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A review of glyphosate application: the health-related effect

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Abstract

Introduction and purpose

The glyphosate (GLY) is a systemic herbicide and crop desiccant registered for use in more than 130 countries. The herbicide is applied to control more than 160 weeds. Despite the declarations about complete biodegradability of herbicide, is difficult to complete elimination of it. GLY may affect the activity of cytochrome P450, the gut microbiome and metals chelation and thus have an adverse health effect. The evidence suggests a relationship between the use of GLY and numerous chronic diseases. The aim of this paper was to review the available literature that examined the health-related effect of GLY.

The state of knowledge

Numerous studies have confirmed the adverse effects of GLY on health. GLY injection in high dose initiate processes involved in cancerogenesis. In human studies, the GLY use was related with 41% higher risk of non-Hodgkin's lymphoma. GLY can lead to endocrine changes, including corticosterone levels and steroidogenesis. In pregnant women population, the higher GLY concentrations in urine were related with shorter pregnancy length. GLY could affects gut

microbiome and leading to the development of intestinal dysbiosis, gut-brain axis and central nervous system changes. The formulated complexes GLY-minerals may damage nephrons. The nephrotoxic effect of herbicide was confirmed in human studies.

Conclusions

Most of the studies assessed the short term health-related effect of GLY. Obtained results do not reflect the environmental exposure which lasting many years. There is an urgent need to assess the long term effect of GLY in small doses in high-quality epidemiological studies.

Keywords: Glyphosate; Roundup; Cancerogenesis, Microbial community; Endocrine disruption; Gut-brain axis

Introduction and purpose

The history of glyphosate using

The glyphosate (N-(phosphonomethyl)glycine; GLY) is a systemic herbicide and crop desiccant. It was discovered in 1950 by Dr Henri Martin – Swiss chemist working in a pharmaceutical company named Cilag. In 1964 Stauffer Chemical patented this compound as a chemical chelator. The company found out substance can bind and eliminate minerals (i.e. calcium, magnesium, manganese, copper and zinc) [1].

The third independent synthesis of GLY was in 1970 by the Monsanto company. Initially, the herbicide was used as a water softener. The company synthesised more than 100 analogues of GLY. Two of the compounds had anti-weed properties, which were too poor to commercialize GLY. John E. Franz the chemist of Monsanto discovered molecule with greater anti-weed potential [1].

In 1974 the herbicide was launched with trade named Roundup. The GLY was used more and more by farmers. The growing popularity of Roundup leads to increasing the number of genetically modified (GMO) plants in the 1990s. The genes modification caused glyphosate-based herbicide (GHB) resistance of plants such as soybean, cotton, rapeseed and corn. The GLY had could be used more frequently in higher amounts [1].

In 2008, agricultural specialists: Stephen O. Duke and Stephen B. Powles described GLY as an “ideal" herbicide [2]. Two years later, Powles recognized the herbicide as a landmark discovery of the last century and hailed him as “penicillin for farmers” [3]. Data from 2012 shows that approximately 127,000 tons in the USA and 700,000 tons globally of GLY are used annually. The usage of the GLY is rising, both at developed and developing countries [4].

Characterisitc of glyphosate

The glyphosate (GLY) is registered for use in more than 130 countries. The herbicide is compound with broad-spectrum of activity – it is applied to control more than 160 weeds [5]. It is a white, odourless, crystalline solid. The mechanism of action is based on inhibition of the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), which occurs in plants, fungi, bacteria. The vertebrates do not have this enzyme. EPSPS catalyze the transformations of the shikimate pathway – crucial for aromatic amino acids synthesis what allow to produce hormones and other important plant-based metabolites [6].

Opportunity or threat?

The GLY translocation in the plant is more effective in the presence of the surfactants. The most often using adjuvants are polyoxyethylene amine (POEA). POEA is the compound of Roundup. The surfactants could strengthen the probable adverse health-effect of GLY. The breakdown of GLY is possible only by some species of microorganism [7]. Despite the declarations about complete biodegradability of herbicide, is difficult to complete elimination of it [8].

