Veterinary and Animal Science 10 (2020) 100126

Contents lists available at ScienceDirect

Veterinary and Animal Science

journal homepage: www.elsevier.com/locate/vas

Glyphosate-based herbicide formulations and reproductive toxicity in animals

Zachery Ryan Jarrell[1], Muslah Uddin Ahammad, Andrew Parks Benson*

Department of Poultry Science, University of Georgia, Athens, GA 30602, United States

ARTICLE INFO

Keywords:
Herbicide
Glyphosate
Reproduction
Residue
Animal

ABSTRACT

The adoption of genetically engineered (GE) crops in agriculture has increased dramatically over the last few decades. Among the transgenic plants, those tolerant to the herbicide glyphosate are among the most common. Weed resistance to glyphosate-based herbicides (GBHs) has been on the rise, leading to increased herbicide applications. This, in turn, has led to increased glyphosate residues in feed. Although glyphosate has been considered to be generally safe to animal health, recent studies have shown that GBHs have potential to cause adverse effects in animal reproduction, including disruption of key regulatory enzymes in androgen synthesis, alteration of serum levels of estrogen and testosterone, damage to reproductive tissues and impairment of gametogenesis. This review emphasizes known effects of GBHs on reproductive health as well as the potential risk GBH residues pose to animal agriculture.

1. Introduction

In modern crop production practices, herbicides have been a revolutionary tool for weed management. Their worldwide uses have increased exponentially because they provide an easy, efficient and cost-effective way of controlling weeds when compared to the alternative methods they have replaced. In addition, their non-invasive nature to the crops and broad-spectrum nature to all varieties of weeds helps increase total crop production value (Schroder et al., 1984; Franz et al., 1997; Coupe & Capel, 2016). The most popular and heavily applied, branded, broad- spectrum commercial herbicide in the world is Roundup, first produced by Monsanto Technology LLC in 1974 in the USA (Duke & Powles, 2008). Like many other herbicides, the Roundup formulation is composed of glyphosate [N-(phosphonomethyl) glycine], a primary active ingredient introduced in 1971, and inert ingredients (Baird et al., 1971; US-EPA, 2012; Guyton et al, 2015; Benbrook, 2016).

In industrial agriculture, the commercial success of glyphosate-based herbicides (GBHs) has dramatically been ameliorated by the introduction of transgenic crops, known as genetically engineered (GE) crops (Qaim & Zilberman, 2003; Qaim & Traxler, 2005; Fernandez-Cornejo et al., 2014). This included the Monsanto Company's 1996 introduction of Roundup Ready cultivars aimed at an increased level of crop protection through increased tolerance towards exposure to GBHs during the entire growth season of the crops (Benbrook, 2012; USDA, 2013a; Powles, 2014; Zilberman et al., 2018). The adoption of glyphosate tolerant (GT) crops has been very fast and the global use of glyphosate has increased 15-fold since 1996 (Benbrook, 2016). The US has approved 165 unique GT crops in 19 plant species, albeit only a few have been widely grown commercially since the late 1990s: soybean, corn, alfalfa, cotton, sugar beet and canola (James, 2017; Brookes & Barfoot, 2015). As of 2013, GT crops were used for production on over 95% of sugar beet, 93% of soy and 90% of all cotton and corn lands in the United States (USDA, 2013b). (USDA 2018a) Based on USDA survey data, the percent of domestic soybean acres planted with GT seeds rose from 17 percent in 1997 to 68 percent in 2001, before plateauing at 94 percent in 2014 and currently 90 percent of domestic corn acres are produced with GT seeds (USDA, 2019). Livestock, worldwide, are the largest consumers of GT crops. Livestock in the US consumes feed comprised 95% of GE ingredients, and livestock outside of the US consumes feed which consists 70-90% of GE ingredients (Flachowsky et al., 2012). A recent report by the USDA (2019) states that 94% of planted soybean and 90% of planted corn in the US is of a GT variety, which further suggests a large amount of GT crops found in animal feed. An estimated 77% of the global soybean production comes from GT soybean and the dominant soy producing countries of USA, Brazil and Argentina have a 94%–100% adoption rate of GT soy (James, 2017). Corn and soybean are the two primary components in livestock feed. For example, a dairy diet in the US typically contains

* Corresponding author. 110 Cedar St. Poultry Science Building, Athens, GA 30602, United States
E-mail addresses: zachery.ryan.jarrell@emory.edu (Z.R. Jarrell), muslah@uga.edu (M.U. Ahammad), dbenson@uga.edu (A.P. Benson).
[1] These authors contributed equally

https://doi.org/10.1016/j.vas.2020.100126
Received 14 November 2019; Received in revised form 17 June 2020; Accepted 18 June 2020
Available online 24 June 2020

Table 1
Effects of glyphosate-based herbicides and their ingredients on the reproductive health of females across species at varying dosages. Dosages listed are the minimum reported dosage to cause an effect. In cases where both *in vitro* and *in vivo* treatments have been investigated, the *in vivo* treatment was represented. ↑ represents an increase in the listed effect, while ↓ represents a decrease. The minimum effect-causing dosage and format of treatment are indicated by a number followed by a two-letter abbreviation of the treatment. In the case of oral gavage (OG), subcutaneous injection (SC) and *in ovo* (IO) treatment, the treatment was reported as mg/kg. For *in vitro* (IT), aquatic exposure (AQ) and topical application on the surface of the egg (TA), the reported level is reported as ppm. The letter given in italics corresponds to the chemical treatment investigated: a commercial GBH formulation (H), glyphosate (G) or POEA (P). Corresponding studies are indicated by the lower-case letter (a-n) on the right of each cell.

	Zebrafish		Red-eared slider		Chicken		Cattle		Rat		Wistar rat		Human	
Aromatase activity													↓ 2000 IT *H*	a
Androgen receptors													↓ 0.5 IT *H*	b
Androgen levels											↑ 50 OG *H*	c		
Estrogen receptors														
Estrogen levels							↓ 5 IT *G*	d			↑ 50 OG *H*	c		
Progesterone levels							↓ 10 IT *H*	e						
FSH activity							↓ 10 IT *H*	e			↑ 50 OG *H*	c		
LH activity											↑ 50 OG *H*	c		
Oxytocin secretion							↑ 0.01 IT *H*	f						
Uterine abnormalities									↑ 2 SC *H*	g,h	↑ 2 SC *H*	i		
Granulosa cell proliferation							↓ 0.1 IT *H*	d,e						
Egg production	↓ 10 AQ *G*	j									↓ 126 OG *G*	k		
Placental function													↓ 10 IT *P*	l
Embryo malformations					↑ 9.9 IO *H*	m								
Embryo mortality	↑ 10 AQ *H*	j	↑ 11206 TA *H*	n	↑ 9.9 IO *H*	m								

aRichard et al., 2005. bGasnier et al., 2009. cRomano et al., 2012. dPerego et al., 2016. ePerego et al., 2017. fWrobel, 2018. gIngaramo et al., 2016. hVarayoud et al., 2017. iSchimpf et al., 2017. jWebster et al., 2014. kHamdaoui et al., 2018. lDefarge et al., 2016. mWinnick, 2013. nSparling et al., 2006.

Table 2
Effects of glyphosate-based herbicides and their ingredients on the reproductive health of males across species at varying dosages. Dosages listed are the minimum reported dosage to cause an effect. In cases where both *in vitro* and *in vivo* treatment has been investigated, the *in vivo* treatment was represented. represents an increase in the listed effect, while ¯ represents a decrease. Represents both a reported increase and a reported decrease at the given level of treatment, and "no" represents no observed effect. The minimum effect-causing dosage and format of treatment are indicated by a number followed by a two-letter abbreviation of the treatment format. In the case of oral gavage (OG), prenatal oral gavage (PG), subcutaneous injection (SC) and *in ovo* (IO) treatment, the treatment was reported as mg/kg. For *in vitro* (IT) and aquatic exposure (AQ) the reported level is reported as ppm. The letter given in italics corresponds to the chemical treatment investigated: a commercial GBH formulation (H), glyphosate (G) or POEA (P). A "/" between any of these treatment abbreviations indicates that both treatments listed resulted in an effect at the indicated level.

	Zebrafish		Duck		Rat		Albino rat		Wistar rat		SD rat		Mouse		Human	
Aromatase activity					↑ 1 IT *G*	a									↓ 10 IT *H*	b
Androgen receptors			↓ 5 OG *H*	c												
Androgen levels			↓ 5 OG *H*	c	10 OG *H*	d,e	↓ 3.6 OG *G*	f			↓ 5 OG *H*	g-i	↓ 1 IT *H*	j,k		
Estrogen receptors															↓ 2 IT *H*	b
Estrogen levels			↓ 5 OG *H*	c	↑ 50 OG *H*	d										
Progesterone levels													↓ 25 IT *H*	l		
FSH activity					↑ 50 OG *H*	d	↓ 3.6 OG *G*	f								
LH activity					↑ 50 OG *H*	d	↓ 3.6 OG *G*	f								
Prolactin levels							↓ 3.6 OG *G*	f								
Testicular abnormalities			↑ 5 OG *H*	c	↑ 50 OG *H*	d,m	↓ 3.6 OG *G*	f	↑ 5 OG *H*	g,h	no 25 OG *H/G*	k				
Epididymal abnormalities			↑ 5 OG *H*	c					↑ 5 OG *G*	i						
Sertoli cell death											↑ 1000 IT *H*	j	↑ 500 IT *H/P*	n		
Leydig cell death					↑ 250 OG *G*	m	↓ 3.6 OG *G*	f			↑ 1000 IT *H*	j				
Germ cell death											↑ 1000 IT *H*	j				
Sperm count					↓ 250 OG *G*	m	↓ 3.6 OG *G*	f	↓ 5 OG *G*	g,i						
Teratospermia							↓ 3.6 OG *G*	f	↑ 50 PG *H*	g						
Sperm viability					↓ 250 OG *G*	m			↓ 5 OG *G*	i						
Sperm DNA integrity	↓ 5 AQ *G*	o														
Sperm motility	↓ 5 AQ *G*	o			↓ 250 OG *G*	m	↓ 3.6 OG *G*	f	↓ 5 OG *G*	i					↓ 0.36 IT *G*	p,q
Mitochondrial function	↓ 5 AQ *G*	o													↓ 0.36 IT *G*	p,q

aClair et al., 2012. bGasnier et al., 2009. cOliveira et al., 2006. dRomano et al., 2012. ePandey & Rudraiah, 2015. fOwagboriaye et al., 2017. gDallegrave et al., 2007. hRomano et al., 2010. iAbarikwu et al., 2015. jClair et al., 2012. kJohansson et al., 2018. lWalsh et al., 2000. mIkpeme et al., 2012. nVanlaeys et al., 2018. oLopes et al., 2014. p Anifandis et al., 2017. qAnifandis et al., 2017.
Corresponding studies are indicated by the lower-case letter (a-q) on the right of each cell.

