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A systematic review and meta-analysis of the impacts of glyphosate on the reproductive hormones

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Abstract

Worldwide use of glyphosate is constantly increasing and its residues are detected in drinking water, agriculture, and food products. There are controversial data regarding the potential reproductive adverse effects of glyphosate herbicide. Therefore, we conducted a systematic review and meta-analysis on the studies in which the alteration of at least one sexual hormone including testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol was reported as a measured outcome in rats. In November 2020, 284 articles were screened, of which eight were eligible for the meta-analysis. An overall considerable effect of glyphosate exposure was found on decreasing of testosterone (7 studies, WMD = − 1.48 ng/mL; 95% CI, − 2.34 to − 0.61; $P = 0.001$), LH (3 studies, WMD = − 2.03 mIu/mL; 95% CI, − 3.34 to − 0.71; $P = 0.003$), and FSH (3 studies, WMD = − 2.28 mIu/mL; 95% CI, − 5.12 to 0.55; $P = 0.115$). According to our results, glyphosate intake could have major effects on the health of reproductive system. Consequently, strict monitoring of the residual glyphosate content in the drinking water, agricultural crops, and food products is necessary.

Keywords Toxicology · Residual herbicides · Environmental/food contaminants · Reproductive disorder · Sexual hormones · Rat

Introduction

Nowadays, due to the increasing population of the world, climate change, industrial development, modern technologies, and overuse of chemical fertilizers and pesticides, people are in potential exposure to various environmental and food contaminants, and these phenomena could affect the food safety and security (Carvalho 2006; Maxwell 1996; Schmidhuber and Tubiello 2007). Glyphosate-based herbicides (GBHs) are widely used on a range of agricultural and food products, including corn, soy, wheat, canola, rice, barley, and edible beans (Myers et al. 2016). Glyphosate (N-(phosphonomethyl) glycine) is known as an organophosphorus systemic herbicide and crop desiccant, which inhibits the plant enzyme 5-enolpyruvylshikimate-3-phosphate synthase, the key enzyme of the shikimate pathway in plants and fungi; however, this pathway is not present in animals (Franz et al. 1997; Leino et al. 2021; Padgette et al. 1995; Zhang et al. 2020). Glyphosate is one of the active ingredients of the various glyphosate-based herbicide (GBH) commercial formulations which also contain different specific adjuvants depending on the formulation (Abarikwu et al. 2015; Manservisi et al. 2019). Many studies have investigated the toxicity and adverse effects of glyphosate and GBHs (Ingaramo et al. 2020; Kier and Kirkland 2013; Zanardi et al. 2020). Although the Environmental Protection Agency (EPA-USA) has reconfirmed that glyphosate is safe for users, however, there are controversial issues in this regard.

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Recently, genetically modified (GM) products have attracted a large amount of media attention and continue to do so (Van Bruggen et al. 2018b). Herbicidal-resistant GM products have generally been reported to be resistant to glyphosate. Under such conditions, all plants on the farm are destroyed except the transgenic plants (Schütte et al. 2017). Consequently, and according to the widespread use of glyphosate and GBHs in agriculture, it is possible to accumulate in food products, water, and soil. Therefore, long-term exposure to glyphosate/GBHs and its main metabolites, such as aminomethylphosphonic acid (AMPA), which is persistent in soils, may have adverse effects and toxicity to human health and animals (Domínguez et al. 2016; Silva et al. 2018).

In 2015, glyphosate was classified by the WHO as probably carcinogenic to humans (category 2); therefore, the risk of various diseases and its carcinogenicity has been reported by many studies (Gillezeau et al. 2019; Greim et al. 2015; Mink et al. 2012; Nerozzi et al. 2020; Van Bruggen et al. 2018a).

Legally, a range of "acceptable" daily intake levels of glyphosate exposures for humans has been legislated in various countries. The US Environmental Protection Agency (EPA) has regularized 1.75 (mg/kg/day) of glyphosate as the chronic reference dose (cRfD), whereas acceptable daily intake (ADI) of glyphosate in the E.U. is adopted 0.3 mg/kg/day in 2002 (Myers et al. 2016). The reported no-observed-adverse-effect level (NOAEL) of glyphosate for reproductive toxicity is about 50 mg/kg (Romano et al. 2012). Despite the benefits of glyphosate in agriculture, some concerns have raised about its effect on environmental health (Gillezeau et al. 2019; Van Bruggen et al. 2018a; Zhang et al. 2020). Therefore, special attention is needed regarding the residue of glyphosate in drinking water, agricultural crops, and food products (Van Bruggen et al. 2018b). The potential source of exposure to glyphosate and possible adverse effect in humans is presented in Fig. 1.