The agricultural corporations have assured that as GMO crops increase, the dependent on the use of potentially toxic agents in the agricultural world will be decrease. Nevertheless, data from the USA reveal the estimated national application of the herbicide has risen by about 36.2% during the three years (from 2006 to 2009). Due to the increased plant resistance to GLY, its use with increased frequency is available [9].

The biochemical oxygen demand and chemical oxygen demand (which reflect the degradation process) indicate that the GLY molecules have not high biodegradation rate. The density of the herbicide is about 1.7 g / cm^3. The compound has also limited volatility, which makes it difficult to evaporate and make stay suspended in the air for a long time after application. GLY has strong chelating properties what allow to, forms immobilizing mineral complexes in soil with micronutrients (f.e. calcium, iron, magnesium, manganese, nickel, zinc). This process making minerals inaccessible for plants. The elimination of GLY from the environment is also limited. Laboratory studies have shown that up to 45% of GLY in the soil can be absorbed by plants. There is also the possibility of GLY absorption by the human. The entry pathways are gastrointestinal tract, inhalation and skin [8].

The lack of shikimate pathway of mammals is the basis for concluding that GLY is a safe substance for humans. The risk of acute toxicity in the case of persons not living around crops and without occupational exposure is low. There is a growing interest in the effect of long-term or sub-chronic effects of GLY exposure, especially in small doses. Although the shikimate pathway does not occur in vertebrates, GLY may affect the activity of cytochrome P450, the gut microbiome and metals chelation and thus have an adverse health effect. The evidence suggests a relationship between the use of GLY and numerous chronic diseases - cancers, kidney and liver damage, endocrine disruptions [6].

The aim of this paper was to review the available literature that examined the health-related effect of GLY. The PubMed database was searched to identify articles.

Cancerogenic or not?

The most lively discussions (which have been going on for decades) concern the impact of the herbicide on the carcinogenesis process. The controversies are results in the lack of clarity of position scientific organizations, conflicting opinions, and sometimes changes in experts decisions concerning on health-related the herbicide effect [8].

In 1985 The US Environmental Protection Agency (EPA) include GLY in a Category C substance (a suspected human carcinogen) [10]. 6 years later, based on this same amount of evidence, EPA classified GLY as a substance do not show carcinogenic potential in at least two animal studies, properly conducted on different species, or in both animal and epidemiological studies (category E) [11].

International Agency for Research on Cancer (IARC) recognized GLY as “probably carcinogenic to humans” and labelled it a category 2A [4]. In the same year, the European Food Safety Authority (EFSA), has published a document which indicates that is 'unlikely' that the GLY is genotoxic or carcinogenic to humans. EFSA proposed new toxicological safety thresholds - an increase in ADI (acceptable daily intake) and DGA (the daily limit for human consumption) from 0.3 mg/kg to 0.5 mg/kg of GLY [12].

In May 2016, World Health Organization (WHO) and United Nations Food and Agriculture Organization (FAO), at a meeting on pesticide residues in the environment and food announced that "GLY is unlikely to be carcinogenic to humans through dietary exposure/consumption" [8].

The scientific debate resulted in a discussion in the world of media - many editors have been published controversial articles that cause anxious of the recipients. Unclearly defined experts position can lead to loss of confidence in the world of science. Nevertheless, there has been growing evidence indicates need to consider the use of GLY and searching for alternative plant protection products [8].

