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Exposure risk and environmental impacts of glyphosate: Highlights on the toxicity of herbicide co-formulants

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ABSTRACT

Glyphosate is an extensively used herbicide globally. Its use dates back to 1970s with increasing numbers over the years. It is an effective weed killer but since it parallelly destroys non-target crops, its use during initial days was restricted. To overcome this, genetically engineered [GE] varieties of many crops entered the market. This led to a significant increase in usage of glyphosate.Over years of extensive usage, many issues related to toxicity, carcinogenicity and GE varieties cropped up. Many researchers studied the toxicological characteristics, health impacts, environmental exposures and ecological impacts of glyphosate and Glyphosate-based herbicides. Many international agencies assessed its carcinogenic potential and grouped and regrouped it based on conclusions of various studies. As an outcome of many studies, an important aspect of toxicity of adjuvants used for technical formulations of glyphosate surfaced and gave a better understanding of its overall toxicity.This review summarizes glyphosate history, global use and hazards related to glyphosate and its technical formulations. It also briefs important studies on Environmental and human health exposures and its impact. Environmental contamination due to glyphosate is studied in detail for water and soil matrices besides its presence in food commodities. Impact of glyphosate on ecosystem, human and animal health has also been detailed. Studies highlighting and inferring the carcinogenic potential of glyphosate are also summed up finally linking the use of glyphosate with the sustainable development goals [SDGs]. The overall conclusions of the review give an insight into the gaps in the current studies particularly mentioning the important role of adjuvants used in technical formulations of pesticides which may go unnoticed for risk assessment studies. Considering the extensive global usage of glyphosate, it is of utmost importance to design toxicological studies and include glyphosate and related adjuvants in the routine monitoring programs of countries. This will help understand the risks and need to restrict or ban the use of glyphosate. Some important inclusions of disclosing toxicity of active as well as other [inert] ingredients/co-formulants on labels should be a mandatory part of pesticide registration.

1. Glyphosate history and global use

In this era of weed management, none other herbicide has influenced the industry and been more prominent than glyphosate (Duke and Powles, 2008). Its historical impact and subsequent genetically modified crops have dramatically changed the scenario of modern farming (Duke and Powles, 2009). Structurally it is a phosphonomethyl derivative of glycine [amino acid], which was discovered in the year 1950 by a swiss researcher, Henri Martin, working in the pharmaceutical company Cilag (Franz et al., 1997). After ten years, the accession of the company was passed on to the laboratory research chemicals distributor, Aldrich Chemical Co., (Székács and Darvas, 2012). Dr. John Franz, a chemist from Monsanto recognized the herbicidal potential of glyphosate in the year 1970 and composed an end-use product named "Roundup". It was first sold by Monsanto in 1974 (Duke and Powles, 2008). This company later on extended the study of Glyphosate concerning their herbicidal activity, and so its potential against ceaseless weeds was perceived (Dill et al., 2010).

From its commencement in the 1974, glyphosate acquired a superior position in the pesticide merchandise. Because of glyphosate's mode of action, quick translocation, and the inability of plants to detoxify the herbicide, it became highly effective and the first preference of many agricultural producers (Shaner, 2006). The supposed mode of action of

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Table 1
Annual global production volume of glyphosate [2008–2012] (Dill et al., 2010; CCM International, 2011; Hilton, 2012; Transparency Market Research, 2014).

	2008	2011	2012
Glyphosate Production volume (in tonnes)	600 000	650 000	720 000

glyphosate in plants is the destruction of the shikimate pathway by inhibition of 5-endopyruvyl-shikimate-3-phosphate synthase (EPSPS) enzyme. This affects the production of vital aromatic amino acids (phenyl amine, tyrosine and tryptophan) (Matozzo et al., 2020). The entire process results in the hampering of protein synthesis and growth and ultimately leads to cellular disarray and death (Salisbury and Ross, 1994).

Despite the edge, the amount of glyphosate sold was limited because it could only be sprayed where farmers wanted to destroy whole vegetation [for example, between the rows in industrial yards, orchards and viticulture etc.]. In 1996, herbicide-tolerant [HT], genetically engineered [GE], and "Roundup Ready" [RR], varieties of cotton, soybean and maize, were given consent for sowing in the United States. This technological advancement made it feasible to use glyphosate as a post-emergence herbicide and lead to a significant increase in the time span for which glyphosate-based herbicides could be used (Benbrook, 2016). In 2000, a great change came about when Monsanto's patent on glyphosate ended and the number of firms manufacturing glyphosate extended from one to thirty (Perry et al., 2019).

Manufacturing and utilization of glyphosate have risen significantly due to the termination of patent protection and launching of genetically modified glyphosate-tolerant[GT] crop varieties in 1996 (Székács and Darvas, 2012). In 2007, the USA(United States of America) used more than 80,000 tonnes of glyphosate (EPA, 1997; EPA, 2011). This was comparable to that in Asia, which shared for around 30% of world's glyphosate demand in 2012 (Transparency Market Research, 2014). In India, 308 tonnes of glyphosate was produced in 2003–2004, which raised to 2100 tonnes in around 2007–2008 (Ministry of Chemicals and Fertilizers, 2008). Glyphosate got certified in around 130 countries until 2010 and was proclaimed to be the most profoundly used herbicide in the world (Dill et al., 2010). Annual global production of glyphosate is in increasing trend as can be seen in Table 1. Global agricultural and non-agricultural use of glyphosate is detailed in Table 2 (Benbrook, 2016).

In addition to its prowess as an effective farming tool, glyphosate has long been considered the safest herbicide in the market as well. In the initial years, Roundup was contemplated to be less toxic to humans, as there had been very little evidence of carcinogenicity or Genotoxicity in mammals (DeRoos et al., 2005). The use of glyphosate and its derivatives as herbicides since its introduction in USA 1974 has increased vastly with the assumption that it has negligible side effects to mammals.

However, increased use and excessive dosage have increased concerns regarding its effects on human health and the environment. Increasingly, significant evidence shows that glyphosate herbicides may indeed affect health, stimulating the need for more surveillance (Benachour and Seralini, 2009). A report of World Health Organization (WHO) in 2015 reclassified glyphosate as probably carcinogenic. Thus, it is important to study the potential hazards of glyphosate, acknowledge the pertinence of public concern, and thoughtfully stabilize the concern against agricultural advantages.

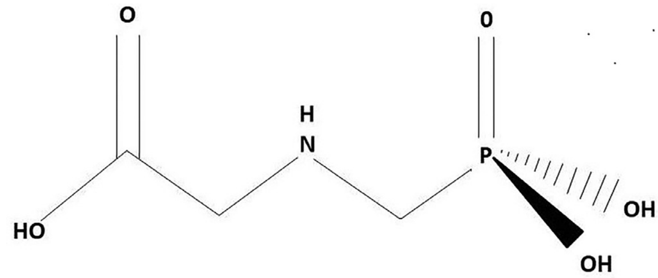

Fig. 1. Chemical structure of glyphosate.

Previous studies and research were assessed in mammals by health authorities such as the U.S. Environmental Protection Agency [EPA] and they found that there is no indication that glyphosate is toxic to the nervous, immune and reproductive system (Henderson et al., 2010). Many contradicting reports exist for glyphosate in the literature as detailed in the upcoming sections, which makes it a suitable candidate for understanding the associated risk based on its hazard potential, toxicity, exposure and environmental and food chain pathways.

In the present review, we will focus on understanding and detailing the parameters which will help us evaluate the hazard and extent of exposure of glyphosate and understand the nature of risk associated with the chemical not only on human beings but also on animal and environmental health.

2. Hazards related to glyphosate

The hazard of the chemical can be primarily evaluated by studying its chemical properties, toxicity and other characteristics which may help to determine its severity of the exposure.

2.1. Chemical properties

Glyphosate is an amphoteric compound which contains a basic 2° amino group in the centre of the molecule with dibasic-phosphonic and monobasic-carboxylic acidic sites at the two ends (Knuuttila and Knuuttila, 1979). Its molecular structure is unique amongst the different herbicides, as it has linear carbon chain with a weaker bond as given in Fig. 1, in comparison to other 95 % herbicides which have aromatic ring structure (NCBI, 2020). This makes glyphosate, presumably, less persistent in the environment.