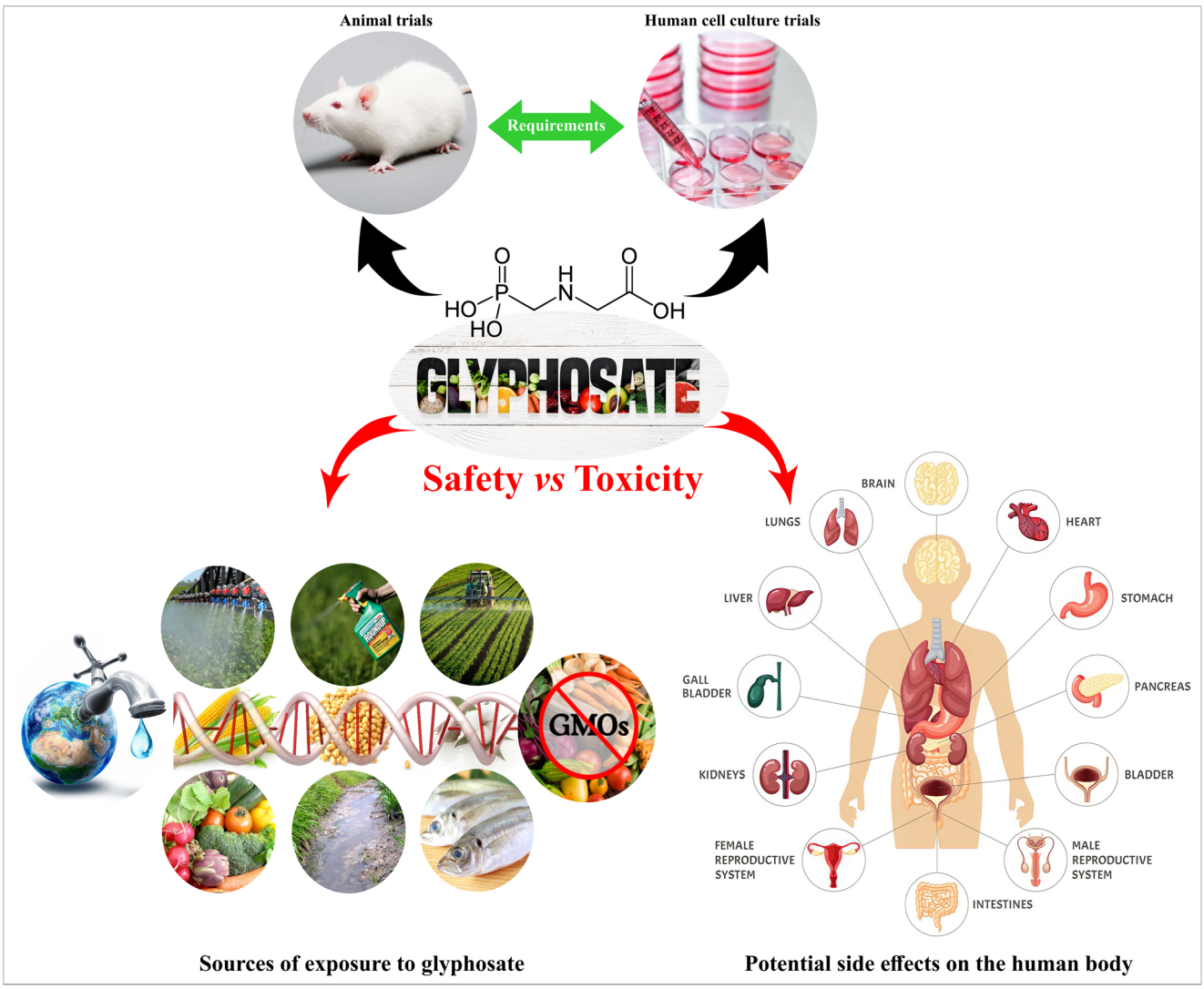

Fig. 1 The potential sources of exposure to glyphosate and possible adverse effects in humans

Accordingly, due to the concerns mentioned earlier and to address these inconsistencies, in this systematic review and dose-response meta-analysis, we comprehensively assessed studies that evaluated the effect of glyphosate exposure on the reproductive hormone levels (testosterone, FSH, LH, and estradiol) in male rats.

Methodology

Search strategy

A comprehensive literature search was conducted to identify peer-reviewed studies investigating the effects of glyphosate on reproductive hormone concentrations. For this purpose, some electronic databases, including the Scopus, PubMed, Embase, and Web of Sciences, were screened from inception up to June 2020 using the following terms and keywords: "Glyphosate AND Reproductive hormones AND Rat ; "Glyphosate AND Estradiol AND Rat ; "Glyphosate AND FSH AND Rat ; "Glyphosate AND LH AND Rat ; "Glyphosate AND Progesterone AND Rat ; "Glyphosate AND Testosterone AND Rat.

Study selection

All the articles were screened based on title, abstract, and keyword fields to identify the qualified studies. Eligible articles met the following inclusion criteria: (1) the article published in the English language, (2) reported mean ± SD (or SEM) of reproductive hormone concentrations, (3) only in vivo experiment performed on a rat model, and also (4) used glyphosate as an intervention. Accordingly, the following studies were excluded: (i) the review articles, (ii) articles with other languages, (iii) studies that did not use rat as experiment model, (iv) reports with unclear measuring units, and (v) the duplicate publications.

Data extraction

Pairs of reviewers performed the extraction of data from eligible studies to reduce the risk of bias. Information, such as first author, date of publication, sample size, experiment animal, the dose of treatment, and mean ± SD (or SEM) value of reproductive hormone concentrations, were extracted in both control and glyphosate exposure groups.

Statistical analysis

Weighted mean difference (WMD) with the 95% CI was applied for estimating the effects of glyphosate exposure on sex hormone levels. The random-effects model with inverse variance method was utilized to estimate the overall effect size (DerSimonian and Laird 1986). The I^2 test was exploited to evaluate the potential heterogeneity among included studies. According to this test, $I^2 > 50\%$ denoted a significant heterogeneity between the studies. On the other hand, Egger's test was conducted to determine the risk of publication bias. Moreover, the association between calculated WMD and potential confounders, including dosage and treatment duration, was assessed via fractional polynomial modeling and random-effects meta-regression analysis method, respectively. All the statistical tests for this meta-analysis were performed with STATA statistical software (version 15.0; Stata Corporation, College Station, TX, USA).

Results

Study selection

The selection process of studies is presented in the PRISMA diagram in Fig. 2. In the systematic search on Scopus, PubMed, Web of Science, Embase, and relevant studies from cross-references, 283 articles were found. After removing duplicates, 136 articles were eligible for title/abstract screening; of them, 54 articles were retrieved for full-text evaluation. Finally, eight studies were eligible for this systematic review and meta-analysis.

Study characteristics

The characteristics of the included studies are summarized in Table 1. Three studies were conducted in Brazil (Dallegrave et al. 2007; Romano et al. 2012; Romano et al. 2010), two in Nigeria (Abarikwu et al. 2015; Owagboriaye et al. 2017), one in China (Dai et al. 2016), one in Iran (Razi et al. 2012), and one in Italy (Manservisi et al. 2019). They were published between 2007 and 2019. The dose of glyphosate and GBHs administered ranged between 1.75 and 500 mg per kg of body weight via gavage. As most eligible studies have investigated the effect of glyphosate and GBH exposure on male rats, the pooled data of male rats were extracted for this analysis. As the change in progesterone level was reported only in one study, this outcome was not considered. The sample size in the included trials ranged from 10 to 66. The duration of treatment ranged from 10 to 91 days (median 37.5 days). Data of 324 samples size were pooled for this analysis.

