues have been detected in all kinds of waters all over the world. Maximum Contaminant Level (MCL) of glyphosate residues in drinking water samples declared by European Union, should be less than 0.1 µg/L. When compared to this declaration, the most of drinking water samples contained higher levels of glyphosate than its MCL. Additionally, the highest concentration of glyphosate was reported in natural waters in Brazil. Reported levels of glyphosate may lead to health problems depending on the levels in waters.
Various concentrations of the residues were found in ground and surface waters. Groundwater is often used as the main source of drinking water supplies, although surface waters may feed into artificial reservoirs. According to the reports on the residues of glyphosate, the highest concentrations were found in regions with intensive agriculture. The finding indicated that the areas where located around the agricultural regions have glyphosate contamination risks in their water supplies. According to the best of our knowledge, there was no report about the residues of glyphosate in drinking waters in Turkey.
The combined maximum residue level (MRL) for glyphosate and its relevant metabolites, including AMPA, in drinking water is 0.1 µg/L in the European Union (34). However, there are no MRLs for surface and ground water, according to the Water Framework Directive and its daughter directive regarding ground water protection. The report of European Food Safety Authority (EFSA) has set an acute reference dose (ARfD) for glyphosate of 0.5 mg per kg of body weight (35).
In Turkey, regulations about waters for human consumption are declared by The Ministry of Health. According to the regulation, determination values for each pesticides should be below 0.1 µg/L and total pesticides in each sample should be below 0.5 µg/L. Table 4 declares the detailed information about the topic.

Table 4. Allowed pesticide concentration limits in drinking waters by the Ministry of Health of The Republic of Turkey (36)

Parameter	Parametric value	Unit	Notes
Pesticides	0.1	µg/L	Note 2, 6 and 7
Total pesticides	0.5	µg/L	Note 2, 6 and 8

Note 2: It is sufficient to monitor these parameters once a year
Note 6: Pesticides signifies that insecticides, herbicides, fungicides, nematocides, acaricides, algicides, rodenticides, slimicides, growth control agents, and respective metabolites, reaction products, degradation products. Possible pesticides that are found in water from the mentioned pesticides are observed.
Note 7: The parametric value is applied for each pesticide. The parametric value for Aldrin, Dieldrin, Heptachlor and Heptachlor epoxide is 0.030 µg /L.
Note 8: "Total pesticides" refers to the sum of each pesticide identified and counted within the monitoring process.

Glyphosate is also being slightly toxic to birds, fish, and aquatic invertebrates (37) some research suggest that glyphosate, at environmentally realistic concentrations, can act synergistically with parasites to reduce fish survival (38).
Cytotoxic effect on human cells, endocrine disruption and, inhibition of estrogen synthesis originated from glyphosate and several glyphosate formulations have been demonstrated by a number of studies. (39-42). Besides, some glyphosate formulations may lead to birth defects or adverse reproductive impacts on vertebrates or cause a variety of human diseases (43-47).
Glyphosate at concentrations used in agriculture (21–42 mM) was found to be toxic to human embryonic and placental cells (39, 40). A great deal of reports showed that there is a relation between glyphosate and reproductive dysfunction, kidney damage, Non-Hodgkin lymphoma (NHL), gastrointestinal irritation, decreased body weight, salivary gland changes (i.e. hypertrophy), mutagenic and carcinogenic effects in live human cells, cytochrome inhibition in the generation of ATP (43,44,46,48-56).
According to the chemical compunds classification of European Chemicals Agency (ECHA), glyphosate is classified as group 1B (57). Group 1B indicates there is limited evidence of carcinogenicity in experimental animals and in humans.
Although, previous studies reported that low doses of glyphosate were considered safe for humans, recent studies show that this compound can induce hepatorenal damage (17). This chemical is also classified as a probable human carcinogen (Group 2A) by The International Agency for Research on Cancer (IARC) (5, 19, 58). Group 2A indicates there is strong evidence that it can cause cancer in humans, but at present it is not conclusive.
Significant increase in the level of DNA damage were detected as a result of assessment studies for glyphosate toxicity (51, 59).
Bradberry et al. reported that commercial glyphosate-based formulations most commonly consisted of various components including anti-foaming and colour agents, biocides and inorganic ions to produce pH adjustment. For this reason, the mechanisms of toxicity of glyphosate formulations was complicated and human poisoning with this herbicide was not with the active ingredient alone but also with variable mixtures (60). Saitúa et al. reported that the glyphosate toxicity depends on all its components in the formulation such as Polyoxyethylene diamine (POE) used as surfactant (61). Benachour and Se´ralini revealed that AMPA and the predominant surfactant, polyethoxylated tallow amine (POEA), separately and synergistically damaged cell membranes of umbilical, embryonic, and placental cells. Penetration level of the cell membranes

has reportedly been amplified with the favour of adjuvants and surfactants in the formulation (40). Due to being non-selective herbicide, glyphosate residues effect non-target organisms as well. Wang et al. pointed out that glyphosate was used as the phosphorus source for marine organisms and wide applications of glyphosate could lead to its accumulation in oceans and coastal waters (62).

CONCLUSION

Glyphosate is a broad-spectrum systemic total herbicide and plant desiccant. This pesticide is one of the most widely used in both agricultural and non-agricultural areas all over the world. Survey studies have been indicated that the residues of glyphosate can be frequently found in drinking water samples due to its high water solubility and high consumption rate. Its health effect is a growing source of concern for the general population. Many regulatory and scholarly reviews have evaluated the toxicity of glyphosate. IARC classified glyphosate in Group 2A (probably carcinogenic to humans). Group 2A is indicated in the literature as there is strong evidence that it can cause cancer in humans, but at present it is not conclusive.

Glyphosate is also widely used in Turkey. The Ministry of Food, Agriculture and Livestock in Turkey was reported the glyphosate usage was 305 tons in 2001, and consumption of glyphosate was reached to 4500 tons in 2013. According to the best of our knowledge, there was no report about the residues of glyphosate in drinking waters in Turkey. In conclusion, to prevent the health effects sourced from the glyphosate, the residues should be monitored in ground, surface and drinking water samples by regulatory organizations in our country.

Competing Interests
All authors hereby have declared that no competing interests exist.

Authors Participations

MFC participated in the study design, data collection and writing all versions of the manuscript. OB participated in the study design, data collection as well as writing all versions of the manuscript.YEK participated in the data collection and in the writing all versions of the manuscript. All authors read and approved the final manuscript.

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