70% corn products and 10% dehulled soybean meal, while poultry diets consist of as much as 35% soybean meal and 65% corn grain (Van Eenennaam & Young, 2014). Poultry flocks, consuming about half of all soybean meal produced, are the single largest domestic consumer of soybean meal, followed by swine (Van Eenennaam & Young, 2014). The USDA (2018b) estimates that 87% of soybean and 57% of corn grain produced are used in livestock diets around the world each year.

This widespread adoption of glyphosate-tolerant crops contributed to global and intensive use of GBHs, including Roundup (Benbrook, 2012; Osteen & Fernandez-Cornejo, 2013; Fernandez-Cornejo et al., 2014; Coupe & Capel, 2016). The diversified application of GBHs as a pre-harvest herbicide or desiccant has also elevated the number of exposures to glyphosate during the crop or weed growing cycle (Monsanto, 2010). In addition, for over a decade, with the widespread emergence of a massive number of glyphosate-resistant "super" weeds by the intensive usage of Roundup, the concentration

and frequency of its application have been on rise (Powles & Preston, 2006; Preston et al., 2009; Cruz-Hipolito et al., 2011; Heap, 2014; Green, 2018, Comont et al., 2019). As a consequence, the worldwide use of Roundup by volume continues to rise at a steady pace (Heap, 2014; Coupe & Capel, 2016). According to estimates by the United States Geological Survey, 287 million pounds of glyphosate was sprayed nationwide in 2016, 20 times as much as was used in 1992. (USGS, 2017). This assures an increased accumulation of glyphosate residues in GT crops, as GT crops have been shown to be capable of absorbing and translocating applied glyphosate at high levels in the entire plant (Hetherington et al., 1999; Satchivi et al., 2000; Feng et al., 2003; Reddy et al., 2004) and grains (Duke et al, 2003; Arregui et al., 2004; Cuhra, 2015; Cuhra et al., 2016). The presence of post-application glyphosate and/or its notable metabolite, aminomethylphosphonic acid (AMPA), in GT crops has been well documented (Arregui et al., 2004; Duke, 2011; Bøhn et al., 2014; Bai et al., 2016). Depending on the frequency of GBH's application and stage of growth, the GT crops have been shown to contain glyphosate and/or its metabolites at a wide range of concentrations (Duke et al., 2003; Arregui et al., 2004; Xu et al., 2019).

Given this evidence of GBH residues incorporated into GE crops, some effort has gone into inspecting the effects of these crops as livestock feed (Bøhn et al., 2014; EFSA, 2014). A large number of studies have focused on evaluating nutrient profile and nutritive value of GE crops as well as the productive performance and health of major food-producing animals fed GE crops. The GE crops, including GT crops, do not have any apparent differences from non-GE crops in terms of nutritional impact (Hollingworth et al., 2003; Flachowsky et al., 2005a; Flachowsky et al., 2005b; Cheng et al., 2008; García-Villalba et al., 2008; Flachowsky et al., 2012; Herman & Price, 2013). Although glyphosate has been considered to be generally safe to animal health and productive performance from a nutrition standpoint, true risk assessment with respect to animal production must give regard to another aspect of animal husbandry, the reproductive health of breeding lines. Recent investigations suggest that GBH residues found on GT crops have the potential to introduce quiet, yet deleterious effects, on the reproductive ability of animals reared for an extended amount of time, such as the parent stock kept for breeding purposes. Our objective in writing this review is to outline the entrance of GBH exposures to livestock production systems, to summarize the current literature on reproductive health as it pertains to GBH exposures and to discuss the potential impacts of continued GBH usage with regard to sustainable animal production practices.

Studies were included in our review if they met the following criteria: (1) published in a peer-reviewed journal; (2) English language; (3) studies and review papers that evaluated the association between glyphosate or Round up with reproductive outcome(s) in animals; (4) industry or government publications concerning glyphosate monitoring and testing in feed commodities. Multiple search strategies were employed to identify literature related to glyphosate exposure and reproductive fitness outcomes. Google Scholar and Web of Science searches were conducted using the term “glyphosate,” and “Round up OR Roundup” in separate searches. These searches were made in conjunction with various terms related to reproduction (e.g., “fertility,” “sperm,” “endocrine,” “embryo,” “gametogenesis”) or animal performance (e.g., “growth,” “nutrition”). In addition, broader searches for articles and government documents related to glyphosate testing and monitoring programs in animal feed and common feed commodities (e.g., “corn,” “soy”) were conducted. To ensure completeness of the search, the reviewers cross checked reference lists in the articles and reviews to identify any studies that might have been missed by the electronic search.

2. Formulations of glyphosate based major herbicides

GBHs typically consist of glyphosate concentrated between 356 and 540 g acid equivalent/L and various additional adjuvants and surfactants (Mertens et al., 2018). Glyphosate, a derivative of glycine, is a weak acid whose water solubility is low (Farmer, 2010). In typical formulations of commercially available GBH products, glyphosate is incorporated in the form of either isopropylamine (IPA), potassium, monoammonium, diammonium, trimethylsulfonium or sesquisodium salt to enhance its water solubility and stabilization, and to make the product easier to handle. The isopropylamine salt of glyphosate is the most commonly used active ingredient in the formulation of GBHs (Mertens et al., 2018). Upon entering into and transportation throughout the plant the glyphosate is separated from its cation, and its herbicidal parent acid is eventually absorbed by the plant to inhibit biosynthesis of aromatic amino acids required for construction of proteins (Mertens et al., 2018). This effect is achieved by blocking the activity of the enzyme enolpyruvylshikimate-3-phosphate synthase in the shikimate pathway (Gomes et al., 2014). In order to function, GBH formulations inevitably require adjuvants (surfactants, spreader stickers, crop oils, anti-foaming materials, buffering agents, and compatibility agents) to facilitate adequate plant coverage with glyphosate salts and the penetration of the salts through the waxy coverings of leaves and stems so they may be transported within the plants without losing the toxic effect of glyphosate (Stock & Holloway, 1993), thereby increasing bioavailability of GBH. By nature of their function, the adjuvants are typically considered by the manufacturer to be “inert” ingredients, meaning that they are physically, chemically, or biologically inactive, and the contents of inert ingredients are generally not declared on product labels for the sake of proprietary secrecy (Mertens et al., 2018). Although the damaging effect of glyphosate was tested exclusively and very extensively, a complete toxicity risk assessment for GBH formulations is often hindered by the lack of adequate product-specific information on the so-called inert ingredients (Cox & Surgan, 2006). Studies have demonstrated that polyethoxylated tallow amine (POEA), the most commonly identified surfactant which is seldom declared on product labels of common GBHs, increases phytotoxicity of herbicide formulations as well as exerts toxic effects on humans, animals, and microorganisms (Mann & Bidwell, 1999; Tsui & Chu, 2003; Cox & Surgan, 2006; Moore et al., 2012; Defarge et al., 2016; Tush & Meyer, 2016). As such, it is increasingly well documented that chemical mixtures in the formulations exhibit far more toxicity than glyphosate alone (Peixoto, 2005; Benachour et al., 2007; Benachour & Seralini, 2009; Gasnier et al., 2010; Frontera et al., 2011; Gasnier et al., 2011; Clair et al., 2012; Moore et al., 2012; Mesnage et al., 2014; Mesnage et al. 2015). Mass spectrometry analysis of GBHs identified both petroleum distillates (Mesenage et al., 2013) and heavy metals (Defarge et al. 2018). It is therefore important to note that studies performed with glyphosate alone are not necessarily representative of the environmental exposure and toxicology of GBHs and this is unfortunately a regular misunderstanding which can make the literature on this subject confusing.

3. Residues of glyphosate and AMPA in GE crops

Testing for glyphosate and/or AMPA residues in crops and food products has been a topic of interest in industrial food production, however, very few large-scale studies of crops have been performed. Among these few studies, grains and legumes have been primary focuses (Arregui et al., 2004; USDA, 2013a; Bøhn et al., 2014; Cuhra, 2015; Cetin et al., 2017; Tarazona et al., 2017). Of the crops studied for presence of glyphosate and AMPA, soy has been the most severe culprit, resulting in residue levels as high as 18.5 and 20.0 ppm and averaging at levels closer to 2.0 and 3.5 ppm, respectively (Duke et al., 2003; Arregui et al., 2004; USDA, 2013a; Bøhn et al., 2014). Residue levels are generally increased with higher frequency of application and/or application closer to time of harvest (Duke et al., 2003; Bøhn et al., 2014). The United States government tested for glyphosate residues in food commodities in 2013 by the United States

Department of Agriculture (USDA) and in 2016 by the United States Food and Drug Administration (FDA). The USDA (2013a) study of soy crops found glyphosate residues in 90.3% of samples, with a range from 0.25 ppm to 18.5 ppm and average of 1.94 ppm. For AMPA, the USDA (2013a) study found 95.7% of samples tested positive with a range from 0.26 ppm to 20 ppm and an average of 2.23 ppm. The most recent FDA (2016) study of soy crops found glyphosate residue in 67% samples with a mean average of 0.79 ppm and maximum detection of 10 ppm and found AMPA in 61% of tested samples with a mean average of 0.84 ppm and maximum detection of 13.9 ppm. As for corn, the FDA (2016) study found glyphosate residues in 66% of samples, mean average of 0.04 ppm and maximum detection of 4.5 ppm, and found AMPA in 39% of samples with a mean average of 0.03 ppm and maximum detection of 5.5 ppm. Both the FDA and USDA surveys found average glyphosate residues below the maximum residue level (MRL) of 20 ppm for soy and 5 ppm for corn. The source and type of the soybean tested by the USDA and FDA are unclear but was likely GT soybean since US farmers used GT soybeans on 93% of all planted soybean acers in 2013 (Fernandez-Cornejo et al., 2014). It should be noted that Bøhn et al., 2014 found higher mean average levels of both glyphosate (3.26 ppm) and AMPA (5.74 ppm) around the same time in GT soybean sourced from the US. Although Bøhn et al. (2014) could not detect either glyphosate or AMPA in either conventional or organic soy, both glyphosate and AMPA has been detected in soils, surface water, ground water and precipitation in the US (Battaglin et al. 2014). These studies (USDA, 2013a; Bøhn et al., 2014; FDA, 2016) used HPLC with fluorescence detector (HPLC/FLD) as their method of detection with a reported limit of detection (LOD) of 0.1 ppm to 50 ppm and a default limit of quantification of 0.01 ppm (FDA, 2016) or LC/MS/MS with a LOD of 0.02 μ/l (Battaglin et al. 2014).