Meta-analysis results

Testosterone level change

For evaluation of the effect of glyphosate and GBH exposure on testosterone level, data from seven articles (Dai et al. 2016; Dallegrave et al. 2007; Manservisi et al. 2019; Owagboriaye

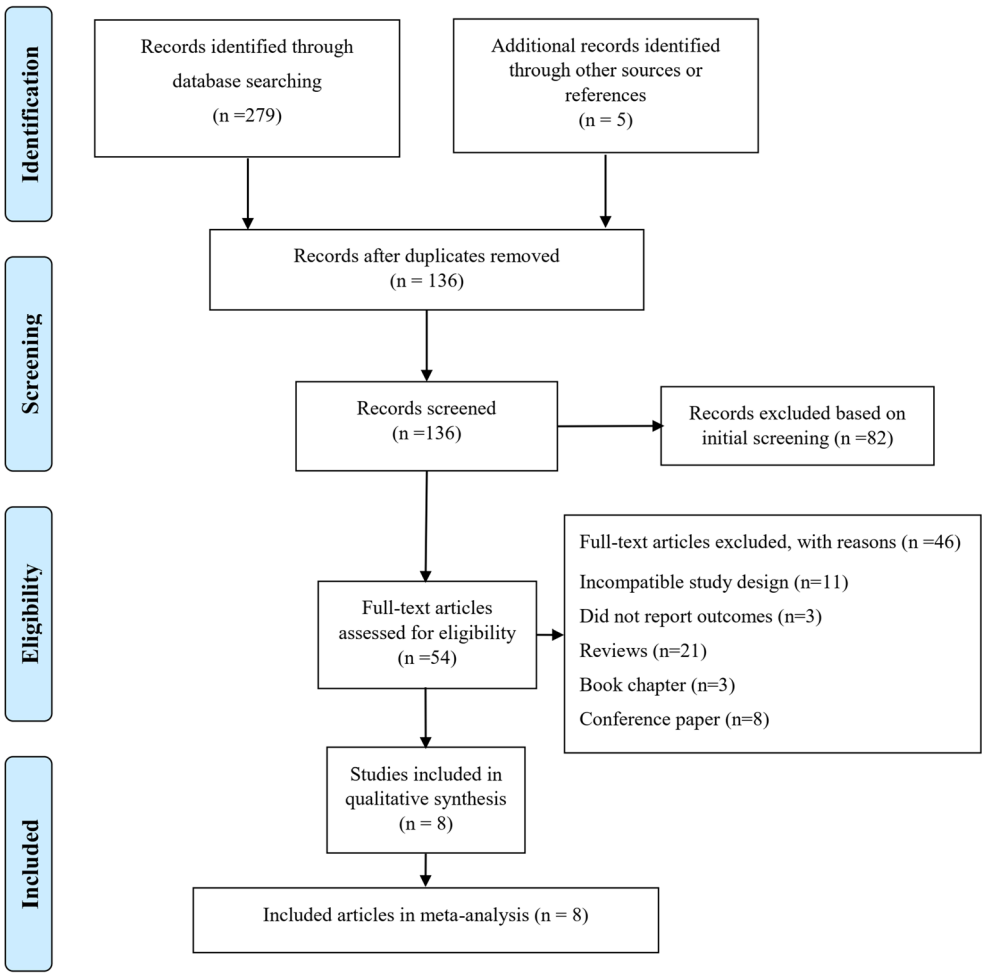

Fig. 2 Preferred Reporting Items for Systematic Reviews and Meta-analysis diagram indicating the method for selection of papers included in the present study

et al. 2017; Razi et al. 2012; Romano et al. 2012; Romano et al. 2010) including 24 different dosing strategy (intervention =220, control = 94, totally = 314) was included for this analysis. Among the included publications which examined changes in testosterone level as an outcome measure, testosterone level significantly decreases by 1.48 ng/mL following exposure to various dosing of herbicide (WMD = − 1.48 ng/mL; 95% CI, − 2.34 to − 0.61; $P = 0.001$) with a significant heterogeneity across studies ($I^2 = 99.7\%$, $P_{\text{heterogeneity}} < 0.001$), as shown in Fig. 3.

LH level change

Three studies (Abarikwu et al. 2015; Owagboriaye et al. 2017; Romano et al. 2012) containing five arms involving a total of 58 rats (intervention =37, control = 21) reported changes in LH concentrations as an outcome measure. Pooled results using the random-effects model demonstrated an overall significant decrease in LH following glyphosate and GBH exposure (WMD = − 2.03 mIu/mL; 95% CI, − 3.34 to − 0.71; $P = 0.003$) with significant heterogeneity ($I^2 = 99.8\%$, $P_{\text{heterogeneity}} < 0.001$), as displayed in Fig. 4.

FSH level change

The alteration in FSH level was reported in three studies (Abarikwu et al. 2015, Owagboriaye et al. 2017, Romano et al. 2012) with five arms (intervention =37, control = 21, totally 58) as an outcome measure. Non-significant reduction of FSH was seen following exposure (WMD = − 2.28 mIu/mL; 95% CI, − 5.12 to 0.55; $P = 0.115$); however, a significant between-study heterogeneity was observed ($I^2 = 99.9\%$; $P_{\text{heterogeneity}} < 0.001$), as confirmed in Fig. 5.

Estradiol level change

By combining effect sizes from four studies (Dai et al. 2016; Manservisi et al. 2019; Romano et al. 2012; Romano et al. 2010) with 11 arms (intervention = 119, control = 55, totally 174), we found that exposure to herbicide administration did not change significantly estradiol level (WMD = 0.21 mIu/mL; 95% CI, − 2.33 to 2.75; $P = 0.874$) with significant heterogeneity among the studies ($I^2 = 76.0\%$; $P_{\text{heterogeneity}} < 0.001$), as shown in Fig. 6.