For commercial use, herbicides containing glyphosate are produced in the form of salts soluble in liquid solutions and granular formulation with the blend of additives, inert ingredients and surfactants. Though these formulations enhance its uptake in plants and increase its water solubility, it contributes significantly towards the toxicity of the herbicide. The commercial herbicides contain glyphosate in the range of 0.96 to 94 w/w% (NPIRS, 2017 and PAN, 2016). For example, Roundup, a common herbicide used contains glyphosate in the range of 0.96 to as much as 71 w/w% (NPIRS, 2017 and PAN, 2016).

Table 2
Worldwide agricultural and non-agricultural utilization of glyphosate [1995 to 2014] (Adapted from Benbrook, 2016).

	Yearly Data (in tonnes)					
	1995	2000	2005	2010	2012	2014
Glyphosate use	67,078	193,485	402,350	652,486	718,600	825,804
Agricultural	51,078	155,367	339,790	578,124	648,638	746,580
Non-Agricultural	16,000	38,118	62,560	74,362	69,962	79,224

2.2. Glyphosate. Toxicity

Toxicity is generally classified into two types. Acute toxicity refers to the hazard associated with exposure of a chemical due to inhalation, dermal and oral exposure during spraying of chemicals. Chronic toxicity refers to the continuous ingestion of small amounts of chemicals in diets and hazard associated with it (Wallace et al., 2010).

For glyphosate, in the context of mammalian toxicity, the acute LD_{50} (Lethal dose, 50%) comes around 5037 mg kg^{-1} and according to EPA registration, any herbicide having LD_{50} more than 5000 mg kg^{-1} will fall in Category IV having least acute toxicity. The LD_{50} values of glyphosate are just at the borderline of the Category IV chemicals (Kniss et al., 2017).

2.3. Glyphosate co-formulants

An important aspect of glyphosate toxicity is due to its formulations. The Glyphosate based herbicides containing formulations and surfactants makes it difficult to establish toxicity due to glyphosate only, as these components contribute to the overall toxicity (Bradberry et al., 2004). Experimental studies have shown that the toxicity of polyoxyethyleneamine [POEA], a surfactant used in herbicide formulation, alone has a higher toxicity than glyphosate and its commercial formulation. Similar results of higher toxicity can also be found in herbicides of glyphosate ammonium whose poly[oxyethylene, oxypropylene]glycol block copolymer surfactant has a higher toxicity than the solvent itself (Song et al., 2012). If we compare it with Fosetyl-aluminium and glufosinate herbicide, the surfactant sodium lauryl ether sulfate and polyoxyethylene lauryl ether respectively used, have relatively mild toxicity(Song et al., 2012).

Exclusive studies have been done to evaluate the toxicity associated with POEA. The results suggest that technical formulations containing POEA and the surfactant POEA are more toxic than pure glyphosate and inhibit fecundity in Drosophila by impairing cell viability through enhanced apoptosis (Bednářová et al., 2020), POE-15 was one of the most toxic principle against human cells and at environmental doses between 1 and 3 ppm, gave negative dose-dependant effects on cellular respiration and membrane integrity (Mesnage et al., 2013). Nerozzi et al., (2020) carried out a study on the effect of glyphosate and Roundup on pig model, concluding that Roundup was found to be more toxic than its main component, glyphosate.

In a experiment conducted by Guilherme and coworkers, they estimated the respective contribution of the ingredient (glyphosate) and the surfactant (polyethoxylated amine; POEA) for genotoxicity of the commercial formulation on *Anguilla anguilla.* The fishes were subjected to equal amount of glyphosate (17.9, 35.7 microg L^{-1}), POEA (9.3, 18.6 micro g L^{-1}) and Roundup (58, 116 microg L^{-1}) for first and third day. The findings demonstrated, Roundup's genotoxicity while also showing the genotoxicity of glyphosate and POEA independently. While both constituent linked to the pesticide formulation's average genotoxicity, the measure of their individual effects was never observed, indicating an antagonistic relationship. Furthermore, when compared to glyphosate and the commercial mixture, POEA caused more DNA damage (Guilherme et al., 2012).Further, toxicological dose indicators of glyphosate-based herbicides (GBH), co-formulants and glyphosate have been discussed in section-impact of coformulants (Table 6).

3. Glyphosate exposure

An important aspect of risk assessment is the exposure to the chemical. A chemical could be highly toxic and persistent but, if the exposure to the chemical is prevented, it may not pose risk except for accidental releases. Exposure assessment includes identification of possible sources and pathways of exposure along with their estimation or measurement. For glyphosate, the exposure can be categorised into human and animal exposure and environmental exposure. Identifying the exposure at these levels would help us understand the risks in all these categories.

3.1. Human and animal exposure

Glyphosate uptake may occur from the skin, concerning workplace use and ingestion of contaminated products. Although assuming 100 percent average concentration consumption, it is necessary to recognize that air penetration is around five times smaller than the appropriate systemic regular intake recommended by the European Food Safety Authority (EFSA, 2015; Chang et al., 2011; Williams et al., 2016). This can be understood by identifying occupational and indirect or mediated exposure from various sources.

Occupational exposure to glyphosate includes the use of the chemical in spraying, handling, manufacturing, etc. It will also include direct "neighbourhood exposure" which can be defined as not using the chemical directly but coming in contact directly with it due to its use or release in the vicinity. In the case of occupational exposure, characteristics like acute toxicity would be very important. Also, the acute toxicity of the co-formulants added along with glyphosate needs to be considered.

Indirect exposure of glyphosate includes exposure through consumption of food and water containing residues of glyphosate. In the case of indirect exposure, it is important to know the transformation in the parent compound during food processing or chemical transformations in water, etc. The toxicity of transformation products like AMPA[Aminomethylphosphonic acid] needs to be assessed. In this case, it is also important to know the persistence in different food commodities. The indirect exposure also includes environmental exposure through the residues or transformation products of glyphosate in various environmental matrices like air, water and soil.

Exposure to a large number of population is expected in case of those living around the agricultural areas, farms and manufacturing and processing plants of glyphosate. In agricultural areas and farms, farmers and gardeners can be exposed to glyphosate via inhalation, dermal contact and/or ocular contact while using glyphosate.

Glyphosate has not been detected in breast milk of lactating mothers who had glyphosate residue in their urine sample (McGuire et al., 2016). The presence of residue chemicals of glyphosate in consumer products, crops, foliage, or soils and their dermal contact or their ingestion amongst people may lead to exposure in the general population. Population that is at high risk of exposure includes agricultural workers and people in immediate vicinity. However, poplulation not in the immediate vicinity is exposed to lower levels of residues via water and food if it contains glyphosate residues (WHO, 2016). Some of the studies on human and animal health impacts are detailed in Table 3.

3.2. Environmental exposure

Production and increased use of glyphosate have lead to its direct release in the environment. In various studies, it has been reported that there is low bio accumulation of glyphosate in the environment as the chemicals are easily degraded by microbial processes and are inactivated by adsorption into the soil (Shushkova et al., 2010; Smith and Oehme, 1992). Due to use in aquatic environments, some trace amount can be found while due to its low vapour pressure [ranging from 1.84×10^{-7} mm Hg to 6.75×10^{-8} mm Hg at 298 K] and ionic nature its presence due to evaporation is negligible (Smith and Oehme, 1992). Its presence in the air can be described due to the spray application and meteorological conditions which can affect the other non-target plants. (Kniss, 2017).

4. Environmental contamination and threats

Glyphosate has been detected in soil, crop products, crop-fed animals, humans, freshwater and organisms living there (Perez et al., 2011). Some results indicate that glyphosate and its derivatives can

Table 3
Impacts associated with the exposure of glyphosate on human/animal health.