Collectively, the World Trade Organization (WTO) is an important international body concerning regulation of glyphosate due to its Agreement on the Application of Sanitary and Phytosanitary measure (SPS Agreement) shared by member nations (WTO, 2012). Jointly, the United Nations Food and Agriculture Organization (FAO) and WTO agreed on MRL for glyphosate in corn, soybean, cereal grains, cotton seed, sorghum straw, wheat, wheat straw, alfalfa and hay set at 5.0, 20, 30, 40, 50, 200, 300, 500 and 500 ppm, respectively (WHO, 1994; WTO, 2012). The FAO suggests that total glyphosate residues should be calculated as the sum of the amount of glyphosate residues and 1.5 times the amount of AMPA residues since AMPA has a similar toxicity profile as glyphosate (Giesy et al. 2000; Bøhn et al., 2014). A recent review by Xu et al. (2019) provides an overview concerning current global testing and regulation of GBHs. It should be noted, as reviewed by Cuhra (2015), that MRLs are largely based on industry studies and more independent research is needed to establish more informed regulatory guidelines.

4. Productive performances of animals fed on GT crops

As to nutrient composition and nutritive value, GT crops have been shown to be equivalent to their non-GE counterparts (Hollingworth et al., 2003; Harrigan et al., 2007; Cheng et al., 2008; García-Villalba et al., 2008; Herman & Price, 2013). Studies have found no difference in the productive performance or health of any beef cattle (Erickson et al., 2003), dairy cattle (Grant et al., 2003; Ipharraguerre et al., 2003; Combs and Hartnell, 2008), broiler (Kan and Hartnell, 2004; Taylor et al., 2007a, 2007b, 2007c); McNaughton et al. 2011), sheep (Hartnell et al., 2005) or quail (Sartowska et al., 2015) fed on GT-based feedstuffs. These analyses concerning livestock, however, do not address potential reproductive issues related to glyphosate or GBHs. Very few studies involved feeding GT crops evaluate the effects of herbicide residues in tissues or organs of animals. In commercial broilers and dairy cows that fed on GT-based diets, glyphosate residue has been detected in the liver, spleen, lungs, intestines, heart, muscles and kidneys (Krüger et al., 2014, Shehata et al., 2014). The residue has also been found in human blood and in the urine of humans, dairy cows, rats, and rabbits (Acquavella et al., 2004; Curwin et al., 2007; Krüger et al., 2013; Zouaoui et al., 2013; von Soosten et al., 2016; Conrad et al., 2017; Mills et al., 2017; Panzacchi et al., 2018).

5. Hormonal effects

Glyphosate and GBHs are well documented endocrine disruptors. GBHs are reported to inhibit aromatase activity and transcription in human cells at levels as low as 10 ppm, well below no-observed-adverse-effect level (NOAEL) of 50 ppm (Gasnier et al., 2010; EFSA, 2015; Defarge et al., 2016; Defarge et al., 2018). At an even lower dose of 1 ppm, glyphosate increased aromatase mRNA levels while causing a simultaneous decrease in testosterone (Clair et al., 2012). This observed increase in aromatase mRNA transcription and lower levels of testosterone is likely due to the inhibition of aromatase activity. Both kinetic and spectral studies show that GBH inhibits aromatase at the active site level in a competitive manner and that this impact of disrupting aromatase is noticeable in human placental cell lines after 18 hours. (Richard et al., 2005).

In the female system, *in vitro* treatment of bovine granulosa cells with glyphosate as low as 5 ppm resulted in a decrease of estrogen levels as well as an increase in progesterone levels (Perego et al., 2017a; Wrobel, 2018). However, *in vivo* murine studies reveal an increase in both estrogen and androgen levels with daily treatment of 50 mg/kg bodyweight (Romano et al., 2012). Glyphosate disrupts expression of estrogen receptors (ER) and progesterone receptors (PR) as well. Glyphosate and GBHs are recorded as decreasing ERα at 2 ppm and 5 ppm, respectively, in the luminal epithelium of the rat uterus (Schimpf et al., 2017; Varayoud et al., 2017). Glyphosate at 2 ppm also increases uterine expression of PR in the murine system (Schimpf et al., 2017). Glyphosate at levels as low as 100 ppb even lead to short term increases in ERα and ERβ in human breast cancer cells (Thongprakaisang et al., 2013). Using a breast cancer cell line which possesses a high level of androgen receptors, Gasnier et al. (2010) demonstrated that GBH at a concentration of 0.5 ppm possesses anti-androgenic behavior and disrupts androgen receptor. Follicle stimulating hormone (FSH) and luteinizing hormone (LH) activities have also shown increase with *in vivo* study of the murine system with treatment at 50 mg/kg bodyweight (Romano et al., 2012). Similar to estrogen, FSH activity is shown to decrease in *in vitro* study of bovine granulosa cells treated with GBH at 10 ppm (Perego et al., 2017a). Furthermore, oxytocin secretion by bovine luteal cells is seen to be increased by both glyphosate and GBH at levels as low as 10 ppb (Wrobel, 2018).

In the male system, estrogen levels are shown to increase with GBH dosage of 50 mg/kg bodyweight in rats but to decrease with dosage of 5 mg/kg bodyweight in drake (Oliveira et al., 2007; Romano et al., 2012). The differences in serum estrogen levels could be species specific, or as suggested by Romano et al. (2012), due to increased level of gonadotropin expression and failure in the interpretation of the negative feedback mechanism at the higher (50 mg/kg) dose. *In vitro* treatment of murine Leydig cells with GBH at 25 ppm displayed a decrease in progesterone levels (Walsh et al., 2000). In studies of both duck and rat males, decreases in serum androgen levels were observed with treatments of GBH as low 5 mg/kg bodyweight, with magnitudes of effect in a dose-dependent manner (Dallegrave et al., 2007; Oliveira et al., 2007; Romano et al., 2010; Clair et al., 2012; Abarikwu et al., 2015; Pandey & Rudraiah, 2015; Nardi et al., 2017; Owagboriaye et al., 2017). It should be noted that one study (Romano et al., 2012) reported an increase in serum androgen levels at a GBH treatment of 50 mg/kg bodyweight which the authors attributed to either their observed increase in LH or failure in the negative feedback mechanism. Another recent study of male rats treated with either oral gavage of glyphosate alone or GBH at 25 mg/kg bodyweight displayed no significant changes to intra-testicular androgen levels, but the GBH formulation resulted in a small

effect on steroidogenic gene expression (Johansson et al. 2018). Male ducks have shown a decrease in androgen receptors with GBH treatment at 5 mg/kg bodyweight (Oliveira et al., 2007). In human liver cell line, HepG2, treatment with GBH at concentration 2 ppm results in an estrogenic effect and disrupts transcriptional activities on both estrogen receptors, ERα and ERβ (Gasnier et al., 2010). Romano et al. (2012) reported increases in FSH and LH levels were observed in albino rats treated with a much lower dose of 3.6 mg/kg bodyweight (Owagboriaye et al., 2017). Male albino rats treated with GBH at doses as low as 3.6 mg/kg bodyweight saw an increase in prolactin levels in a dose dependent manner (Owagboriaye et al., 2017). Excess of prolactin disrupts release of gonadotropin-releasing hormone, which leads to decreased testosterone levels (Zeitlin & Rajfer, 2000). High levels of prolactin in males tends to impede gonadal development, further decreasing reproductive function (Corsello et al., 2003). It should be noted that despite the research outlined above, the European Food Safety Authority conducted a review and concluded that glyphosate does not have endocrine disrupting properties (EFSA 2017)

6. Effects on reproductive tissues

Subcutaneous injection of female rats with GBH at 2 mg/kg bodyweight resulted in uterine morphological changes. Abnormal uterine decidualization as well as increases in uterine luminal epithelial, stromal and myometrial thickness were observed (Ingaramo et al., 2016; Schimpf et al., 2017; Varayoud et al., 2017). *In vitro* treatment of bovine granulosa cells with glyphosate or GBH resulted in decreased cell proliferation at levels as low as 0.1 ppm (Perego et al., 2017a, 2017b).