Table 1 Characteristics of included studies

Author/ publication year	Species tested/age (days)	Sample size; intervention arms of measured outcomes	Sample size; control arm	Duration of exposure (days)	Intervention groups dose (mg/kg)	Glyphosat formulations	Route of exposure	Control group	Measured outcome(s)	Hormone measurement assays
Manservisi et al. 2019	Sprague-Dawle (SD) rats/119	36 (8, 8, 10, 10/group)	18 (8, 10)	42, 91	1.75	Both active ingredient and commercial formulation	Oral (gavage)	Distilled water	TEST, EST	ELISA
Owagboriaye et al. 2017	Albino rats/NR	24 (8, 8, 8/group)	8	84	3.8, 50.4, 248.4	Commercial formulation	Oral (gavage)	Distilled water	TEST, LH, FSH	ELISA
Dai et al. 2016	Sprague-Dawle (SD) rats/56	22 (8, 8, 6/group)	8	35	5, 50, 500	Active ingredient	Oral (gavage)	Deionized water	TEST, EST	RIA
Abarikwu et al. 2015	Wistar rats/21–28	5 (5/group)	5	52	5	Commercial formulation	Oral (gavage)	Corn oil	LH, FSH	ELISA
Razi et al. 2012	Wistar rats/42	32 (8, 8, 8, 8/group)	16	10, 20, 30, 40	125	Active ingredient	Oral (gavage)	Corn oil	TEST	RIA
Romano et al. 2012	Wistar rats/90	12 (12/group)	12	60	50	Commercial formulation	Oral (gavage)	Deionized water	TEST, LH, FSH, EST	RIA
Romano et al. 2010	Wistar rats/21	49 (15, 16, 18/group)	17	30	5, 50, 250	Commercial formulation	Oral (gavage)	Deionized water	TEST, EST	RIA
Dallegrave et al. 2007	Wistar rats/90	45 (15, 15, 15/group)	15	23	50, 150, 450	Commercial formulation	Oral (gavage)	Water	TEST	RIA

TEST testosterone, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *EST* estradiol, *NR* not reported, *ELISA* enzyme-linked immunosorbent assays, *RIA* radioimmunoassay

Dose-response and meta-regression

We explored meta-regression analysis to evaluate the association of the intervention (days) duration and changes in hormone levels. We carried out dose-response analysis using fractional polynomial modeling to find the non-linear dose-response relationship between glyphosate and GBHs' different dose exposures and hormone levels. Subsequent analysis of the relationship between duration of exposure with testosterone level revealed a negative correlation (Coefficient = − 0.012, P = 0.514), as displayed in Fig. S1 (Supplementary data). Non-significant reduction of testosterone level was seen following dose-response evaluation when different doses were compared in a non-linear fashion (Fig. S2).

A non-significant negative correlation was also observed when the effect of various exposure duration to glyphosate and GBHs on LH level was evaluated (coefficient = − 0.12, P = 0.179), as shown in Fig. S3. Following dose-response evaluation, different doses of herbicide did not change LH level significantly in a non-linear fashion (Fig. S4). Regarding FSH, there was no significant association when the different duration of exposure was compared in relation to changes in FSH level (coefficient = − 0.13, P = 0.134), represented in Fig. S5. A non-significant negative correlation was seen between glyphosate and GBH dose and reduction in FSH level in a non-linear fashion (Fig. S6).

As shown in Fig. S7, the relationship between the duration of exposure and the estradiol level revealed a non-significant negative correlation (coefficient = − 0.06, P = 0.431). Non-significant reduction of estradiol level was seen when the dose-response analysis was conducted to compare the effect of different doses of glyphosate and GBHs in a non-linear fashion (Fig. S8).

Publication bias and sensitivity analysis

Egger's tests did not find a significant publication bias among the studies which reported testosterone, LH, FSH, and estradiol as an outcome measure (P = 0.614, 0.168, 0.275, and 0.995, respectively). Evaluation of publication bias by visual inspection of funnel plot illustrated no evidence of publication bias.

Discussion

As described previously, glyphosate (N-(phosphonomethyl) glycine) and GBHs are considered systemic herbicides belonging to the organophosphorus class. Glyphosate is available as phosphonate form, which inhibits the enzyme 5-enolpyruvylshikimate-3-phosphate synthase in the plants (Franz et al. 1997; Padgette et al. 1995; Zhang et al. 2020). Despite its benefits in agriculture and widespread use in this