S.No	Subject	Impact	References
1	Human	Glyphosate was significantly associated with atopic asthma	Hoppin et al., 2008
2		Hypotension, hyperkaliemia coma, renal and respiratory dysfunction were the most common symptoms of toxicity. Neurotoxic impact or/and ischaemia, especially in marked hypotension incidents through haemodialysis	Potrebić et al., 2009 and references mentioned in Agostini, 2020)
3		Respiratory dysfunction, metabolic acidosis, tachycardia, enhanced creatinine and hyperkalemia are weak prognostic indicators when present	Chang and Chang, 2009
4		Shows DNA damage effect at high or toxic dose levels but it's due to cytotoxicity rather than genotoxicity.	Kier and Kirkland, 2013
5		Risk of ASD with intellectual disability, autism spectrum disorder (ASD)	Von Ehrenstein et al., 2019
6	Southwestern Australian Frogs	No mortality observed after treated with glyphosate	Mann and Bidwell, 1999
7	Rats and mouse	The study concluded that glyphosate is non carcinogenic	Greim et al., 2015
8	Mice	Neurobehavioral changes that stem from the impairment of neuronal developmental processes when subjected to glyphosate	Ait Bali et al., 2017
9	Cattles and goats	Gastrointestinal and neurological signs; the kidneys and gastrointestinal tract (mucosal irritation) were identified as target organs in ruminants when exposed to glyphosate	EFSA (European Food Safety Authority), 2018
10	Danish pigs	Decrease in piglet survival rate, Malformations in newborn piglets after exposure to Roundup (glyphosate)	
11	Cross-bred swine	No health effects observed after exposure to Roundup (glyphosate)	
12	Pregnant mice ovarium	Pure glyphosate or Roundup caused histopathological alteration in ovary, hormonal imbalances and oxidative stress in pregnant mice, interfered expression of steroidogenesis	Ren et al., 2018

also spread through water and wind erosion of soil (Silva et al., 2018). Traces of glyphosate have also been detected in dust in non-agricultural homes, indicating that glyphosate exposure is beyond occupational (Curwin et al., 2005). Once glyphosate is degraded in the environment it results in the formation of AMPA and carbon dioxide and decreases the pH of water (Meyer et al., 2009). Usually, the environmental persistence of glyphosate ranges from 4 to 180 days, rendering it a highly polluting source for soil and possibly even for groundwater (Borggaard and Gimsing, 2008; Vereecken, 2005).

Many experimental studies have shown that the plants over which glyphosate is sprayed take up more than 45 percent of the glyphosate added to the soil (Samsel and Seneff, 2013). The physical methods of removing glyphosate from the environment are very restricted. Microbial deterioration can substantially remove glyphosate from the soil which is dependant on the availability of oxygen and can differ considerably based on the soil's properties and the range of pH at which reaction may occur (Williams et al., 2000). Several authors have reported that the glyphosate's half-life in the soil is around 47 days [which can range from 2 to approximately 200 days based on the form of soil and varied according to environmental circumstances](GMO, 2013; Székács and Darvas, 2012; Borggaard and Gimsing, 2008; Vereecken, 2005). The maximum level of AMPA found in soils is approximately 20% of the glyphosate added under aerobic circumstances and 0.5% under anaerobic circumstances (Torreta et al., 2018). Some studies have also indicated the presence of the adjuvants like POEA in soil and sediment beds due to its high binding capacity(Tush and Meyer, 2016; Tush et al., 2018).

In interaction with water, glyphosate rapidly converts into its primary metabolite, i.e., AMPA, that holds most of its precursor's harmful properties and becomes far more persistent, such that its half-life lasts between 76 and 240 days (Vereecken, 2005). The period taken to degrade 50% glyphosate existing in water, measured in the laboratory, is less than 14 days in aerobic environments and around 14–22 days in anaerobic environments(Williams et al., 2000). While in water, an oxidation process takes approximately 28 days to remove 50% of glyphosate present, particularly depending on the form of light radiation (Samsel and Seneff, 2013).The rate of degradation in water is substantially slower than in other soils owing to less water-borne microorganisms than in soils (Tu et al., 2001 and references therein).

Glyphosate, as stated in the usage guidelines and the harmful clauses mentioned in the health data sheet (P273- Safety data sheet 2014) and (H411-Safety data sheet 2007), should not be released in the environment since it is harmful to marine organisms, with long-term impact (Sikorski et al., 2019) studied the effect of glyphosate addition on plant tissues of *Lemna minor* (common duckweed) which resulted in reduced yield and growth, prevents the synthesis of carotenoids and chlorophyll a and b, and declines the photosystem II photochemical functions.

Fig. 2 explains the pathways of environmental contamination of Glyphosate.

4.1. Glyphosate contamination in soil

Glyphosate has a high potential for soil adsorption which restricts its environmental movement. Glyphosate's typical half-life in soil is 47 days (Tu et al., 2001 and references therein). Slow degradation of AMPA and a half-life reaching to more than 300 to 428 days is also observed (Borggard et al., 2008). Some field experiments suggest (Szekacs and Darvas, 2012) that glyphosate's half-life ranges from some days to a year in some cases, it persists over the winters in a colder climate where the soil is frozen seasonally(Laitinen et.al., 2006).

Glyphosate is water–soluble but it can also be attached to soil particles under certain conditions (Shushkova et al., 2009), specifically in clays. So that it may wipe out of sandy soil easily or persist in soils with large clay content (Bergström et al., 2011). Even though connected to soil particles, this may later degrade back through soil and water in the form of phosphates (Simonsen et al., 2008). Glyphosate could also develop complexes with metal ions (Eker et al., 2006), possibly impacting the nutrient supply of soil. The hazard of the environment getting polluted is determined by how effectively the compound is absorbed into the soil and by the leaching of compounds from the soil into the water. Studies have stated that the sorption capacity of glyphosate is quite higher than that of other pesticides which reduce the risk of leaching (Hagner et al., 2015). Some studies indicate that the noted alterations in the compositions of soil ecosystem are due to application of glyphosate (Kremer and Means, 2009).