In males, a variety of effects on testicular and epididymal tissues have been observed with respect to glyphosate and GBH treatment at levels as low as 5 mg/kg bodyweight. An increase in seminiferous tubule lumen diameter was observed in ducks and rats (Oliveira et al., 2007; Romano et al., 2010). With regard to seminiferous tubule epithelia, differing results have been noted, these being both increases and decreases in epithelium height, degeneration of the epithelium, vacuolization of the tubule and separation of the tubule epithelium from interstitial cells (Dallegrave et al., 2007; Oliveira et al., 2007; Romano et al., 2010, 2012; Ikpeme et al., 2012; Owagboriaye et al., 2017). Rat studies have reported decreases in interstitial cells with GBH treatment at 50.4 mg/kg bodyweight but increases in interstitial space at 250 mg/kg bodyweight treatment of GBH due to invasion by inflammatory cells (Ikpeme et al., 2012; Owagboriaye et al., 2017). Recently, a study of male rats exposed by oral gavage to either glyphosate or a GBH formulation at 25 mg/kg bodyweight revealed no significant changes to the histology of testes (Johansson et al., 2018). Reduction in epididymal tissues was observed in rat and duck studies at treatments with glyphosate and GBH as low as 5 mg/kg bodyweight (Oliveira et al., 2007; Ikpeme et al., 2012; Abarikwu et al., 2015). Clair et al. (2012) reported death of murine Sertoli, Leydig and germ cells with *in vitro* treatment of GBH at 1000 ppm. Other murine studies have reported death of Sertoli cells with *in vitro* treatment of GBH and POEA at 500 ppm and death of Leydig cells with *in vivo* treatment with glyphosate at levels as low as 3.6 mg/kg bodyweight (Ikpeme et al., 2012; Owagboriaye et al., 2017; Vanlaeys et al., 2018).

7. Effects on gametogenesis

The effects of GBHs on oogenesis has been a topic of little study. One investigation utilizing zebrafish reports reduction in egg production in an aquatic environment containing glyphosate at 10 ppm, while investigation using a murine model reports reduction in follicular development with treatment of glyphosate at 126 mg/kg bodyweight (Webster et al., 2014; Hamdaoui et al., 2018).

Contrary to oogenesis, spermatogenesis has been a larger topic of study. Murine studies of males treated with oral gavage of glyphosate at levels as low as 3.6 mg/kg bodyweight have reported a reduction in sperm count (Ikpeme et al., 2012; Abarikwu et al., 2015; Owagboriaye et al., 2017) as well as an increase in sperm morphological abnormalities (Owagboriaye et al., 2017). Dallegrave et al. (2007) investigated prenatal exposure to GBH at a concentration of 50 mg/kg bodyweight of gestating rat mothers and reported decreased sperm count and increased sperm morphological abnormalities in male offspring. Sperm viability has been reported to decrease in murine systems with doses of glyphosate as low as 5 mg/kg bodyweight (Ikpeme et al., 2012; Abarikwu et al., 2015). Reduction in sperm DNA integrity has been shown in zebrafish treated in an aquatic environment containing glyphosate at 5 ppm (Lopes et al., 2014). Oral gavage of rats with glyphosate doses as low as 3.6 mg/kg bodyweight has resulted in reduction of sperm motility (Ikpeme et al., 2012; Abarikwu et al., 2015; Owagboriaye et al., 2017). Similarly, treatment of zebrafish in an aquatic environment containing glyphosate at 5 ppm resulted in decreased sperm motility and decreased mitochondrial function (Lopes et al., 2014), as did *in vitro* treatment of human sperm cells with GBH at 1 ppm and glyphosate at 0.36 ppm (Anifandis et al., 2017, 2018). The toxic effect of GBH on spermatozoa is likely mediated through the induction of oxidative stress and mitochondrial impairment (Peixoto, 2005; Modesto et al. 2010; Lopes et al. 2014,; Zhang et al. 2019).

8. Developmental toxicity

In viro treatment with POEA at 10 ppm is reported to decrease human placental cell function (Defarge et al., 2016). In ovo injection of either GBH at 9.9 or glyphosate at 19.8 mg/kg egg weight in chicken eggs at day 6 of incubation has resulted in reduction in embryo mass, heart and liver mass, tibiotarsus length and beak length as well as increases in embryo mortality (Winnick, 2013). Aquatic treatment of zebrafish with GBH at 10 ppm resulted in increased embryo mortalities and premature hatching (Webster et al., 2014). In a study of red-eared sliders, fertilized eggs at day 7 of incubation given a topical application of GBH at 11206 ppm exhibited an increase in embryo mortality as well as a decrease in hatch weight (Sparling et al., 2006). In a study of female rats treated with neonatal exposure to GBH at 2 mg/kg bodyweight, the dams exhibited reduced reproductive performance and increased post-implantation embryo loss, thought to be caused by irregular endometrial decidualization as a result of GBH treatment (Ingaramo et al., 2016).

9. GBH as potential threat to reproductive health of livestock

Considering the above body of literature, summarized in Table 1 and Table 2 concerning the deleterious effects of GBHs and their ingredients on reproductive health and performance of a variety of model animals and cell lines across a wide range of dosage levels, all of which are well within the nonlethal dosage and many of which are well within the MRLs allowed, consideration must be paid to the potential effect of GBH exposures on the reproductive health of livestock. Given the variety of negative effects on reproductive health reported to be associated with GBH exposure in the animals discussed, it is likely that similar effects may be observed in animals of agricultural importance.

Unfortunately, very few studies have investigated the effects of these exposures on agriculturally important animals, and the majority of those that have, have given no concern to reproductive health and performance (Erickson et al., 2003; Grant et al., 2003; Ipharraguerre et al., 2003; Taylor et al., 2007a, 2007b; Kan and Hartnell, 2004; Hartnell et al., 2005; Combs and Hartnell, 2008; McNaughton et al. 2011; Sartowska et al., 2015). This is due, in part, to the fact that for an overwhelming majority of any livestock population, the reproductive health and performance is of no concern for a producer. There is, however, a small subset of every livestock population which is maintained for breeding purposes, in order to provide a steady

supply of offspring for food production. Typically, this subset of the population is reared for much longer than their offspring, which are, in the case of meat production, only grown to market weight. These breeding populations, in most cases, receive similarly formulated if not identical feed to that of their offspring reared for food production. Their risk of daily exposure to GBH residues through feed is similar to that of their offspring, but chronic exposure over a longer period of rearing results in even higher potential for negative effects on reproductive health.

Losses in fertility of genetic stock has long been recognized as an impending issue in animal agriculture which has potential to cause economic strain on the industry (Pollock, 1999; Berry et al., 2016). The cause behind these issues is expected to be multifaceted, and the remedy to these issues will likely be multifaceted, as well. Given what is known about the effects of GBH exposure on reproductive health and the expected risk for GBH exposure posed to agriculturally important animals, it is expected that GBH exposure could be one of the causes for gradual loss in fertility of genetic stock. Therefore, characterization and neutralization of this expected risk could prove helpful in ameliorating the strain which losses in fertility present for animal agriculture industries.

Given the effectiveness and wide-spread use of GBHs, one strategy to reduce the potential impact on reproductive fitness in livestock is through neutralization. Several studies have reported that glyphosate can be absorbed by humic acids (Piccolo et al. 1996; Bata et al. 2009; Mazzi and Piccolo, 2012). The inclusion of humic acids at 0.25% has been reported to improve feed conversion in broilers (Kocabagli et al. 2002) and 0.2% inclusion was shown to improve feed conversion in hens (Yoruk et al, 2004). Recently, Shehata et al. (2014) showed that feed supplementation at 0.2% lead to a significant decrease in glyphosate content in broilers without impacting production parameters. More studies are needed to identify neutralizing agents that have the potential to ameliorate the potential impact of glyphosate on reproductive fitness in livestock.

10. Conclusion

Based on the literature reviewed in this paper, some ingredients of GBHs, both active and inert, appear to act as reproductive toxicants, having a wide range of effects on both the male and female reproductive systems, including endocrine disruption, tissue damage and dysfunction of gametogenesis. Further study is needed of the effects of GBHs and their ingredients on the long- term reproductive health of livestock. More large-scale analysis of GBH residues on livestock feeds is needed, as is investigation of the absorption of GBH residues from feed consumed by livestock. Should the minimum level of GBH exposure required to produce negative effects on the reproductive health of livestock prove to be lower than typical GBH residue levels found in feed, attention should be given to investigation of potential methods for minimizing the threat posed by GBH exposures. Potential methods for reducing the expected threat could include addition of neutralizing agents to feed containing GBH residues, introduction of stricter regulation to ensure responsible application of GBH to crops used for animal feed or exploration of GBH-free alternatives as livestock feed. Comprehensive investigation of these unknowns will inform future usage of GBHs on feed crops and the usage of these feed crops in livestock production to ensure sustainable production in animal agriculture industries.

Funding

This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version. This manuscript has not been submitted to, nor is under review at, another journal or other publishing venue. The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript

References

Abarikwu, S. O., Akiri, O. F., Durojaiye, M. A., & Adenike, A. (2015). Combined effects of repeated administration of Bretmont Wipeout (glyphosate) and Ultrazin (atrazine) on testosterone, oxidative stress and sperm quality of Wistar rats. *Toxicology Mechanisms and Methods, 25*(1), 70–80. https://doi.org/10.3109/15376516.2014.989349.

Acquavella, J. F., Alexander, B. H., Mandel, J. S., Gustin, C., Baker, B., Chapman, P., & Bleeke, M. (2004). Glyphosate biomonitoring for farmers and their families: results from the Farm Family Exposure Study. *Environmental Health Perspectives, 112*(3), 321–326. https://doi.org/10.1289/ehp.6667.

Anifandis, G., Amiridis, G., Dafopoulos, K., Daponte, A., Dovolou, E., Gavriil, E., Gorgogietas, V., Kachpani, E., Mamuris, Z., Messini, C. I., Vassiou, K., & Psarra, A. G. (2017). The in vitro impact of the herbicide Roundup on human sperm motility and sperm mitochondria. *Toxics, 6*(1), e2. https://doi.org/10.3390/toxics6010002.

Anifandis, G., Katsanaki, K., Lagodonti, G., Messini, C., Simopoulou, M., Dafopoulos, K., & Daponte, A. (2018). The Effect of Glyphosate on Human Sperm Motility and Sperm DNA Fragmentation. *International Journal of Environment Research and Public Health, 15*(6), e2. https://doi.org/10.3390/ijerph15061117.

Arregui, M. C., Lenardon, A., Sanchez, D., Maitre, M. I., Scotta, R., & Enrique, S. (2004). Monitoring glyphosate residues in transgenic glyphosate-resistant soybean. *Pesticide Management Science, 60*(2), 163–166. https://doi.org/10.1002/ps.775.