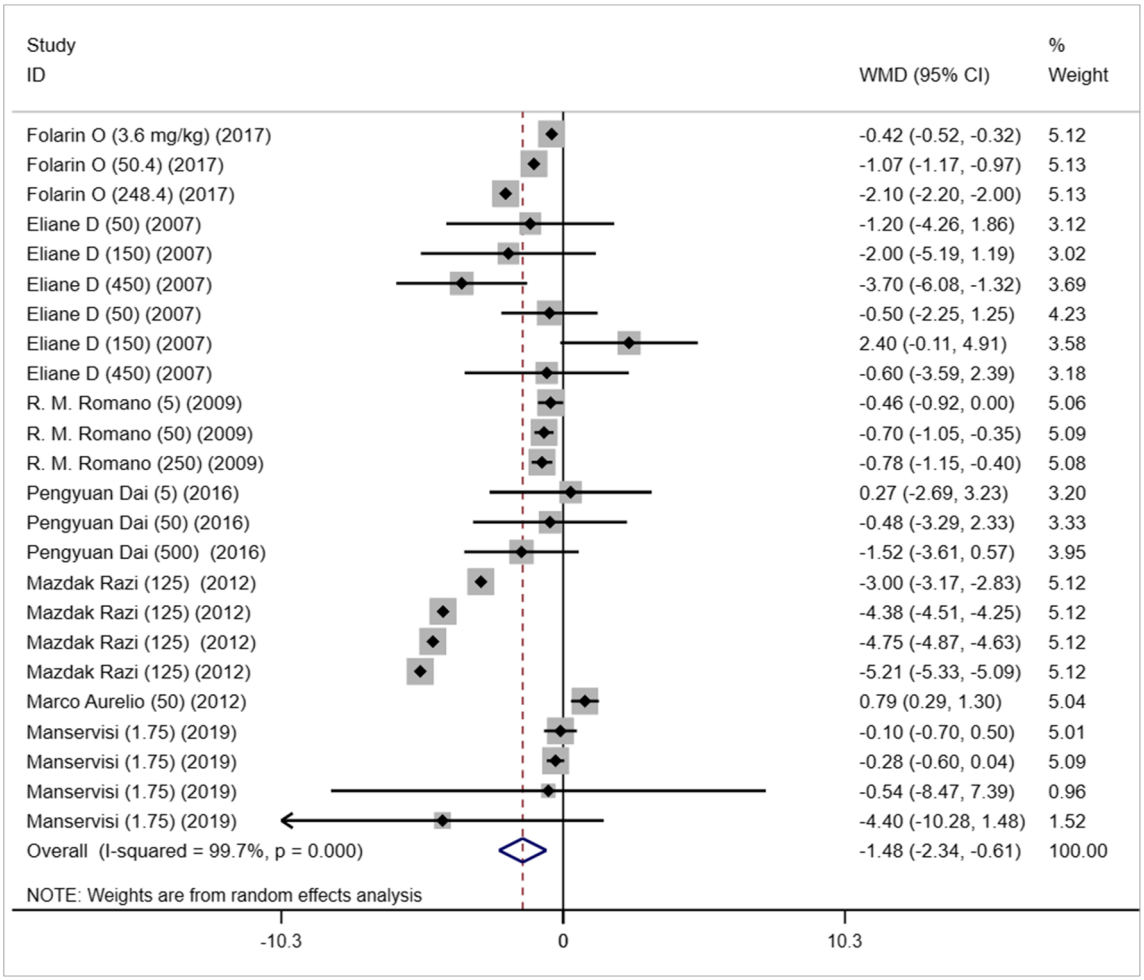

Fig. 3 Forest plot presenting mean difference (WMD) and 95% CI for the effect of glyphosate exposure on testosterone levels in overall population

context, some concerns have been raised regarding its impact on the environment, human health, endocrine side effects, and cancer risk (Gillezeau et al. 2019; Mink et al. 2012; Van Bruggen et al. 2018a; Zhang et al. 2020). Considering that glyphosate does not degrade rapidly in plants and accumulates in some food and agriculture products, therefore, it could have significant impacts on health outcomes. There have been rising concerns and uncertainty about reports attributing the numerous toxicity induced by a commercial formulation of glyphosate-based herbicide to its active ingredient. Therefore, various studies have been performed to compare the toxicity of the active ingredient glyphosate versus GBHs (Braconi et al. 2006; Chaufan et al. 2014; Jacques et al. 2019; Janssens and Stoks 2017; Owagboriaye et al. 2019; Slaby et al. 2020). Most of them concluded that the addition of inert ingredients increased the toxicity of the active ingredient glyphosate in various studied models.

On the other hand, the toxicity and effects of glyphosate and GBHs on endocrine systems, such as the decrease in androgen level due to inhibition of some critical enzymes, alteration in estrogen level, and disruptive damage to reproductive organs in animals, have been proposed by some studies (Gomez et al. 2019; Jarrell et al. 2020; Pham et al. 2019; Warner et al. 2020). Consequently, it is essential to investigate and assess the endocrine safety of this herbicide.

The results of our meta-analysis reflected a significant association between glyphosate and GBH exposure and a decrease in testosterone and LH level in male rats. The reduction of FSH and estradiol levels was also seen; however, these results were not statistically significant. One of the most important findings of this systematic review is the statistically significant associations between the duration of exposure to glyphosate and GBHs and its effect on testosterone levels; in contrast, the association between duration of exposure and alteration in other hormone levels was not significant. Another important finding was the reduction in included hormone levels when different doses of herbicide were administered, although it was not statistically significant for the measured outcomes.

Nevertheless, different mechanisms have been suggested for the results mentioned above, as shown in Fig. 7. It has been shown that the glyphosate and GBHs could inhibit

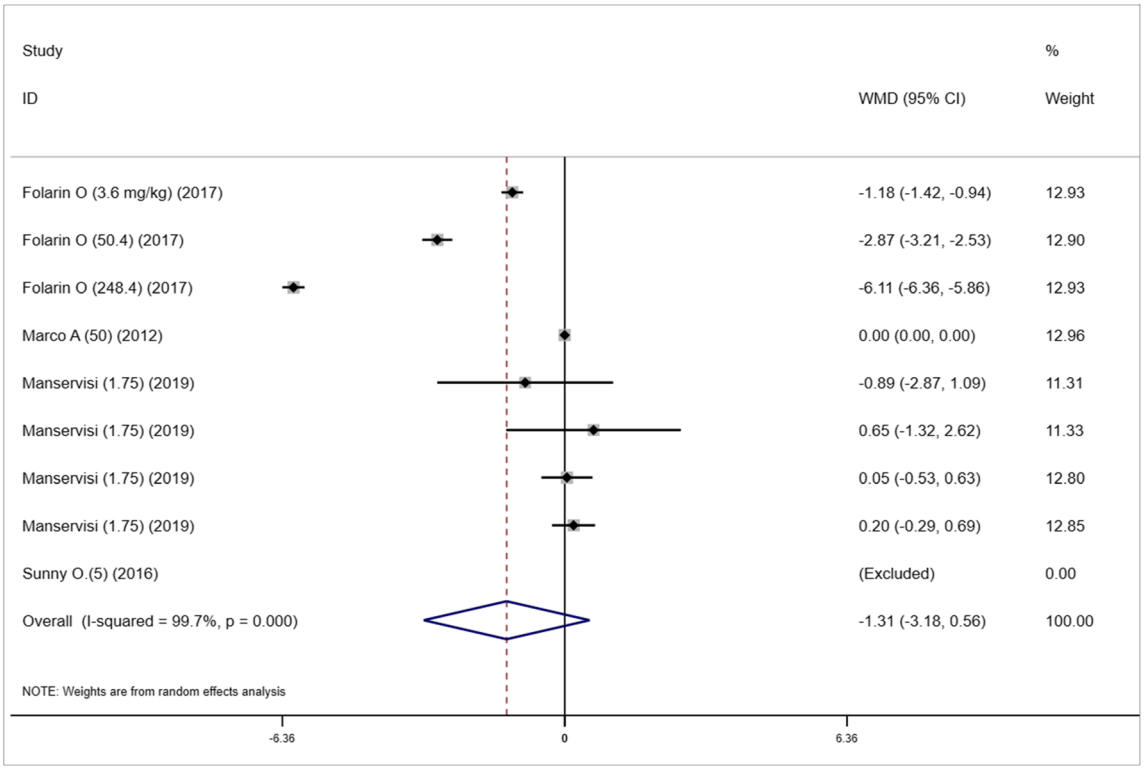

Fig. 4 Forest plot presenting mean difference (WMD) and 95% CI for the effect of glyphosate exposure on LH levels in overall population.