The health effects of GLY exposure - the state of the knowledge

Cancers

Numerous studies have confirmed the adverse effects of GLY on health, including processes involved in cancer genesis. In in vitro studies, GLY injection in high dose initiate DNA strand breaks, increase chromosomal changes and markers of genetic damage: 8-hydroxydeoxyguanosine, purine and pyrimidine oxidation. The DNA damage was higher in lower Roundup than GLY amounts (5 μM versus 250 μM and 500 μM) [13].
The number of studies of GLY carcinogenic effect is so large that in 2016 a systematic meta-analytical review was made. The paper assessed the relationship between exposure to GLY or GBH and micronucleus formation (which is a determinant of chromosomal numerical aberrations). Analysis of 81 experiments confirmed the relationship between exposure to GLY / GBH and micronucleus formation. The unfavorable effect was stronger with mixtures like Roundup than pure GLY. Interestingly, the response was not strictly dependent on the dose and/or time of exposure [14].
In the northeastern border of Ecuador, the GHB was applied by the Government of Colombia. After exposure to herbicide, researchers interviewed with 144 people and perform laboratory analysis of 182 blood samples. Examined population showed no significant changes in chromosomes and/or DNA damage [15].
In 2019 the meta-analysis revealed the effect of GLY on non-Hodgkin's lymphoma was published. Data from 6 studies were summarized: 5 of them were case-control studies: (2,836 cases out of 8,868 participants), and one was prospective study: (53,760 participants and 575 new lymphoma cases). The GLY use was related with 41% higher risk of non-Hodgkin's lymphoma (meta-RR = 1,41, 95% CI: 1,13–1,75). The results are confirming by model studies which indicate the relationship between GLY exposure and immunosuppression, endocrine/genetics disruption – which are related to lymphomagenesis. The effect on disease could have adjuvants which occurring in pesticide. GBH mixtures may have more adverse effects on health [16].

Endocrine disruption

Roundup can inhibit the activity of the hypothalamic-pituitary-adrenal (HPA) axis, affect corticosterone levels and steroidogenesis [17].

A dose of 10 mg/kg body weight, Roundup lowered corticosterone levels in males rats. Higher (250 mg kg body weight) doses of Roundup caused apoptosis of reproductive cells which was not observed at exposure on lower doses (10 mg/kg body weight) [17]. The toxicity linked with reproduction is an effect of StAR protein and aromatase enzyme inhibition. As a result, a decrease in testosterone and estradiol synthesis is observed [18]. GLY exposure caused hyperplasia of the mammary gland linked with higher collagen production and proliferation of mast cells. These pathological processes are observed in breast cancer [19].

The adverse effect of GLY on reproduction is also confirmed in a study with pregnant women. The analysis including 71 urine samples showed the GLY residues in 93% of them. There was no relationship between GLY concentration in urine samples and fetal growth indicators. However, the higher GLY concentrations in urine were related with shorter pregnancy length. The results suggest the potential effect of the herbicide on miscarriage risk [20].

Liver damage

Chronic GLY exposure may also be involved in the disruption of liver metabolism. Ultra-low doses of GLY contributed to the changes in the metabolome and proteome of the liver that overlap with biomarkers of non-alcoholic fatty liver disease and its progression [21].

Microbiome

Some of microorganism show resistance to GLY, however, there are also bacteria and fungi which are sensitive to the relatively small concentration of herbicide. The effect is depending on the enzyme system of microbiome also. The difference in the metabolism of the herbicide could have a great impact on the microbiome composition – in plants, soil and gastrointestinal tract of animals [22].

Exposure to contaminated water may be changing the microbiota composition of farm animals. Lactic acid bacteria, which show the ability to produce natural antibiotics, are sensitive to GLY [22]. Reduction of lactic acid bacteria leads to an excessive amount of potentially harmful bacteria. In recent years, there has been observed an increase in C. botulinum mediated diseases in cattle, as well as higher amounts of GLY in their feed and urine. The higher concentration of GLY in urine has also been shown to be associated with an increase in the density of adverse Mucorales in the rumen of dairy cows [22].

Researchers have proposed the possible scenario of increasing the infections risk and hospital infections as a result of excessive GLY use. Some of the mechanisms of GLY resistance overlap with those that cause antibiotic resistance. There is a possibility of transferring a soil microbiome (resistant to GLY) to animals and then, transmitted to humans - health care workers and patients [22].

Central Nervous System

GLY effects on the development of intestinal dysbiosis and mediates in the gut-brain axis and central nervous system changes. Administration of GLY in 250, 500 mg doses (about 7- and 14-fold higher than the acceptable daily intake for a person weighing 70 kg) during 6 and 12 weeks led to changes in the microbiota composition – diversity and amount of gut bacteria. Acute exposition to GLY had no impact on the microbiota composition. Intestinal dysbiosis in exposure animals was related to the severity of depression and anxiety symptoms [23].