Bai, S. H., & Ogbourne, S. M. (2016). Glyphosate: Environmental contamination, toxicity and potential risks to human health via food contamination. *Environmental Science and Pollution Research International, 23*(19), 18988–19001. https://doi.org/10.1007/s11356-016-7425-3.

Baird, D. D., Upchurch, R. P., Homesley, W. B., & Franz, J. E. (1971). Introduction of a new broad-spectrum postemergence herbicide class with utility for herbaceous perennial weed control. *Proceedings North Central Weed Control Conference, 26*, 64–68.

Banta, G., Hansen, P., & Jacobsen, O. (2009). The influence of organic matter on sorption and fate of glyphosate in soil-comparing different soils and humic substances. *Environmental Pollution, 157*(10), 2865–2870. https://doi.org/10.1016/j.envpol.2009.04.004.

Battaglin, W. A., Meyer, M. T., Kuivila, K. M., & Dietze, J. E. (2014). Glyphosate and its degradation product AMPA occur frequently and widely in U.S. soils, surface water, ground water, and precipitation. *JAWRA, 50*(2), 275–290. https://doi.org/10.1111/jawr.12159.

Benachour, N., & Seralini, G. E. (2009). Glyphosate formulations induce apoptosis and necrosis in human umbilical, embryonic, and placental cells. *Chemical Research in Toxicology, 22*(1), 97–105. https://doi.org/10.1021/tx800218n.

Benachour, N., Sipahutar, H., Moslemi, S., Gasnier, C., Travert, C., & Séralini, G. E. (2007). Time- and dose-dependent effects of Roundup on human embryonic and placental cells. *Archives of Environmental Contamination and Toxicology, 53*(1), 126–133. https://doi.org/10.1007/s00244-006-0154-8.

Benbrook, C. M. (2012). Impacts of genetically engineered crops on pesticide use in the US - the first sixteen years. *Environmental Science Europe, 24*, 1–13. https://doi.org/10.1186/2190-4715-24-24.

Benbrook, C. M. (2016). Trends in glyphosate herbicide use in the United States and globally. *Environmental Science Europe, 28*(1), e3. https://doi.org/10.1186/s12302-016-0070-0.

Berry, D. P., Friggens, N. C., Lucy, M., & Roche, J. R. (2016). Milk production and fertility in cattle. *Annual Review on Animal Bioscience, 4*, 269–290. https://doi.org/10.1146/annurev-animal-021815-111406.

Bøhn, T., Cuhra, M., Traavik, T., Sanden, M., Fagan, J., Primicerio, R., 2014. Compositional differences in soybeans on the market: Glyphosate accumulates in Roundup Ready GM soybeans, Food Chem., 153 pp. 207-215, 10.1016/j.foodchem.2013.12.054.

Brookes, G., & Barfoot, P. (2015). Global income and production impacts of using GM crop technology 1996-2013. *GM Crops Food, 6*(1), 13–46. https://doi.org/10.1080/21645698.2016.1176817.

Cetin, E., Sahan, S., Ulgen, A., Sahin, U., 2017. DLLME-spectrophotometric determination of glyphosate residue in legumes, Food Chem., 230 pp. 567-571, 10.1016/j.foodchem.2017.03.063.

Cheng, K. C., Beaulieu, J., Iquira, E., Belzile, F. J., Fortin, M. G., & Strömvik, M. V. (2008). Effect of transgenes on global gene expression in soybean is within the natural range of variation of conventional cultivars, J. *Agriculture and Food Chemistry, 56*(9), 3057–3067. https://doi.org/10.1021/jf073505i.

Clair, E., Mesnage, R., Travert, C., & Seralini, G. E. (2012). A glyphosate-based herbicide induces necrosis and apoptosis in mature rat testicular cells in vitro, and testosterone decrease at lower levels, Toxicol. *In Vitro, 26*(2), 269–279. https://doi.org/10.1016/j.tiv.2011.12.009.

Combs, D. K., & Hartnell, G. F. (2008). Alfalfa containing the glyphosate-tolerant trait has not effect on feed intake, milk composition, or milk production of dairy cattle. *Journal*