aromatase enzymes involved in the biosynthesis of estradiol and testosterone hormones (Defarge et al. 2016; Richard et al. 2005). This inhibition was observed in both kinetic and spectral studies competitively (Jarrell et al. 2020). In addition, the inhibitory effect of glyphosate and GBHs on androgen receptors and aromatase mRNA by using gene reporter tests

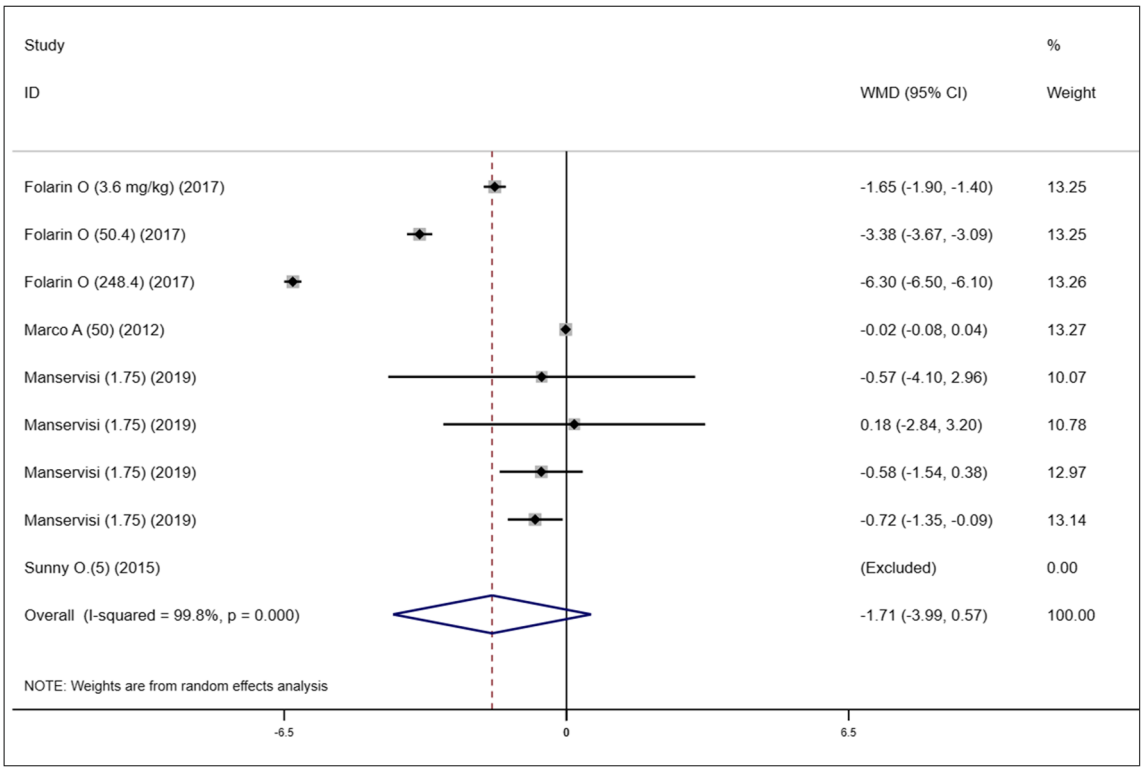

Fig. 5 Forest plot presenting mean difference (WMD) and 95% CI for the effect of glyphosate exposure on FSH levels in overall population