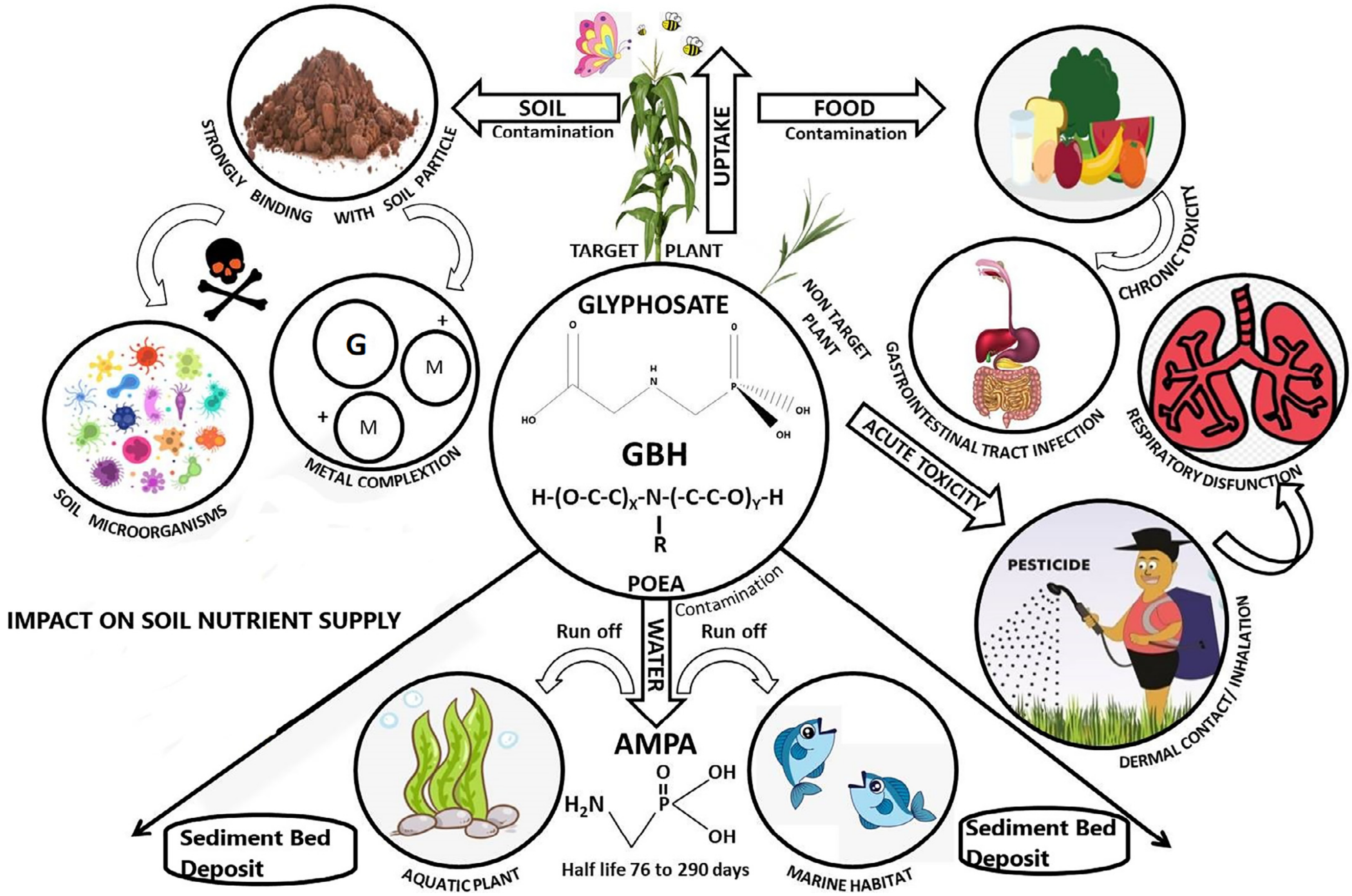

Fig. 2. Environmental contamination of glyphosate
G: Glyphosate, M: Metal ion, GBH: Glyphosate Based Herbicide, POEA: Polyoxyethyleneamine, AMPA: Aminomethylphosphonic acid.

Though some soil micro-organisms can utilize glyphosate as an energy source and nutrients, raising their population numbers, it may also be harmful to certain species (Haney et al., 2000; Wardle and Parkinson, 1990). In soils treated with glyphosate (Zobiole et al., 2011), an upsurge in the population of certain fungal species which trigger diseases in the plant, has been observed. Kuklinsky-Sobral et al., (2005) reported glyphosate's interferance with endophytic bacterial community's equilibrium, which is beneficial for plant growth. Thus, glyphosate existence in the soil may alter the equilibrium of bacteria and fungi, thereby modifying the functions of soil ecosystems and plant health. Argentine scientists have found in laboratory studies that glyphosate based herbicides, may even be harmful to earthworms, causing harm to cells and DNA at rates "similar to the applied environmental concentrations" (Piola et al., 2013). In related research, earthworms were noticed to resist soils treated with glyphosate, the growing levels of certain earthworms were decreased by the usage of herbicides containing glyphosate and the cocoons hatching was postponed (Casabé et al., 2007).

Considering its extensive usage in forestry, there have been limited reports of the impact of glyphosate on forest soils, but it has been observed to persist for 360 days at 16–18 percent during initial levels (Feng and Thompson, 1990) in the upper organic layers of forest soil showing the capacity for everlasting effects. It is also possible that glyphosate addition to natural environments may reduce the nitrogen fixation (Kremer and Means, 2009) found in glyphosate-resistant soya crops.

Hagner et al., (2019) observed that destroying plants by hoeing had pronounced impacts on soil fauna, growing and separating these consequences from direct effects of glyphosate is critically important when determining the hazards of glyphosate in soils. According to the author's opinion, Roundup's impact on soil fauna were comparatively minimal and temporary, no traces of glyphosate were detected in the soil during the closure of the experiment.

4.2. Glyphosate contamination in water

Glyphosate transforms into AMPA as soon as it comes into contact with water while maintaining toxic aspects of its precursor. This even makes it more lasting with 76 to 240 days of half-life (Vereecken, 2005). Because of overspray application on fields or spray drifts glyphosate could even reach the surface and groundwater mostly through runoff (Ruiz-Toledo et al., 2014) . Hence, a trace amount of the herbicide glyphosate could be found in a significant percentage in water samples.

Glyphosate can interfere with water-soluble organic matter, clay particles, and colloidal iron oxides. This connection could therefore contribute to colloidal associated transportation of glyphosate (Vereecken, 2005). Various concentrations of the residues were found in ground and surface waters. Usually, groundwater has been utilized as the essential source of drinking water supply. There are several reports which suggest that the water supplies in areas having intensive agricultural activities might be at high risk of glyphosate contamination (Cengiz et al., 2017). Presence of glyphosate in water has been studied by several researchers; these studies have been presented in Table 4.

4.3. Glyphosate contamination in food

The main source of chronic exposure to glyphosate could be food. Residues of glyphosate have been found in crops, drinking water and tissues of animals that are destined for the consumption of humans.

Table 4
Occurence of glyphosate in water.

Sr.No	Water Source	Contaminant Analysed	Contaminant Concentration	References
1	Lakes, ponds or streams	Glyphosate	5153 µg/litre after direct aerial application	CCME, 1989
2	Pond water	Glyphosate and AMPA	90–1700 µg/litre Glyphosate and 2–35 µg/litre AMPA	IPCS, 1994
3	Surface water		0.5– 1 µg/litre Glyphosate and 6 µg/litre of the metabolite AMPA	
4	Surface water	Glyphosate	Low concentrations obtained in samples from various countries (0.1 to 2.5 µg/litre)	Skark et al., 1998
5	River water		Glyphosate was found in two tributaries of Ruhr river, up to 0.59 μg/ litre	
6	Stream water	Glyphosate and AMPA	Both AMPA and glyphosate were detected in 35% of the 154 Samples. The maximum observed glyphosate concentration was 8.7 μg/litre, and the maximum AMPA concentration was 3.6 μg/litre.	Battaglin et al., 2005
7	Stream water	Glyphosate and AMPA	Glyphosate was measured at the highest concentration i.e, 328 μg/l and AMPA 41 μg/litre.	Battaglin et al., 2009
8	Surface Water	Glyphosate and AMPA	Glyphosate detected in about 30% of samples and 23% above 0.1 μg/litre. AMPA has been detected in about 50% of samples and 45% above 0.1 μg/litre*.	Horth, 2010
9	Ground water		Glyphosate has been detected in about 1% of samples and 0.7% above 0.1 μg/litre. AMPA has been detected in about 1.7% of samples and 0.9% above 0.1 μg/litre.	
10	Boreholes	Glyphosate and AMPA	Glyphosate and its metabolite AMPA are found at concentrations over 0.1 μg/litre, with 26.7% and 38.2% respectively of Danish stream samples, which indirectly affects the groundwater.	Malaguerra et al., 2012
11	River water	Glyphosate and AMPA	The annual load as a percentage of use (LAPU) was calculated for the four agricultural basins which ranged from 0.009 to 0.86%	Coupe et al., 2012
12	Ground water	Glyphosate	Out of 140 samples; 41% found positive, with a maximum of 2.5 μg/litre and an average of 0.2 μg/litre	Sanchis et al., 2012; Friends of the Earth Europe, 2013
13	Drinking water		In raw water samples, destined for public supply, 2.9% of samples found above the maximum concentration of Glyphosate permitted in drinking water (0.1 μg/litre).	
14	Wells		8.8% of the wells analysed, with 3.4% exceeding the maximum concentration of Glyphosate permitted in drinking water (0.1 μg/litre).	
15	Ground water	Glyphosate and AMPA	Residues of glyphosate were found up to 1.42 μg/litre in all groundwater samples.	Rendón-von Osten and Dzul-Caamal, 2017

* The maximum contaminant level (MCL) of glyphosate residues approved by the european union in drinking water samples is 0.1 µg / l (Cengiz et al., 2017).