of Dairy Science, 91, 673–678. https://doi.org/10.3168/jds.2007-0611.
Comont, D., Hicks, H., Crook, L., Hull, R., Cocciantelli, E., Hadfield, J., Childs, D., Freckleton, R., & Neve, P. (2019). Evolutionary epidemiology predicts the emergence of glyphosate resistance in a major agricultural weed. *New Phytologist, 223*(3), 1584–1594. https://doi.org/10.1111/nph.15800.
Conrad, A., Schroter-Kermani, C., Hoppe, H. W., Ruther, M., Pieper, S., & Kolossa-Gehring, M. (2017). Glyphosate in German adults - Time trend (2001 to 2015) of human exposure to a widely used herbicide. *International Journal of Hygiene and Environmental Health, 220*(1), 8–16. https://doi.org/10.1016/j.ijheh.2016.09.016.
Corsello, S. M., Ubertini, G., Altomare, M., Lovicu, R. M., Migneco, M. G., Rota, C. A., & Colosimo, C. (2003). Giant prolactinomas in men: efficacy of cabergoline treatment. *Clinical Endocrinology, 58*(5), 662–670.
Coupe, R. H., & Capel, P. D. (2016). Trends in pesticide use on soybean, corn and cotton since the introduction of major genetically modified crops in the United States. *Pest Management Science, 72*(5), 1013–1022. https://doi.org/10.1002/ps.4082.
Cox, C., & Surgan, M. (2006). Unidentified inert ingredients in pesticides: implications for human and environmental health. *Environmental Health Perspectives, 114*(12), 1803–1806. https://doi.org/10.1289/ehp.9374.
Cruz-Hipolito, H. E., Rojano-Delgado, A., Dominguez-Valenzuela, J. A., Heredia, A., Luque-de Castro, M. D., & De Prado, R. (2011). Glyphosate tolerance by Clitoria ternatea and Neonotonia wightii plants involves differential absorption and translocation of the herbicide. *Plant and Soil, 347*(1), 221–230. https://doi.org/10.1007/s11104-011-0840-9.
Cuhra, M. (2015). Review of GMO safety assessment studies: Glyphosate residues in Roundup Ready crops is an ignored issue. *Environmental Science Europe, 27*, e20. https://doi.org/10.1186/s12302-015-0052-7.
Cuhra, M., Bøhn, T., & Cuhra, P. (2016). Glyphosate: Too much of a good thing? *Frontiers in Environment Science, 4*, e28. https://doi.org/10.3389/fenvs.2016.00028.
Curwin, B. D., Hein, M. J., Sanderson, W. T., Striley, C., Heederik, D., Kromhout, H., Reynolds, S. J., & Alavanja, M. C. (2007). Urinary pesticide concentrations among children, mothers and fathers living in farm and non-farm households in Iowa. *Annals of Occupational Hygiene, 51*(1), 53–65. https://doi.org/10.1093/annhyg/mel062.
Dallegrave, E., Mantese, F. D., Oliveira, R. T., Andrade, A. J., Dalsenter, P. R., & Langeloh, A. (2007). Pre- and postnatal toxicity of the commercial glyphosate formulation in Wistar rats. *Archives of Toxicology, 81*(9), 665–673. https://doi.org/10.1007/s00204-006-0170-5.
Defarge, N., Takacs, E., Lozano, V. L., Mesnage, R., Spiroux de Vendomois, J., Seralini, G. E., & Szekacs, A. (2016). Co-formulants in glyphosate-based herbicides disrupt aromatase activity in human cells below toxic levels. *International Journal of Environmental Research and Public Health, 13*(3), e264. https://doi.org/10.3390/ijerph13030264.
Defarge, N., Spiroux de Vendomois, J., & Seralini, G. E. (2018). Toxicity of formulants and heavy metals in glyphosate-based herbicides and other pesticides. *Toxicology Reports, 5*, 156–163. https://doi.org/10.1016/j.toxrep.2017.12.025.
Duke, S. O. (2011). Glyphosate degradation in glyphosate-resistant and -susceptible crops and weeds,. *Journal of Agricultural and Food Chemistry, 59*(11), 5835–5841. https://doi.org/10.1021/jf102704x.
Duke, S. O., & Powles, S. B. (2008). Glyphosate: a once-in-a-century herbicide. *Pest Management Science, 64*(4), 319–325. https://doi.org/10.1002/ps.1518.
Duke, S. O., Rimando, A. M., Pace, P. F., Reddy, K. N., & Smeda, R. J. (2003). Isoflavone, glyphosate, and aminomethylphosphonic acid levels in seeds of glyphosate-treated, glyphosate-resistant soybean,. *Journal of Agricultural and Food Chemistry, 51*(1), 340–344. https://doi.org/10.1021/jf025908i.
EFSA. (2014). The 2011 European Union report on pesticide residues in food. *EFSA Journal, 12*(5), e3694. https://doi.org/10.2903/j.efsa.2014.3694.
EFSA. (2015). Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate. *EFSA Journal, 13*(11), 4302. https://doi.org/10.2903/j.efsa.2017.4979.
EFSA. (2017). Peer review of the pesticide risk assessment of the potential endocrine disrupting properties of glyphosate. *EFSA Journal, 13*(11), 4302. https://doi.org/10.2903/j.efsa.2017.4979.
Erickson, G. E., Robbins, N. D., Simon, J. J., Berger, L. L., Klopfenstein, T. J., Stanisiewski, E. P., & Hartnell, G. F. (2003). Effect of feeding glyphosate-tolerant (roundup-ready events GA21 or nk603) corn compared with reference hybrids on feedlot steer performance and carcass characteristics, J. *Animal Science, 81*(10), 2600–2608. https://doi.org/10.2527/2003.81102600x.
Farmer, D. (2010). Chapter 92 – Inhibitors of aromatic acid biosynthesis. In R. Krieger (Ed.). *Hayes' handbook of pesticide toxicology* (pp. 1967–1972). (3rd edition). Cambridge, MA: Academic Press. https://doi.org/10.1016/b978-012-374367-1.00092-6.
FDA2016. Pesticide residue monitoring program. Fiscal year 2016 pesticide report. https://www.fda.gov/food/pesticides/pesticide-residue-monitoring-2016-report-and-data.
Feng, P. C. C., Chiu, T., & Sammons, R. D. (2003). Glyphosate efficacy is contributed by its tissue concentration and sensitivity in velvetleaf (Abutilon theophrasti). *Pesticide Biochemistry and Physics, 77*, 83–91.
Fernandez-Cornejo, J., Nehring, R., Osteen, C., Wechsler, S., Martin, A., & Vialou, A. (2014). *Pesticide use in US agriculture: 21 selected crops, 1960-2008.* Washington, DC: US Department of Agriculture, Economic Research Service. https://www.ers.usda.gov/webdocs/publications/43854/46734_eib124.pdf.
Flachowsky, G., Halle, I., & Aulrich, K. (2005a). Animal nutrition with feeds from genetically modified plants. *Archives of Animal Nutrition, 59*(1), 1–40. https://doi.org/10.1080/17450390512331342368.
Flachowsky, G., Halle, I., & Aulrich, K. (2005b). Long term feeding of Bt-corn—a ten-generation study with quails. *Archives of Animal Nutrition, 59*(6), 449–451. https://doi.org/10.1080/17450390500353549.
Flachowsky, G., Schafft, H., & Meyer, U. (2012). Animal feeding studies for nutritional and safety assessments of feeds from genetically modified plants: A review. *J. Verbraucherschutz Lebensmittelsicherh, 7*, 179–194. https://doi.org/10.1007/s00003-012-0777-9.
Franz, J. E., Mao, M. K., & Sikorski, J. A. (1997). *Glyphosate, a unique global herbicide.* Washington, DC: American Chemical Society.
Frontera, J. L., Vatnick, I., Chaulet, A., & Rodriguez, E. M. (2011). Effects of glyphosate and polyoxyethylenamine on growth and energetic reserves in the freshwater crayfish Cherax quadricarinatus (Decapoda, Parastacidae). *Archives of Environmental Contamination and Toxicology, 61*(4), 590–598. https://doi.org/10.1007/s00244-011-9661-3.
García-Villalba, R., León, C., Dinelli, G., Segura-Carretero, A., Fernández-Gutiérrez, A., Garcia-Cañas, V., & Cifuentes, A. (2008). Comparative metabolomic study of transgenic versus conventional soybean using capillary electrophoresis-time-of-flight mass spectrometry. *Journal Chromatography A. 1195*(1-2), 164–173. https://doi.org/10.1016/j.chroma.2008.05.018.
Gasnier, C., Benachour, N., Clair, E., Travert, C., Langlois, F., Laurant, C., Decroix-Laporte, C., & Seralini, G. E. (2010). Dig1 protects against cell death provoked by glyphosate-based herbicides in human liver cell lines,. *Journal of Occupational Medicine and Toxicology, 5*, e29. https://doi.org/10.1186/1745-6673-5-29.
Gasnier, C., Laurant, C., Decroix-Laporte, C., Mesnage, R., Clair, E., Travert, C., & Seralini, G. E. (2011). Defined plant extracts can protect human cells against combined xenobiotic effects. *Journal of Occupational Medicine and Toxicology, 6*, e3. https://doi.org/10.1186/1745-6673-6-3.
Gisey, J. P., Dobson, S., & Solomon, K. R. (2000). Ecotoxicological risk assessment for Roundup herbicide. *Reviews of Environmental Contamination and Toxicology, 167*, 35–120.
Gomes, M. P., Smedbol, E., Chalifour, A., Henault-Ethier, L., Labrecque, M., Lepage, L., Lucotte, M., & Juneau, P. (2014). Alteration of plant physiology by glyphosate and its by- product aminomethylphosphonic acid: An overview,. *Experimental Botany, 65*(17), 4691–4703. https://doi.org/10.1093/jxb/eru269.
Grant, R. J., Fanning, K. C., Kleinschmit, D., Stanissiewski, E. P., & Hartnell, C. F. (2003). Inflence of glyphosate-tolerant (event nk603) and corn rootworm protected (event MON863) corn silage and grain on feed consumption and milk production in Holstein cattle. *Journal of Dairy Science, 86*, 1707–1715. https://doi.org/10.3168/jds.
Green, J. M. (2018). The rise and future of glyphosate and glyphosate-resistant crops. *Pest Managagement Science, 74*(5), 1035–1039. https://doi.org/10.1002/ps.4462.
Guyton, K. Z., Loomis, D., Grosse, Y., El Ghissassi, F., Benbrahim-Tallaa, L., Guha, N., Scoccianti, C., Mattock, H., & Straif, K. (2015). International Agency for Research on Cancer Monograph Working Group, IARC, Lyon, France, Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. *The Lancet Oncology, 16*(5), 490–491. https://doi.org/10.1016/S1470-2045(15)70134-8.
Hamdaoui, L., Naifar, M., Rahmouni, F., Harrabi, B., Ayadi, F., Sahnoun, Z., & Rebai, T. (2018). Subchronic exposure to kalach 360 SL-induced endocrine disruption and ovary damage in female rats. *Archives of Physiology and Biochemistry, 124*(1), 27–34. https://doi.org/10.1080/13813455.2017.1352606.
Harrigan, G. G., Stork, L. G., Riordan, S. G., Reynolds, T. L., Ridley, W. P., Masucci, J. D., Macisaac, S., Halls, S. C., Orth, R., Smith, R. G., Wen, L., Brown, W. E., Welsch, M., Riley, R., McFarland, D., Pandravada, A., & Glenn, K. C. (2007). Impact of genetics and environment on nutritional and metabolite components of maize grain,. *Agriculture and Food Chemistry, 55*(15), 6177–6185. https://doi.org/10.1021/jf070494k.
Heap, I. (2014). Global perspective of herbicide-resistant weeds. *Pest Management Science, 70*(9), 1306–1315. https://doi.org/10.1002/ps.3696.
Hartnell, G. F., Hvelplund, T., & Weisbjerg, M. R. (2005). Nutrient digestability in sheep fed diets containing Roundup Read or conventional fodder beet, sugar beet, and beet pulp. *Journal of Animal Science. 83*, 400–407. https://doi.org/10.2527/2005.832400x.
Herman, R. A., & Price, W. D. (2013). Unintended compositional changes in genetically modified (GM) crops: 20 years of research,. *Journal of Agriculture and Food Chemistry, 61*(48), 11695–11701. https://doi.org/10.1021/jf400135r.
Hetherington, P. R., Reynolds, T. L., Marshall, G., & Kirkwood, R. C. (1999). The absorption, translocation and distribution of the herbicide glyphosate in maize expressing the CP-4 transgene,. *Journal of Experimental Botany, 50*(339), 1567–1576. https://doi.org/10.1093/jxb/50.339.1567.
Hollingworth, R. M., Bjeldanes, L. F., Bolger, M., Kimber, I., Meade, B. J., Taylor, S. L., & Wallace, K. B. (2003). Society of Toxicology ad hoc Working Group, The safety of genetically modified foods produced through biotechnology. *Toxicological Sciences, 71*(1), 2–8.
Ikpeme, E. V., Udensi, O., Ekaluo, U. B., & Solomon, T. O. (2012). Efficacy of ascorbic acid in reducing glyphosate-induced toxicity in rats. *British Biotechnology J. 2*(3), 157–168. https://doi.org/10.9734/BBJ/2012/1634.
Ingaramo, P. I., Varayoud, J., Milesi, M. M., Schimpf, M. G., Munoz-de-Toro, M., & Luque, E. H. (2016). Effects of neonatal exposure to a glyphosate-based herbicide on female rat reproduction. *Reproduction (Cambridge, England), 152*(5), 403–415. https://doi.org/10.1530/REP-16-0171.
Ipharraguerre, I. R., Younker, R. S., Clark, J. H., Stanisiewski, E. P., & Hartnell, G. F. (2003). Performance of lactating dairy cows fed corn as whole plant silage and grain produced from a glyphosate-tolerant hybrid (event NK603). *Journal of Dairy Science, 86*, 1734–1741. https://doi.org/10.3168/jds.S0022-0302(03)73759-X.
James, C., 2017. Global status of commercialized biotech/GM crops: 2017. International Service for the Acquisition of Agribiotech Applications Brief No. 46, Ithaca, NY.
Johansson, H. K. L., Schwartz, C. L., Nielsen, L. N., Boberg, J., Vinggaard, A. M., Bahl, M. I., & Svingen, T. (2018). Exposure to a glyphosate-based herbicide formulation, but not glyphosate alone, has only minor effects on adult rat testis. *Reproductive Toxicology, 82*, 25–31. https://doi.org/10.1016/j.reprotox.2018.09.008.

Kocabagli, N., Alp, M., Acar, N., & Kahraman, R. (2002). The effects of dietary humate supplementation on broiler growth and carcass yield. *Poultry Science, 81*, 227–230. https://doi.org/10.1093/ps/81.2.227.

Mann, R. M., & Bidwell, J. R. (1999). The toxicity of glyphosate and several glyphosate formulations to four species of southwestern Australian frogs. *Archives of Environmental Contamination and Toxicology, 36*(2), 193–199.

Kan, C. A., & Hartnell, G. F. (2004). Evaluation of broiler performance when fed Roundup-Ready wheat (event MON 71800), control, and commercial wheat varieties. *Poultry Science, 83*, 1325–1334 10:1093/ps/83.8.1325.

Krüger, M., Schrödl, W., Neuhaus, J., & Shehata, A. A. (2013). Field investigations of glyphosate in urine of Danish dairy cows,. *Journal of Environmental and Analytical Toxicology, 3*(5), e186. https://doi.org/10.4172/2161-0525.1000186.

Krüger, M., Schledorn, P., Schrödl, W., Hoppe, H., Lutz, W., & Shehata, A. A. (2014). Detection of glyphosate residues in animals and humans, Journal of. *Environmental and Analytical Toxicology, 4*(2), Article e1000210. https://doi.org/10.4172/2161-0525.1000210.