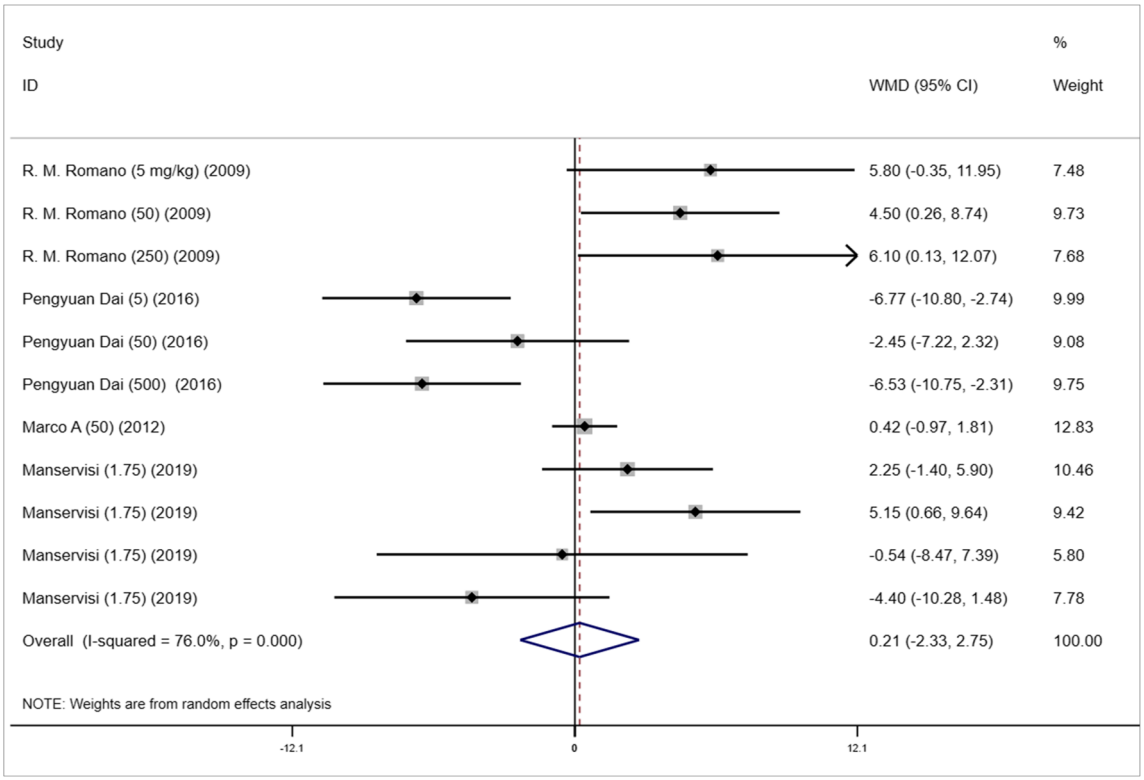

Fig. 6 Forest plot presenting mean difference (WMD) and 95% CI for the effect of glyphosate exposure on estradiol levels in overall population

was postulated (Ingaramo et al. 2020). Some studies reported that the glyphosate and GBHs reduce testosterone level even at doses as low as about 5 mg/kg in a dose-dependent fashion (Clair et al. 2012; Owagboriaye et al. 2017). Other involved mechanisms are inhibition of cell proliferation through the enzyme serine hydroxymethyltransferase and induction of apoptosis (Li et al. 2013). This inhibitory effect of this herbicide on the androgen level and receptor was also seen in cell line studies (Gasnier et al. 2009). The estrogen receptor expression was disrupted after exposure to GBHs in multiple animal studies (Guerrero Schimpf et al. 2017; Varayoud et al. 2017). There were controversies regarding the effect of glyphosate and GBHs on the gonadotropins (LH and FSH) hormone levels. The reduction of LH and FSH levels was observed in one report (Manservisi et al. 2019), while in some studies, the opposite findings were seen mainly due to activation of negative feedback secondary to low testosterone level (Owagboriaye et al. 2017; Romano et al. 2012).

In accordance with our results, it has been shown that GBH exposure had decreased testosterone concentration by 35% at each dose level in rats (Clair et al. 2012). This decrease in the level of testosterone can cause a secondary alteration of LH level following glyphosate exposure. Moreover, the change in aromatase enzyme activity may affect the level of estradiol and testosterone. Similarly, in another study, glyphosate and GBHs disrupted mice's reproductive system and decreased serum testosterone content in males (Pham et al. 2019). On the other side, exposure of weaned piglets to this herbicide increased testosterone and LH-releasing hormone levels, whereas the level of FSH was considerably decreased compared to the control group.

The other potential effects of glyphosate on the reproductive system and ovarian function were also demonstrated in a previous in vitro study that showed that glyphosate, even at low levels, may impair the production of the steroids from ovarian (Perego et al. 2017b). They suggested that exposure to glyphosate can affect the cattle reproductive system, directly influencing ovarian activity. One study reported that glyphosate exposure at different concentrations did not significantly impact on the 17β-estradiol level in mice (Ganesan and Keating 2020). Similarly, a study conducted in Italy indicated that estradiol production was not affected at both treatment doses by GBHs (Perego et al. 2017a). On the other hand, in contrast to our finding, estradiol production decreased after exposure to glyphosate in in vitro models (Perego et al. 2017b).

Teleken and colleagues investigated the effects of GBH exposure during pregnancy and lactation on the development of male reproductive systems (Teleken et al. 2020). Their hypothesis was that maternal exposure to GBHs during pregnancy and lactation affects male reproductive organs' growth and impairs male fertility in the mice model. In this study, female mice received GBHs (0.5%) through drinking water from the fourth day of pregnancy up to the lactation period.