Analysis of honey samples was conducted for the concentration of glyphosate, 59 % [41 out of 61] samples were found with a concentration range of 17 to 163 ng/g, this was above LOQ[Limit of quantification] [15 ng/g]. Similarly, soy sauce samples [36 %-10 out of 28] showed the concentration of glyphosate in range of 88 and 564 ng/mL, these were found above LOQ [75 ng/mL] (Rubio and Kamp, 2014). The residues of glyphosate and AMPA were detected in plant products. The observed concentration of glyphosate in legumes (soy crops) was0.25–18.5 mg kg^{-1} and AMPA was 0.26-20mg/kg (Jarrell et al., 2020).Highest residues of glyphosate during various trials were reported as:cottonseeds [28 mg kg^{-1}], cereals [3- 20 mg kg^{-1}]and various types of fodder [0.79– 344 mg kg^{-1}]. (Codex, 2013; Cuhra, 2015; EPA, 2013; FAO Pesticide Residues in Food –2005 2005).Various studies have been carried out to detect the concentrations of glyphosate in barley [<0.45 mg/kg], wheat [0.67 mg/kg], oats [<0.08 mg/kg] (Granby et al., 2003; Botero-Coy et al., 2013). Zoller et al., (2018) found concentration of glyphosate [<0.001–0.291 mg/kg] and AMPA [<0.0025–0.010 mg/kg].The detectable glyphosate residue found in fresh or processed fruits and vegetables [0.0002–0.15 ppm], other grains i.e., whole grain, arrowroot, buck weak, rice, rye [0.005–5.9 ppm] (Miller et al., 2020). Glyphosate residue reported positive in wine [0.0048 mg/kg], fruit juice [0.0019 mg/kg], honey [0.0046 mg/kg] (Zoller et al., 2018). In another glyphosate residue study, they found rye crispbread [0.26 mg/kg] and millet [0.086 mg/kg] (Baden-Wurttemberg, 2012).

5. Glyphosate impacts

Though herbicide-containing glyphosate is used to kill the weeds and other vegetation, other plants, bacteria, invertebrates and animals may also be exposed in many ways to the herbicide. Insects or animals can become exposed to the glyphosate during spray, consuming the treated crop, or feeding on the prey that may have been exposed to glyphosate. The non-target species have direct impacts and the changes in environment indirectly affect them (Tarazona et al., 2017).

The supposed mode of action of glyphosate in plants is the destruction of the shikimate pathway (Matozzo et al., 2020). It is mentioned that glyphosate is not detrimental to mammals or humans because the said pathway is not present in all animals (Herrmann and Weaver, 1999). However, glyphosate also influences other pathways which are based on humans and animals. Glyphosate and its side effects have become a major concern due to widespread use and its concentration in the edible products (Tarazona et al., 2017).

5.1. Impact of glyphosate on ecosystems

In the freshwater environment, glyphosate dissolves in inorganic clays, organic compounds and sediments [the main sink for glyphosate in water bodies] by dilution, oxidation and adsorption (Tu et al., 2001 and references therein). With its prolonged half-life and capacity to induce death of species in marine habitats, it is advised that glyphosate is used as a marine herbicide at any one time to manage approximately one-third to half of the body of water (Tu et al., 2001).Glyphosate has a typical half-life of 12 days to 10 weeks in water (Tu et al., 2001). Polyoxyethylene amine [POEA], a surfactant, has been identified in this respect as the key source of Roundup's extremely high toxicity of many freshwater invertebrates and fish (Tsui and Chu, 2003; Giesy et al., 2000). Glyphosate of a technical grade is mild to very strongly toxic, with recorded LC_{50} [Lethal concentration] values greater than 55 mg/L and No observed effect concentration (NOEC) value of 21 days of 100 mg/L (Tsui and Chu, 2003; Giesy et al., 2000).

Glyphosate has been detected in surface waters in recent years even after it was used to combat aquatic plants, but it is widely known to have low ability to contaminate surface waters (Mensah et al., 2014; Glusczak et al., 2007). Indeed, its mode of action was intended to impact only plants (Stenersen, 2004), but in previous years, several studies have documented adverse effects on non-targeted animals (Tsui and Chu, 2003; Giesy et al., 2000; El-Shebly et al., 2008). *Limnoperna fortunei* has been used to decrease the level of glyphosate in formulations which are commercially available but the depletion of glyphosate enhances the production of P-PO_4^{3-} and N–NH_4^+. If such type of glyphosate depletion occurs in natural water ecosystem it can lead to eutrophication (Gattás et al., 2020). Iummato et al., (2018) studied the effects of algae contaminated with glyphosate through dietary exposure in *Limnoperna fortune* which revealed that glyphosate produces alterations in metabolism related to detoxification process. However, no effects were observed in oxidative stress variables. There is a growing concern on the decrease in the abundance of amphibian species globally in the past years. (Williams, 2004; Cheron and Brischoux, 2020) observed the presence of concentrations of AMPA in environment disturbs the survival of embryos, the time required for development and morphology of hatchling in Bufo spinosus [Spined toads].

Glyphosate was also studied as a potential trigger for the amphibian decline (Relyea, 2005), and variety of reports are a matter of concern regarding the exposure of amphibians to the glyphosate and having an effect on its development. Frog embryos subjected to the dilutions of glyphosate-based herbicides displayed cranial and facial malformations in experimental studies, also shortening of the neck, damaged eyes and narrower heads (Paganelli et al., 2010). Likewise, the length of adult frogs reduced snout-vent due to exposure to the glyphosate-based herbicide(Paetow et al., 2012). The larval cycle of American toads has been extended by showing exposure to herbicides including glyphosate (Williams and Semlitsch, 2010), which has triggered changes in the function of a central enzyme associated in the nervous system of the frog [*Rhinella arenarum*] tadpoles (Lajmanovich et al., 2011). Exposure in one study induced alterations in the shape of tadpoles, such as the deepening of their tail fins. The authors noticed that the modifications (deepening of tail fins) were reported to be similar to the adaptive morphological changes induced by predators (Relyea, 2012).

The effects of glyphosate-based herbicides on species living in waterways, marine waters and lakes have been studied as well. Microorganisms are important to the habitats of aquatic and freshwater as they shape the base of food chains. In experiments, the development and distribution of organisms in aquatic microbial communities have been studied. Glyphosate contamination was found in water bodies due to land run-off (Stachowski-Haberkorn et al., 2008).Vera et al., (2010) found that diatoms were far more sensitive to glyphosate in periphyton populations than cyanobacteria, and subsequently, a change in the diversity of these populations resulted over a period of time.

Research showed that glyphosate-containing herbicides prevented photosynthesis in freshwater cyanobacteria (Vera et al., 2012). Similar observations were done by Pérez et al., (2007), an increase in the abundance by 40-fold was observed with the addition of Roundup in picocynobacteria, whereas tiny aquatic species known as rotifers showed to have lowered life expectancy and reproductive levels, longer growth periods and the lower total populations (Vera et al., 2012). Higher up the coastal and terrestrial food chains were also found to have harmful impacts. Pure glyphosate, glyphosate-containing herbicide 'Roundup' and surfactant additives have shown to be highly responsive to freshwater mussels (Bringolf et al., 2007). Upon exposure to Roundup herbicide (at concentrations 40- to 20-fold lower than the standard agricultural application), the freshwater carp displayed swelling of mitochondria as well as disappearance of its internal membrane and myelin-like structures in the cytoplasm. Also, in liver of many of the carp fishes, mononuclear infiltration cells were observed. (Szarek et al., 2000). Research on European eel reported that "Roundup amounts that are biologically significant may present a safety danger for populations of fish" and showed that it induced DNA damage in the exposed fish (Guilherme et al., 2009).

Glyphosate is used for pre-harvest desiccation, glyphosate may persist in seeds and this can result in a reduction in germination and seedling formation (Blackburn and Boutin, 2003; Baig et al., 2003). Findings of Cederlund, (2017) suggests that a limit of < 5 g / ha will have a good protection level against adverse effects of glyphosate spray drifting for non-target terrestrial vascular plants. The drift rates up to 1–2 g / ha would be completely protecting plants from harmful impacts.