Lopes, F. M., Varela, A. S., Jr., Corcini, C. D., da Silva, A. C., Guazzelli, V. G., Tavares, G., & da Rosa, C. E. (2014). Effect of glyphosate on the sperm quality of zebrafish Danio rerio. *Aquatic Toxicology (Amsterdam, Netherlands), 155*, 322–326. https://doi.org/10.1016/j.aquatox.2014.07.006.

Mazzei, P., & Piccolo, A. (2012). Quantitative evaluation of noncovalent interactions between glyphosate and dissolved humic substances by NMR spectroscopy. *Environmental Science & Technology, 46*(11), 5939–5946. https://doi.org/10.1021/es300265a.

McNaughton, J., Roberts, M., Rice, D., Smith, B., Hinds, M., Delaney, B., Iiams, C., & Sauber, T. (2011). Evaluation of broiler performance and carcass yields when fed diets containing corn grains from transgenic stacked-trait product DAS-Ø15Ø7-1xDAS-59122-7 x MON-ØØ81Ø-6xMON-ØØ6Ø3–6. *Journal of Applied Poultry Research, 20*, 542–553. https://doi.org/10.3382/japr.2011-00367.

Mertens, M., Hoss, S., Neumann, G., Afzal, J., & Reichenbecher, W. (2018). Glyphosate, a chelating agent-relevant for ecological risk assessment? *Environmental Science and Pollution Research International, 25*(6), 5298–5317. https://doi.org/10.1007/s11356-017-1080-1.

Mesnage, R., Defarge, N., Spiroux de Vendomois, J., & Seralini, G. E. (2014). Major pesticides are more toxic to human cells than their declared active principles. *BioMed research international, 2014*, Article e179691. https://doi.org/10.1155/2014/179691.

Mesnage, R., Defarge, N., Spiroux de Vendomois, J., & Seralini, G. E. (2015). Potential toxic effects of glyphosate and its commercial formulations below regulatory limits. *Food Chemical Toxic. 84*, 133–153. https://doi.org/10.1016/j.fct.2015.08.012.

Mills, P. J., Kania-Korwel, I., Fagan, J., McEvoy, L. K., Laughlin, G. A., & Barrett-Connor, E. (2017). Excretion of the herbicide glyphosate in older adults between 1993 and 2016. *Jama, 318*(16), 1610–1611. https://doi.org/10.1001/jama.2017.11726.

Modesto, K. A., & Martinez, C. B. (2010). Roundup causes oxidative stress in liver and inhibits acetylcholinesterase in muscle and brain of the fish Prochilodus lineatus. *Chemosphere, 78*, 294–299. https://doi.org/10.1016/j.chemosphere.2009.10.047.

Monsanto, 2010. The agronomic benefits of glyphosate in Europe – benefits of glyphosate per market use. (REVIEW) pp. 1-82.

Moore, L. J., Fuentes, L., Rodgers, J. H., Jr., Bowerman, W. W., Yarrow, G. K, Chao, W. Y., & Bridges, W. C., Jr. (2012). Relative toxicity of the components of the original formulation of Roundup to five North American anurans. *Ecotoxicology and Environmental Safety, 78*, 128–133. https://doi.org/10.1016/j.ecoenv.2011.11.025.

Nardi, J., Moras, P. B., Koeppe, C., Dallegrave, E., Leal, M. B., & Rossato-Grando, L. G. (2017). Prepubertal subchronic exposure to soy milk and glyphosate leads to endocrine disruption. *Food and Chemical Toxicology, 100*, 247–252. https://doi.org/10.1016/j.fct.2016.12.030.

Oliveira, A. G., Telles, L. F., Hess, R. A., Mahecha, G. A., & Oliveira, C. A. (2007). Effects of the herbicide Roundup on the epididymal region of drakes Anas platyrhynchos. *Reproductive Toxicology, 23*(2), 182–191. https://doi.org/10.1016/j.reprotox.2006.11.004.

Osteen, C. D., & Fernandez-Cornejo, J. (2013). Economic and policy issues of U.S. agricultural pesticide use trends. *Pest Management Science, 69*(9), 1001–1025. https://doi.org/10.1002/ps.3529.

Owagboriaye, F. O., Dedeke, G. A., Ademolu, K. O., Olujimi, O. O., Ashidi, J. S., & Adeyinka, A. A. (2017). Reproductive toxicity of Roundup herbicide exposure in male albino rat. *Experimental and Toxicologic Pathology, 69*(7), 461–468. https://doi.org/10.1016/j.etp.2017.04.007.

Pandey, A., & Rudraiah, M. (2015). Analysis of endocrine disruption effect of Roundup ((R)) in adrenal gland of male rats. *Toxicology Reports, 2*, 1075–1085. https://doi.org/10.1016/j.toxrep.2015.07.021.

Panzacchi, S., Mandrioli, D., Manservisi, F., Bua, L., Falcioni, L., Spinaci, M., Galeati, G., Dinelli, G., Miglio, R., Mantovani, A., Lorenzetti, S., Hu, J., Chen, J., Perry, M. J., Landrigan, P. J., & Belpoggi, F. (2018). The Ramazzini Institute 13-week study on glyphosate-based herbicides at human-equivalent dose in Sprague Dawley rats: study design and first in-life endpoints evaluation. *Environmental Health, 17*(1), e52. https://doi.org/10.1186/s12940-018-0393-y.

Peixoto, F. (2005). Comparative effects of the Roundup and glyphosate on mitochondrial oxidative phosphorylation. *Chemosphere, 61*(8), 1115–1122. https://doi.org/10.1016/j.chemosphere.2005.03.044.

Perego, M. C., Caloni, F., Cortinovis, C., Schutz, L. F., Albonico, M., Tsuzukibashi, D., & Spicer, L. J. (2017a). Influence of a Roundup formulation on glyphosate effects on steroidogenesis and proliferation of bovine granulosa cells in vitro. *Chemosphere, 188*, 274–279. https://doi.org/10.1016/j.chemosphere.2017.09.007.

Perego, M. C., Schutz, L. F., Caloni, F., Cortinovis, C., Albonico, M., & Spicer, L. J. (2017b). Evidence for direct effects of glyphosate on ovarian function: glyphosate influences steroidogenesis and proliferation of bovine granulosa but not theca cells in vitro,. *Journal of Applied Toxicology, 37*(6), 692–698. https://doi.org/10.1002/jat.3417.

Piccolo, A., Celano, G., & Conte, P. (1996). Absorption of glyphosate by humic substances. *Journal of Agricultural and Food Chemistry, 44*, 2442–2446. https://doi.org/10.1021/jf950620x.

Pollock, D. L. (1999). A geneticist's perspective from within a broiler primary breeder company. *Poultry Science, 78*(3), 414–418. https://doi.org/10.1093/ps/78.3.414.

Powles, S. (2014). Global herbicide resistance challenge. *Pest Management Science, 70*(9), 1305. https://doi.org/10.1002/ps.3808.

Powles, S. B., & Preston, C. (2006). Evolved glyphosate resistance in plants: Biochemical and genetic basis of resistance. *Weed Technology, 20*(2), 282–289. https://doi.org/10.1614/WT-04-142R.1.

Preston, C., Wakelin, A. M., Dolman, F. C., Bostamam, Y., & Boutsalis, P. (2009). A decade of glyphosate-resistant Lolium around the world: Mechanisms, genes, fitness, and agronomic management. *Weed Science, 57*(4), 435–441. https://doi.org/10.1614/WS-08-181.1.

Qaim, M., & Zilberman, D. (2003). Yield effects of genetically modified crops in developing countries. *Science, 299*(5608), 900–902. https://doi.org/10.1126/science.1080609.

Qaim, M., & Traxler, G. (2005). Roundup Ready soybeans in Argentina: Farm level and aggregate welfare effects. *Agriculture and Economy, 32*, 73–86. https://doi.org/10.1111/j.0169-5150.2005.00006.x.

Reddy, K. N., Rimando, A. M., & Duke, S. O. (2004). Aminomethylphosphonic acid, a metabolite of glyphosate, causes injury in glyphosate-treated, glyphosate-resistant soybean, J. *Agriculture and. Food Chemistry, 52*(16), 5139–5143. https://doi.org/10.1021/jf049605v.

Richard, S., Moslemi, S., Sipahutar, H., Benachour, N., & Seralini, G. E. (2005). Differential effects of glyphosate and roundup on human placental cells and aromatase. *Environmental Health Perspectives, 113*(6), 716–720. https://doi.org/10.1289/ehp.7728.

Romano, R. M., Romano, M. A., Bernardi, M. M., Furtado, P. V., & Oliveira, C. A. (2010). Prepubertal exposure to commercial formulation of the herbicide glyphosate alters testosterone levels and testicular morphology. *Archives of Toxicology, 84*(4), 309–317. https://doi.org/10.1007/s00204-009-0494-z.

Romano, M. A., Romano, R. M., Santos, L. D., Wisniewski, P., Campos, D. A., de Souza, P. B., Viau, P., Bernardi, M. M., Nunes, M. T., & de Oliveira, C. A. (2012). Glyphosate impairs male offspring reproductive development by disrupting gonadotropin expression. *Archives of Toxicology, 86*(4), 663–673. https://doi.org/10.1007/s00204-011-0788-9.

Sartowska, K. E., Korwin-Kossakowska, A., & Sender, G. (2015). Genetically modified crops in a 10-generation feeding trial on Japanese quails–Evaluation of its influence on birds' performance and body composition. *Poultry Science, 94*(12), 2909–2916. https://doi.org/10.1093/ps/pev271.

Satchivi, N. M., Wax, L. M., Stoller, E. W., & Briskin, D. P. (2000). Absorption and translocation of glyphosate isopropylamine and trimethylsulfonium salts in Abutilon theophrasti and Setaria faberi. *Weed Sciences, 48*(6), 675–679. https://doi.org/10.1614/0043-1745(2000)048[0675:AATOGI]2.0.CO;2.