The herbicide has also a direct influence on CNS, which include monoaminergic neurotransmitters levels changes. Acute exposure to Roundup resulted in oxidative stress and neurons apoptosis [24]. An animal model study provides that GLY during pregnancy disrupt maternity care probable by changes in dopaminergic and serotoninergic system changes. The exposure of offspring caused delayed in reflex development [25].

The observed changes in the composition of the intestinal microbiota and the brain development after GLY exposure was the basis of the hypothesis put by the international team of researchers. The scientists suggest GLY as a risk factor for autism spectrum disorder (ASD) development. GLY could lead to ASD by a negative effect on gut microbiota. There is the relationship between Clostridium colonization and ASD diagnosis and severity of ASD symptoms. The GLY exposure effects on gut flora and could promote excessive growth of Clostridia which are resistant to the herbicide [26].

Nephrotoxicity

There is also another scenario of negative GLY effect on the human organism. The herbicide is a potential risk factor of development of chronic kidney disease (CKD) of unknown aetiology in Sri Lanka [27]. The support is model studies – exposure to GLY was related to changes in proximal tubules, dilatation of the Bowman capsule space, degeneration of renal tubules in animals. In the long-term study, exposure rats to GLY (by eating maize) increased serum creatinine, blood urea, and reduced the kidney weight [28].

GLY can formulate highly stable complexes with minerals. Some of the metals i.e. cadmium, chrome, nickel and lead have nephrotoxic potent. The scientists are mentioning three potential sources of exposure on GLY-metal complexes:

a. GLY + Ca / Mg / Fe / Sr in drinking water.

b. GLY+ Cd / Cr / Ni / Co / Pb / V / As in food.

c. GLY from skin / respiratory tract + small amount of metals from water and food [27].

The support of the hypothesis is the fact that diagnosis of CKD is less frequently in persons drinking bottled water and in the northern region, where herbicide and chemical fertilizer use has been limited. The formulated complexes GLY-minerals could bypass detoxification in the liver. In glomerulus-proximal tubules, differences pH and numerous metabolic factors, i.e. a high concentration of NH + 4 ions allow easying release metals from the formulated network. GLY and nephrotoxic metals may damage nephrons. Reabsorption of As, Cd, Cr, Ni, Co, Pb, V lead to further nephrons damage [27].

The study of workers of sugar cane cultivation (n=210) in 3 of the Sri Lanka regions (permanently exposed to GLY - more than 10 years) confirm the nephrotoxic effect of herbicide. Workers had a higher concentration of GLY in urine and markers of early kidney damage (NGAL, KIM) compared to the control group. There was also a positive relationship between GLY and: NGAL, a ratio of albumins to creatinine and a negative relationship between GLY exposure and glomerular filtration rate (GFR) [29].

Should we be afraid of GLY - the risk of exposure

Taking into consideration increasing evidence confirm the negative impact of GLY on health, there is urgent need to assess the risk of exposure in general population.

The systematic review assessed the GLY exposure in humans was published in 2019. 19 studies were included: 5 of them examined occupational exposure, 11 assessed exposure in general populations, 3 checked both occupational and the general population exposure. The average concentration of GLY in the urine of workers with occupational exposure ranged from 0.26 to 73.5 µg / l; in case of environmental exposure concentrations in examined samples ranged from 0.16 to 7.6 µg / l. Researchers concluded that the current evidence of GLY exposure is insufficient and the further papers are recommended. However, the detection of GLY residues in general population samples suggest the possibility of chronic exposure to low doses of the herbicide [30].

Summary

Most of the studies assessed the health-related GLY effect during 16-40 days. Obtained results could be only an indicator to further studies because do not reflect the environmental exposure which lasting many years. The substantial increase using of GLY indicate the necessity for conducting accurate risk assessments, especially in more vulnerable populations (e.g. pregnant women, children). The analysis should including a more realistic scenario of exposure – long term effect of GLY in small doses in high-quality epidemiological studies.

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