Popular weeds in agricultural areas can be essential sources of food for animal species, bee and birds. Weeds offer food as well as nectar sources for insects, on which birds feed on later. Seeds of weed may also be essential winter food for several endangered species of birds, such as bunting corn and skylark (Voříšek et al., 2010). Between 1999 and 2003, Farm Scale Assessments [FSE] of Genetically Modified [GM] crops in the United Kingdom analysed the amount of weeds and their seed output in the non-GM intensively controlled beet fields relative to those in Genetically Modified [GM] glyphosate resistant crops. The findings revealed that the GM glyphosate tolerant sugar beet had a large reduction of weeds and plant seeds relative to traditional crops (Heard et al., 2003).

Likewise, the decrease of North America's Monarch butterfly populations from the mid of 1990s has been related [partly] to use of glyphosate-based herbicides on the soya crops and GM maize. The usage of glyphosate, while not specifically harmful to the butterflies, inhibits the caterpillar stage of their lifecycle (Zobiole et al., 2011). Common milkweed plants were killed from glyphosate-resistant crops fields at very high levels (Hartzler, 2010), and it is projected that common milkweed was completely removed from US cropland of 100 million hectares after implementation of glyphosate-resistant crops (Monarch Watch, 2008).

5.2. Impacts of glyphosate on human and animal health

The impacts of Glyphosate on human health rely on the amount of glyphosate present, duration and the frequency of exposure. It often depends upon a person's health and other environmental factors too (National Pesticide Information Centre, 2020). To obtain the cytotoxic and DNA-damaging effects of glyphosate and Roundup on its occupational exposure to humans, Koller et al., (2012), reported an in-vitro study on exposure of human derived buccal epithelial cell line, for 20-minutes to 10–20 mg/L of glyphosate and roundup-ultramax which lead to a rise in nuclear aberrations. The study thus indicated that inhalation of the said herbicides may cause damage to DNA in exposed humans.(Koller et al., 2012).

In living plants, glyphosate undergoes degradation to form AMPA [Aminomethylphosphonic Acid] (Arregui et al., 2004) which is also toxic to various organisms (Gomes et al., 2016; Kwiatkowska et al., 2014). Hence, in the residue analysis, the concentration of both glyphosate and its degradation product AMPA are considered (Codex, 2013; EPA, 2013). It is not effectively metabolized in animals, so is primarily excreted into the urine with no change (Myers et al., 2016). After glyphosate inhalation, very low amount of AMPA has been detected in blood, it indicates ineffective metabolism in humans too; nevertheless, this oxidation must be mediated by microbial intestinal oxidation(Motojyuku et al., 2008). In support of this hypothesis, a test in rats confirmed low amounts of AMPA in the colon after two hours of the oral glyphosate ingestion, which was mainly due to the glyphosate's intestinal microbial metabolism (Brewster et al., 1991).

When examining the influence of Roundup containing glyphosate on aromatase, the enzyme involved in the development of oestrogen, at nontoxic levels, it was noted that glyphosate interferes with the levels of aromatase and mRNA and thus has both endocrinal and toxic effects The research suggests that Roundup containing glyphosate is lethal to placental cells of the human within 18 hours of exposure, at amounts lower than those for agricultural use, thus raising concern for workers exposed to glyphosate during pregnancy (Richard et al., 2005). Glyphosate herbicides blocked the activity of the masculinizing hormone that is an androgen, in an in vitro experiment in the human cells, at values up to 800 times lower than the permitted glyphosate residues in some GM crops that are used for animal feed in the United States. At these levels, DNA damage has been observed in human cells being treated with glyphosate-based herbicides (Gasnier, 2009).

These herbicides were also found to interfere with action and the production of oestrogen, which is feminizing hormone. The first toxic effect was observed at a dose of 5 ppm and first endocrine disruption at 0.5 ppm which is 800 times less than a quantity of 400 ppm permitted for certain animal feed (Gasnier, 2009). This herbicide has caused dysregulation of the huge number of genes in breast cancer cells of human which were grown in vitro in the laboratory at the environmentally acceptable exposure levels [0.00023 percent dilution of commercial formulation]. Out of 1550 genes studied, a 680 expression either got increased or decreased. It was able to substitute and work symbiotically with oestrogen which is necessary for the growth of breast's cancer cells. This indicates the high endocrine-disrupting capability of glyphosate in this kind of hormonal environment (Hokanson et al., 2007). Through in vitro oestrogen mechanisms, proliferation of oestrogen-dependant breast cancer cells increases by pure glyphosate itself (Thongprakaisang, 2013).

It is also reported (Samsel and Seneff, 2015) that glyphosate is a metal chelator, and since manganese influences sperm motility, they concluded that glyphosate could partially explain higher levels of infertility and birth defects. Also, these metal chelating properties are often linked with diseases like anxiety disorder, inflammatory intestinal disease, thyroid dysfunction, Parkinson's disease, Alzheimer's disease, autism, renal lithiasis, osteomalacia and infertility (Samsel and Seneff, 2015). Acquavella et al., (1999), carried out a study for understanding the exposure of Roundup herbicide also known as isopropylamine salt of glyphosate on the human eyes. It revealed that it had no permanent damage to the human eye, but there were chances of temporary or minor injury to the person exposed to it.

Relations amongst microbes and health of humans have been examined in recent years, but lesser evidence and studies are known on the potential impact of glyphosate on this relationship (Berg et al., 2014). Glyphosate has an influence on the intestinal microbial community from contaminated animal feed and water that can damage human and animal health (Van Bruggen et al., 2018). While acute toxicity of glyphosate to mammals is low, it has been found that products with glyphosate formulations are more harmful than glyphosate itself, which has raised concerns about its potential impact on humans as a contributor of many cancers and mental disorders in specific (Richard et al., 2005). Multiple experiments have identified a possible correlation between the effects of glyphosate-based herbicides and cancer (Agostini et al., 2020). Laboratory studies have demonstrated absorption of glyphosate in human gastrointestinal tract and absorption of glyphosate via dermal route, ingestion and inhalation (Torretta et al., 2018). Liver failure has been reported due to glyphosate exposure (Khot et al., 2018).

Some of the studies showing glyphosate concentrations in human samples have been mentioned in the Table 5.

5.3. Impact of coformulants

As detailed in the earlier sections, many of the studies reported understanding the impact of glyphosate has been carried out using glyphosate or its technical mixtures. Most of them have reported that the technical mixtures have higher toxicities than the Glyphosate alone.

As reported in the earlier sections, glyphosate is always used with adjuvants which facilitate its entry into the plant cuticles (Relyea, 2005). The surfactants like POEA used as adjuvants are reportedly more toxic than glyphosate when tested. POEA, which has been prominently present in most of the technical formulations of glyphosate is reported to act as a herbicide when studied on its own. As mentioned in Table 6, it has significantly high toxicological values, in comparison with glyphosate alone. Since the disclosure of active ingredient is mandatory and adjuvants are not, these compounds go unnoticed along with the glyphosate sprays into the environment (Mesnage et al., 2019). And considering high toxicity quotient particularly for aquatic species, they will disturb the ecosystems significantly.

Due to the low reported toxicities of Glyphosate alone, which does not give a clear picture of its acute and chronic effects due to technical mixtures, it is more relevant to consider studies based on the formulation for the toxicity values, because in many cases, the co-formulants are not inert ingredients but significantly burden the environment and disturb the ecological cycles. Even the other ingredients like heavy metals (presence of Arsenic, Chromium, cobalt etc. in glyphosate based formulations such as Bayer GC, Glyphogan, Radical Tech^{+} etc. reported by Defarge et al., (2018) have been reported to contaminate the ground water and these usually go unnoticed while understanding the fate of pesticides. (Defarge et al., 2018 and references there in)

6. Risk of cancer associated with glyphosate

Glyphosate is intensively used herbicide globally, with carcinogenic characteristics. Since its registration from 1974 the carcinogenic potential of glyphosate has been evaluated by EPA and other health authorities several times and in several studies. However, opinions on the risk of cancer due to the exposure of glyphosate are divided. Since 1985, the early peer-review paper of glyphosate was studied in treaty with the Guidelines for carcinogenic risk assessment. The scientist studied on mice tumours and further, they classified it as Group C chemical [Possible Human Carcinogen] in that particular year.