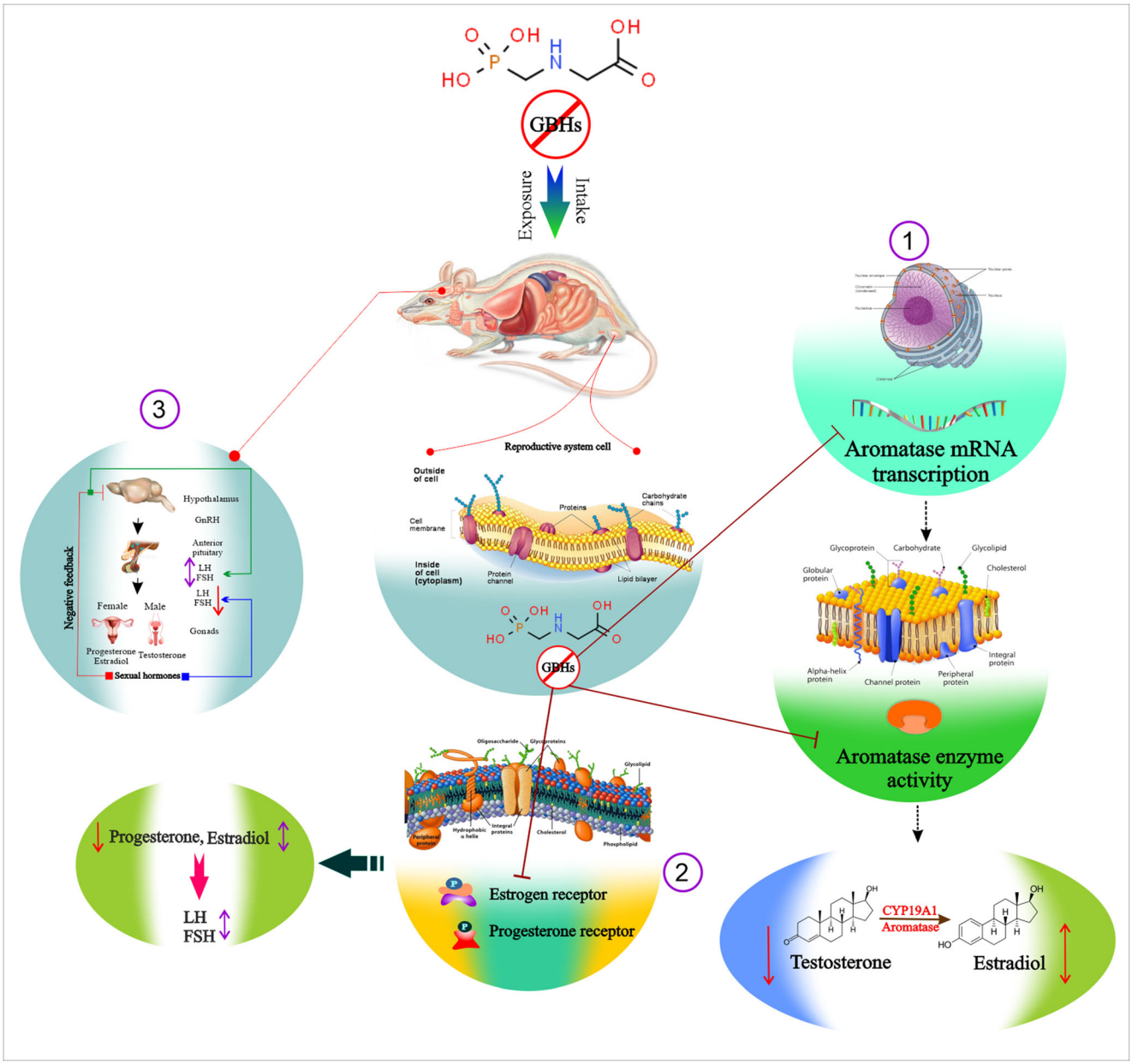

Fig. 7 The schematic representation of proposed mechanisms for the reproductive toxicity of glyphosate. (1) Inhibition of aromatase mRNA gene transcription and aromatase enzyme activity. (2) Alteration in the function of estrogen and progesterone receptors and changes in levels of these hormones. (3) Direct and indirect effect of GBHs on levels of LH and FSH hormones

They reported that the bodyweight of female mice treated with glyphosate reduced during gestation, while the litter size was not altered. Nevertheless, their results proved that maternal exposure to GBHs during pregnancy and lactation may lead to reduction in spermatogenesis and disruptions in hypothalamus–pituitary–testicular axis regulation in treated mice.

In another study, the endocrine effect of GBHs on the adrenal gland of male Wistar rats was evaluated (Pandey and Rudraiah 2015). They observed considerable changes in rats exposed to GBHs during 2 weeks of testing, especially in the biosynthesis route of steroid hormones. They reported that GBH exposure caused downregulation of mRNA levels of the steroidogenic acute regulatory protein (StAR), and decreased total and phosphorylated StAR protein expression. Correspondingly, GBH exposure decreased adrenocorticotropic hormone (ACTH) levels.

In addition to glyphosate and GBHs, many studies have reported that exposure to other herbicides may lead to metabolic and endocrine disorders. For example, Harper et al. studied the chronic exposure of male mice to atrazine (5 mg/kg/day) by drinking water and its effects on the metabolic, endocrine, and reproductive systems (Harper et al. 2020). Exposure to atrazine led to a reduction in liver weight, changes in androgen conversion in the testis, and altered liver and testis

gene expression. Furthermore, they observed that exposure to atrazine significantly reduced epididymal sperm concentration and embryo cell numbers generated in the 12-week males.

In another research, the effect of quinalphos as an organophosphorus pesticide on sperm functional competence and fertilization potential in Swiss albino mice was evaluated (Kumari et al. 2021). Their study showed that exposure to quinalphos herbicides significantly reduced sperm motility and increased sperm head defects and DNA damage. Also, the pharmacokinetic analysis revealed a threefold rise in the concentration of quinalphos in the testis than serum. Notably, quinalphos administration caused a decrease in testosterone levels and increased estradiol levels and aromatase and cytochrome P450 transcripts. In this regard, the sperm functional competence and fertilizing ability rate were significantly reduced in herbicide-treated mice.

One study also investigated the systemic and reproductive toxicity of acetochlor herbicides in male mice (Song et al. 2019). Their findings indicated that exposure to acetochlor herbicide caused significant disturbances in metabolic functions and endocrine and reproductive system. In this study, the testosterone hormone levels also increased after acetochlor administration compared to the control group in a dose-independent fashion.

The primary strength of this meta-analysis was a comprehensive overview of the effect of glyphosate exposure on reproductive hormones and the potential exposure to this herbicide from agricultural and food products, which is a worthwhile endeavor. To the best of our knowledge, this was the first systematic review and dose-response meta-analysis to evaluate the effect of glyphosate exposure on the endocrine system. We were also able to stratify analyses based on the duration of exposure and dosage of glyphosate. All of the reproductive hormones were assessed in this paper; therefore, the impact of the obtained results on the endocrine system should be considered in human studies. Another strength of our analysis was the low publication bias in included studies.

Notwithstanding, our study has some limitations. The glyphosate was administered in various dosing and duration ranges in the included studies, which could influence the results of our study. One more limitation of our review was the high heterogeneity and the relatively small sample sizes among the final included studies.

Conclusion

This review summarized existing studies that explored the relationship between the administration of glyphosate and alteration in sex hormone levels. The primary result indicates a statistically significant decrease in testosterone and LH levels following glyphosate exposure compared to the control group. The non-significant changes in estradiol and FSH levels were also observed compared to the control group. Based on these results, glyphosate intake could significantly affect reproductive health systems, so the close and strict monitoring of the residual glyphosate contents in the drinking water, agricultural crops, and food products should be considered. Likewise, long-term, well-designed animal bioassays and human clinical studies must be conducted further to evaluate the effects of glyphosate on different health outcomes.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11356-021-16145-x.

Author contribution Keyhan Mohammadi, Mahmood Alizadeh Sani, Payam Safaei, and Jamal Rahmani: conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing—original draft. Ebrahim Molaee-Aghaee and Seid Mahdi Jafari: conceptualization, investigation, methodology, project administration, supervision, visualization, writing—review and editing.

Data availability None.

Declarations

Competing interests The authors declare no competing interests.

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