Schimpf, M. G., Milesi, M. M., Ingaramo, P. I., Luque, E. H., & Varayoud, J. (2017). Neonatal exposure to a glyphosate based herbicide alters the development of the rat uterus. *Toxicology, 376*, 2–14. https://doi.org/10.1016/j.tox.2016.06.004.

Schroder, D., Headley, J. C., & Finley, R. M. (1984). The contribution of herbicides and other technologies to corn production in the corn belt region, 1964 to 1979. *N. Cent. Journal of Agricultural Economics, 6*(1), 95–104. https://doi.org/10.2307/1349304.

Shehata, A. A., Schrödl, W., Schledorn, P., & Krüger, M. (2014). Distribution of glyphosate in chicken organs and its reduction by humic acid supplementation. *Poultry Science, 51*, 333–337. https://doi.org/10.2141/jpsa.0130169.

Sparling, D. W., Matson, C., Bickham, J., & Doelling-Brown, P. (2006). Toxicity of glyphosate as Glypro and LI700 to red-eared slider (trachemys scripta elegans) embryos and early hatchlings. *Environmental Toxicology and Chemistry, 25*(10), 2768–2774.

Stock, D., & Holloway, P. J. (1993). Possible mechanisms for surfactant induced foliar uptake of agrochemicals. *Pest Manag. Sci. 38*(2-3), 165–177. https://doi.org/10.1002/ps.2780380211.

Tarazona, J. V., Court-Marques, D., Tiramani, M., Reich, H., Pfeil, R., Istace, F., & Crivellente, F. (2017). Glyphosate toxicity and carcinogenicity: a review of the scientific basis of the European Union assessment and its differences with IARC. *Archives of Toxicology, 91*(8), 2723–2743. https://doi.org/10.1007/s00204-017-1962-5.

Taylor, M., Hartnell, G., Nemeth, M., Lucas, D., & Davis, S. (2007a). Comparison of broiler performance when fed diets containing grain from second-generation insect-protected and glyphosate-tolerant, conventional control or commercial reference corn. *Poultry Science, 86*(9), 1972–1979. https://doi.org/10.1093/ps/86.9.1972.

Taylor, M., Lucas, D., Nemeth, M., Davis, S., & Hartnell, G. (2007b). Comparison of broiler performance and carcass parameters when fed diets containing combined trait insect- protected and glyphosate-tolerant corn (MON 89034 x NK603), control, or conventional reference corn. *Poultry Science, 86*(9), 1988–1994. https://doi.org/10.1093/ps/86.9.1988.

Taylor, M., Hartnell, G., Lucas, D., Davis, S., & Nemeth, M. (2007c). Comparison of broiler performance and carcass parameters when fed diets containing soybean meal produced from glyphosate-tolerant (MON 89788), control, or conventional reference soybeans. *Poultry Science, 86*(12), 2608–2614. https://doi.org/10.3382/ps.2007-00139.

Thongprakaisang, S., Thiantanawat, A., Rangkadilok, N., Suriyo, T., & Satayavivad, J. (2013). Glyphosate induces human breast cancer cells growth via estrogen receptors. *Food and Chemical Toxicology, 59*, 129–136. https://doi.org/10.1016/j.fct.2013.05.057.

Tsui, M. T., & Chu, L. M. (2003). Aquatic toxicity of glyphosate-based formulations: comparison between different organisms and the effects of environmental factors.

Chemosphere, 52(7), 1189–1197. https://doi.org/10.1016/S0045-6535(03)00306-0.
Tush, D., & Meyer, M. T. (2016). Polyoxyethylene Tallow Amine, a Glyphosate Formulation Adjuvant: Soil Adsorption Characteristics, Degradation Profile, and Occurrence on Selected Soils from Agricultural Fields in Iowa, Illinois, Indiana, Kansas, Mississippi, and Missouri. *Environmental Science & Technology, 50*(11), 5781–5789. https://doi.org/10.1021/acs.est.6b00965.
USDA, 2013 a. Appendix C: Distribution of residues in soybean by pesticide, Pesticide data program annual summary, program year 2011, US Department of Agriculture, Agricultural Marketing Service, Washington, DC, https://www.ams.usda.gov/sites/default/files/media/2011%20PDP%20Annual%20Summary.pdf.
USDA, 2013 b. Acreage, US Department of Agriculture, National Agricultural Statistics Service, Washington, DC, http://usda.mannlib.cornell.edu/usda/nass/Acre/2010s/2013/Acre-06-28-2013.pdf.
USDA, 2018 a. Genetically engineered varieties of corn, upland cotton, and soybeans, by State and for the United States, US Department of Agriculture, Economic Research Service, Washington, DC, https://www.ers.usda.gov/webdocs/DataFiles/47649/alltables.xls?v=42928.
USDA, 2018 b. Grain: World markets and trade, US Department of Agriculture, Foreign Agricultural Service, Washington, DC, https://apps.fas.usda.gov/psdonline/circulars/grain.pdf.
USDA, 2019. Adoption of genetically engineered crops in the U.S., US Department of Agriculture Economic Research Service, Washington, DC, https://www.ers.usda.gov/data-products/adoption-of-genetically-engineered-crops-in-the-us/recent-trends-in-ge-adoption.aspx.
US-EPA, 2012. Glyphosate. section 3 registration concerning the application of glyphosate to carrots, sweet potato, teff, oilseeds (crop group (CG) 20) and to update the CG definitions for bulb vegetable (CG 3-07), fruiting vegetable (CG 8-10), citrus fruit (CG 10-10), pome fruit (CG 11-10), berry (CG 13-07), human health risk assessment, Decision No.: 459870 p. 28.
USGS, 2017. Pesticide National Synthesis Project: Estimated annual agriculture pesticide use. US Geological Society, Washington, DC, https://water.usgs.gov/nawqa/pnsp/usage/maps/show_map.php?year=2016&map=GLYPHOSATE&hilo=L.
van Eenennaam, A. L., & Young, A. E. (2014). Prevalence and impacts of genetically engineered feedstuffs on livestock populations, J. *Animal Science, 92*(10), 4255–4278. https://doi.org/10.2527/jas.2014-8124.
Vanlaeys, A., Dubuisson, F., Seralini, G. E., & Travert, C. (2018). Formulants of glyphosate- based herbicides have more deleterious impact than glyphosate on TM4 Sertoli cells. *Toxicology in Vitro, 52*, 14–22. https://doi.org/10.1016/j.tiv.2018.01.002.
Varayoud, J., Durando, M., Ramos, J. G., Milesi, M. M., Ingaramo, P. I., Munoz-de-Toro, M., & Luque, E. H. (2017). Effects of a glyphosate-based herbicide on the uterus of adult ovariectomized rats. *Environmental Toxicology, 32*(4), 1191–1201. https://doi.org/10.1002/tox.22316.
von Soosten, D., Meyer, U., Huther, L., Danicke, S., Lahrssen-Wiederholt, M., Schafft, H., Spolders, M., & Breves, G. (2016). Excretion pathways and ruminal disappearance of glyphosate and its degradation product aminomethylphosphonic acid in dairy cows,. *Dairy Sci, 99*(7), 5318–5324. https://doi.org/10.3168/jds.2015-10585.
Walsh, L. P., McCormick, C., Martin, C., & Stocco, D. M. (2000). Roundup inhibits steroidogenesis by disrupting steroidogenic acute regulatory (StAR) protein expression. *Environmental Health Perspectives, 108*(8), 769–776. https://doi.org/10.1289/ehp.00108769.
Webster, T. M. U., Laing, L. V., Florance, H., & Santos, E. M. (2014). Effects of glyphosate and its formulation, roundup, on reproduction in zebrafish (Danio rerio). *Environmental Science & Technology, 48*(2), 1271–1279. https://doi.org/10.1021/es404258h.
WHO, 1994. Glyphosate, Environmental Health Criteria 159, World Health Organization, Geneva, http://www.inchem.org/documents/ehc/ehc/ehc159.htm.
Winnick, B.E., 2013. The effects of glyphosate based herbicides on chick embryo morphology during development, thesis, (digital.library.unt.edu/ark:/67531/metadc500146/: accessed January 23, 2019), University of North Texas Libraries, Digital Library, digital.library.unt.edu;.
Wrobel, M. H. (2018). Glyphosate affects the secretion of regulators of uterine contractions in cows while it does not directly impair the motoric function of myometrium in vitro. *Toxicology and Applied Pharmacology, 349*, 55–61. https://doi.org/10.1016/j.taap.2018.04.031.
WTO, 2012, The WTO agreement on the application of sanitary and phytosanitary measures (SPS agreement), Geneva, https://www.wto.org/english/tratop_e/sps_e/spsagr_e.htm.
Xu, J., Shayna, S., Smith, G., Want., W., & Li, Y. (2019). Glyphosate contamination in grains and foods: An overview. *Food Control*. https://doi.org/10.1016/j.foodcont.2019.106710 106 Article 10670.
Yoruk, M., Gul, M., Hayiril, A., & Macit, M. (2004). The effects of supplementation of humate and probiotic on egg production and quality parameters during the late laying period in hens. *Poultry Science, 83*, 84–88. https://doi.org/10.1093/ps/83.1.84.
Zeitlin, S. I., & Rajfer, J. (2000). Hyperprolactinemia and erectile dysfunction. *Review Urology, 2*(1), 39–42.
Zhang, J. W., Xu, Ding-Qi, & Feng., Xi-Zeng (2019). The toxic effects and possible mechanisms of glyphosate on mouse oocytes. *Chemosphere, 237*(2019), Article 124435. https://doi.org/10.1016/j.chemosphere.2019.124435.
Zilberman, D., Holland, T. G., & Trilnick, I. (2018). Agricultural GMOs - What we know and where scientists disagree. *Sustainability, 10*(1514), 1–19. https://doi.org/10.3390/su10051514.
Zouaoui, K., Dulaurent, S., Gaulier, J. M., Moesch, C., & Lachatre, G. (2013). Determination of glyphosate and AMPA in blood and urine from humans: about 13 cases of acute intoxication. *Forensic Science International, 226*(1-3), e20–e25. https://doi.org/10.1016/j.forsciint.2012.12.010.