The Scientific Advisory Panel [SAP] and Federal Insecticide, Fungicide, and Rodenticide Act [FIFRA] provide autonomous scientific assistance to the EPA on wellbeing issues related to glyphosate (EPA, 2019). FIFRA again in 1986 reviewed glyphosate and classified it as non-carcinogenic to Humans and advised the agency to issue a data call-in notice for further studies in rats to clarify the unsolved queries (FIFRA SAP Report, 1986). After a re-evaluation of the referred mouse study, the US EPA changed its classification to evidence of non-carcinogenicity in humans [Group E] in 1991 (IARC, 2015).

Recently, to understand the severity and risk of glyphosate, many international agencies took part to evaluate its carcinogenic potential. The subdivision of the World Health Organization [WHO], International Agency for Research on Cancer [IARC], studied that glyphosate was a probable carcinogen and classified in group 2A on March 2015 (IARC, 2015). There are some studies which suggest cancer risk due to exposure of glyphosate while there are others who don't. The study done by IARC was aimed at identifying the hazards which will result in the possibility of cancer and did not consider the risk associated with exposure to doses present in the environment.

The EPA has proposed its conclusions that "The strongest support is for "not likely to be carcinogenic to humans at doses relevant to human health risk assessment(US Environmental Protection Agency, 2017). In IARC's summary statement, it is found that there was no link between glyphosate traces of food and cancer. The group found "limited evidence" of carcinogenicity in the agricultural workers exposed to glyphosate for prostate cancer and non-Hodgkin lymphoma. But the panel of the working group found "sufficient evidence" of carcinogenicity in the experimental animals (Valavanidis, 2018).

The conclusions made by EPA and IARC differ due to mainly three basis; first was the core tables collected by the IARC and EPA, IARC focused primarily on peer-reviewed research, 81 assays were performed to investigate certain genotoxic effects (oxidative stress and sex hormones), positive outcomes obtained in 62 of them whereas the EPA was based primarily on registrant-commissioned, unpublished regulatory reports, 99 percent of which were negative. Secondly, IARC's analysis put a high emphasis on the findings of formulated GBH and AMPA assays, while the EPA's assessment consisted primarily based on data from technical glyphosate studies. Third probable reason was assessment by IARC contains information from average diet,occupational and elevated expo-

Table 5
Human sample studies on glyphosate occurence.

SNo	Contaminant Analysed	LOD/LOQ and Analytical Method	Concentration	References
1	G & AMPA	LOD G: 100 μg/L LOD AMPA: 50 μg/L Analytical method: Gas chromatography containing ECD	Samples of urine for G persist < LOD, Single urine samples analysed further contains 85 μg/L G;Samples of urine prevailed <LOD of AMPA.	Jauhiainen et al., 1991
2	G	LOD G: 1 μg/L Analytical method: HPLC	Samples of urine Geometric mean (Farmers) ± SD: 3.2 ± 6.4 μg/L (range < 1–233) on day of application; On post application i.e. day 3- 1.0 ± 3.6 (< 1–68) μg/L. Detectable range was found in lower than 25% of children spouses.	Acquavella et al., 2004
3	G & AMPA	LOD G: 0.5 μg/L LOD AMPA: 1.0 μg/L Analytical method: Gas chromatography with electron micro capture detector	Samples of urine G: 7.6 ± 18.6 μg/L(Mean± SD; range: 0–130 μg/L); 4/42subjects. Detectable G levels had measurable AMPA levels: mean G:58.8 μg/L (range: 28–130 μg/L).	Varona et al., 2009 and references in Gillezeau et al. 2019)
4	G & AMPA	LOD G(Milk): 1.0 μg/L LOD AMPA(Milk): 1.0 μg/L LOD G(Urine): 0.03 μg/L LOD AMPA(Urine): 0.02 μg/L Analytical Method: LC-MS	Samples of milk and urine from healthy lactating women were collected. Milk: G < LOD. Urine: G mean: 0.28 ± 0.38 μg/L, G observable in 37/40 urine.	McGuire et al., 2016
5	G& AMPA	LOQ G: 0.1 μg/L LOQ AMPA: 0.1 μg/L Analytical method: GC–MS	Samples of urine: 127 samples of G (31.8%) > LOQ, AMPA: 160 (40.1%) > LOQ.	Conrad et al., 2017
6	G	LOD G: 0.4 μg/L Analytical method: HPLC	Median of maternal serum: 17.5 (range 0.2–189.1) μg/L; Serum of umbilical cord: 0.2(range 0.2–94.9) μg/L,46.3% serum samples maternal < LOD, 50.7% of umbilical cord serum samples <LOD.	Kongtip et al., 2017
7	G	LOD G: 0.5 μg/ L Analytical method: LC-MS	47 samples contained urinary creatinine, Between ⟨ 3.0 or ⟩ 30 nmol/L. Samples having G levels >LOD (20 %), Median of samples with G levels above the detection limit (Range): 0.87 (0.80–1.35) μg/L.	Connolly et al., 2018

G-Glyphosate, AMPA- Aminomethylphosphonic acid, LOD-limit of detection, LOQ- Limit of quantification, ECD- Electron Capture Detector, HPLC- High Performance Liquid Chromatography

sure scenarios, but EPA's assessment concentrated on ordinary, dietary exposures of common population considering legal, usage of food-crop whereas on other hand, neglected higher occupational risks and exposures (Benbrook, 2019).

Many studies have been considered afterwards which are determining glyphosate and its cancer-causing hazard. The European Food Safety Authority [EFSA] determined that it is not likely to pose a cancer-causing hazard in November 2015 (EFSA, 2015) and The Joint Food and Agriculture Organization *WHO/FAO* concluded that glyphosate was not likely to create cancer-causing probability to the individuals which were subjected through food (WHO, 2016). IARC categorized glyphosate as "probable human carcinogen" (IARC, 2015), in the similar year, EFSA stated that "glyphosate is not likely to pose a carcinogenic hazard to individuals" (EFSA, 2015) and according to US EPA it is "not probable to be carcinogenic" as per non-occupational exposures (US Environmental Protection Agency, 2017). The consequences of the studies on glyphosate explained in many EFSA and EPA's review papers. The arguments on glyphosate as a cancer-causing group is placed on several characteristics, this includes the variations in weightage given to the results of epidemiological research in human.

Kwiatkowska and co-workers studied DNA damage caused due to glyphosate and methylation of DNA in PBMCs (peripheral blood mononuclear cells). DNA damage occurred at the rate of 0.5 to 10 mM, also led to elevated gene promoter methylation subsequently with 0.25 mM and 0.5 mM when treated with glyphosate (Kwiatkowska et al., 2017). Lymphocytes based chromosomal damage (exchange of sister-chromatid) was observed at ≥1000 μg/ml (Bolognesi et al., 1997) but not for ≤6 mM (chromosome distortions) (Manas et al., 2009) on exposure with glyphosate. Glyphosate based herbicides triggered breakage of DNA strand of HepG2 cells with 5 ppm (29.6 μM) concentration (Gasnier et al., 2009) and cells of buccal epithelial carcinoma from 20 μg/ml (118.3 μM) (Koller et al., 2012).

In a review, glyphosate and glyphosate-based herbicides depicts cytotoxic and genotoxic effects, significantly raise oxidative stress, disrupt the oestrogen pathway, affect several other cognitive processes, and are thought to be associated with certain cancers. Mammals, considering humans, glyphosate primarily seems to have cytotoxic and genotoxic impacts, inflammation and interferes with functions of lymphocyte, immune system and the microbial interactions (Peillex and Pelletier, 2020)

However, the Joint WHO/FAO meetings on Pesticide Residues (WHO, 2016) concluded glyphosate is unlikely to be a human carcinogen (Soumis, 2018). In addition to that EPA has systematically assessed possible human well-being risk with exposure to glyphosate and determined that no risks to human health from the currently registered uses and glyphosate is not likely to be cancer-causing to individuals (Reaves, 2020). Very recently, USEPA also endorsed that glyphosate use as per the manufacturer's instructions does not pose any human health risks (Meftaul et al., 2020).

Cities, states and countries throughout the world have taken paths to either restrict or ban glyphosate (Goldman, 2020). Farmers, agriculture practitioner, landscapers and gardeners who are using Roundup weed killers or other herbicides based on glyphosate have a chance of developing non-Hodgkin lymphoma and other types of cancer (Schinasi et al., 2014). It was reported by Zhang et al., (2019) that the probability to develop non-Hodgkin lymphoma was increased to 41% on exposure to glyphosate based herbicides There are many lawsuits filed against the Glyphosate to raise its carcinogenic impacts on humans. A California pair alleged their non-Hodgkin's lymphoma cancer resulted through using Roundup since 1975 and 2011 the case was won in May 2019 reported by Roundup Cancer Attorneys and Lawsuits representing Penn-

Table 6
Toxicological dose indicators of glyphosate-based herbicides (GBH), Co-formulants and Glyphosate investigated in various studies.

	Product Name	Declared Active Ingredient (DAI)	DAI (Concentraion/ Percentage)	% of POEA present	Study done on	NOEC* (pm)	LOEC* (ppm)	LC50 (ppm)	References
GBH	Roundup Classic	G	–	–	Daphni–a magna	–	–	>20	Székács et al., 2014
	Glyfos	IPA	360 g/l	9	Human cells	75	85	86	Defarge et al., 2016
	Roundup WeatherMAX	Potassium salt of G	540 g/l	–	Human cells	60	70	71	Defarge et al., 2016
	Atanor 48 (ATN)	G	–	–	Zebrafish	–	1.7	76.5	Rodrigues et al., 2019
Co-Formulants	POEA	POEA	100%	100	Daphnia magna	–	–	>3.1	Székács et al., 2014
	POEA	POEA	100%	100	Human cells	3	3.5	3.9	Defarge et al., 2016
	QAC	QAC	30%	–	Human cells	35	50	58	Defarge et al., 2016
	POEA	Polyethoxylated tallow amine	100%	100	Zebra fish	–	0.4	5.49	Rodrigues et al., 2019
G	G	IPA	360 g/l	–	Human cells	3100	4600	7878	Defarge et al., 2016

IPA- Glyphosate-isopropylammonium, QAC- Quaternary ammonium compound, POEA-Polyethoxylated tallow amine, G-Glyphosate, NOEC-No Observed Effect Concentration, LOEC-Lowest Observed Effect Concentration. [NOEC and LOEC respectively correspond to the highest concentration without significant cytotoxic effect and to the lowest concentration with significant cytotoxic effect in ppm]

sylvania, Delaware, Philadelphia, New York, New Jersey and Nationwide. Also, there are more than 13,400 lawsuits across the United States involving Roundup, whose active ingredient is glyphosate is taken by Chemicals Company Bayer AG (Kline and Specter, 2019).

The carcinogenic risk needs to be evaluated not only for active ingredient but also for adjuvants. The declaration of individual toxicities of adjuvants should be clear in the technical formulations. This is particularly important in light of excessive global usage of the herbicide.

7. SDG goals and glyphosate

The sustainable development goals [SDGs] are comprised of 17 goals which can be inferred as a roadmap to approach sustainability and improved life for all beings (UN, 2020). Global agricultural activities, directly or indirectly link to many of the SDGs. Therefore, the agricultural activities must be carried out in a manner aiming to support for achieving the SDGs. Agricultural activities involve and affects not only human beings but also the environment. Indiscriminate use of pesticides in the previous decades has to lead many ecological disturbances besides some unidentified causes of deteriorated human well being.

The SDGs 2 aiming at zero hunger requires food security to meet the needs of all. Keeping the SDG 12 [Responsible Production and consumption] in mind, we should limit the use of agricultural chemicals especially those which pose a threat to sustainability. This will help us achieve SDG 8 [Decent work and economic growth]. We can prevent farmers deaths caused due to the acute toxicities and chronic exposures of many such pesticides or their adjuvants to the producers and end-users. Implementing sustainable agricultural practices will ultimately lead to SDG 3 on Good health and well being for all and improved Life below water and life on Land and [SDG 14 and 15, respectively].

Glyphosate is an extensively used herbicide before, during and in some cases even after the agricultural growing cycles. During the review, it was understood that glyphosate, as reported, may have relatively low toxicity in comparison to the adjuvants added to it. The adjuvants themselves are reported to have pesticidal action and have toxicities at very low concentrations levels. This aspect needs to be the background of risk assessment studies of glyphosate, besides the risk to non-target organisms, reduced bioavailability of soil nutrient [due to chelation] and impact on beneficial soil microbes.

The options of organic agriculture and plant-based natural herbicides need to be explored. Organic agriculture contributes significantly to SDG's and evidence of the same explained SDG 3 on health, SDG 5 on gender, SDG 6 on water, SDG 11 on the sustainable community, SDG 12 on responsible consumption and production, SDG 13 on climate action, SDG 14 on life underneath the water, SDG 15 on life on land, and SDG 17 on partnership for the goals (Setboonsarng and Gregorio, 2017). In addition to all studies, healthy soil producing healthy food and better nutrition is been discussed in the SDG's 1, 2, 11, 12 and 15 which is enhancing soil health and restoring land. Removal of biological matter from the soil, unnecessary tilling & irrigation by using poor quality water and overuse of synthetic pesticides are leading to damage the soil fertility, pollution and degradation and also vulnerable to approach SDG's goals (UN, 2020).

Conclusions

Glyphosate use has been on an increasing trend since its introduction. The ending of patent protection and introduction of GE crops which were resistant to the herbicide led to significant use of the herbicide globally.

Structurally the active ingredient may have relatively low chronic toxicity but there are many aspects of toxicity which needs to be extensively studied. Though the persistence of glyphosate in the environment is very low, its occupational exposure may lead to acute toxicity. Also, the toxicity posed by its co-formulants and transformation products like AMPA needs to be taken into account rather than glyphosate alone. This includes surfactants such as polyoxyethyleneamine (POEA) present herbicide formulations like Roundup.

Some environmental impacts of glyphosate are briefed in the review. Glyphosate can change the soil properties and affect the growth of soil microorganisms as for few it can act as a nutrient source but in some cases, it may raise the number of pathogenic microorganisms. Glyphosate half-life might vary according to the climate and it may last from days to years.It is also dependant on pH and soil type.

After coming in contact with water, glyphosate primarily breaks down into AMPA. Various studies reported the residual values of glyphosate as well as AMPA greater than MCL(Maximum contaminant level) after monitoring of water samples from various sites.Some studies indicate the presence of low amount of AMPA due to an ineffective metabolism of glyphosate in humans and animals. Some detailed studies also indicate that the co-formulants have high toxicological values than the glyphosate alone and some of the coformulants may act as herbicides even when used alone.

Though glyphosate-containing herbicides are used to kill weeds and unwanted vegetation, it is also adversely affecting the ecosystem due to its exposure to non-target species. The human health impacts mainly depend on the presence, duration and exposure of glyphosate-based herbicides.

According to WHO, (IARC, 2015) glyphosate has probable carcinogenic property. But there was no link between glyphosate traces of food and cancer as per the study. Glyphosate poses the risk of cancer mainly through Roundup or other herbicide based on glyphosate.

The review give an insight into the gaps in the current studies particularly about technical formulation containing coformulants, the impacts of which need to be assessed separately in detail.

As glyphosate and herbicides containing glyphosate have an substantial usage globally, it is of utmost importance to perform toxicological studies on all the major components of technical formulataions which could likely pose a threat to human health and environment. Also, glyphosate and related adjuvants should be included in the routine monitoring programs of countries where it is used extensively.

Declaration of Competing Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Chapter 1 Dill, G.M., Sammons, R.D., Feng, P.C.C., Kohn, F., Kretzmer, K., Mehrsheikh, A., Bleeke, M., Honegger, J.L., Farmer, D., Wright, D., Haupfear, E.A, 2010. Glyphosate:

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